Antiseptic-containing silicone elastomers

The invention relates to compositions comprising silicone elastomers and antiseptics in homogeneous distribution, to a process for the preparation thereof and to the use thereof in medical articles.

Medical articles made of plastics (e.g. catheters) are currently used in a large number of applications for diagnostic and therapeutic purposes. Central venous catheters are used for example in modern intensive care for invasive monitoring and treatment strategies such as continuous haemofiltration. Urinary tract catheters are an essential component of modern medical care and are indispensable, for example in the treatment of impairments of the flow of urine. Although modern medical articles have substantially improved the treatment of intensive-care patients, their application is associated with considerable risks. The frequent use of plastics articles such as, for example, catheters has led to a drastic increase in so-called polymer-associated infections. Polymer-associated infections are in general mainly caused by multiresistant nosocomial pathogens which adhere to the article's plastics surface and then colonize it (*Urogenitale Infektionen, Ed. A. Hofstetter, Springer 1999, 241-64).*

Catheter-associated infections currently represent an important cause of morbidity and mortality of intensive-care patients. Recent studies demonstrate that 70 to 90% of nosocomially acquired urinary tract infections are associated with an instrumentation (catheterization) of the urinary tract. A single catheterization of the urinary bladder is followed by bacteriuria for example in 0.5 to 28% of patients. The incidence of catheter-associated urinary tract infections moreover depends on the catheter time and the age, sex and condition (immunocompetence) of the patient (*Urogenitale Infektionen, Ed. A. Hofstetter, Springer 1999, 241-64*). However, the use of catheters not only involves a higher risk of infection for the patients, but also causes high follow-up therapy costs. Givens and Wenzel were able to show that nosocomial urinary tract infections increase the postoperative inpatient stay by an average of 2.4 days and cause corresponding additional costs (*J. Urol. 1980, 124:*

646-48). Prevention of catheter-associated infections therefore has the highest priority in modern medicine for both medical and economic reasons.

Catheter-associated infections, possibly developing into sepsis, are, besides traumatic and thromboembolic complications, a serious problem on use of central venous catheters in intensive care.

Numerous studies have revealed that coagulase-negative staphylococci, the transient organism Staphylococcus aureus and various Candida species are the main causes of catheter-associated infections. During application of the catheter, these microorganisms, which are ubiquitously present on the skin, penetrate the physiological barrier of the skin and thus reach the subcutaneous region and eventually the bloodstream. Adhesion of the bacteria to the plastics surface is regarded as an essential step in the pathogenesis of foreign-body infections. Adhesion of the cutaneous organisms to the polymer surface is followed by the start of metabolically active proliferation of the bacteria with colonization of the polymer. This is associated with production of a biofilm through bacterial excretion of extracellular glycocalix. The biofilm assists adhesion of the pathogens and protects them from attack by certain cells of the immune system. In addition, the film forms a barrier which is impenetrable by many antibiotics. Extensive proliferation of the pathogenic organisms on the polymer surface may finally be followed by septic bacteriaemia. Therapy of such infections requires removal of the infected catheter because chemotherapy with antibiotics would require unphysiologically high doses.

The incidence of bacterially induced infections with central venous catheters averages about 5%. Overall, central venous catheters prove to be responsible for about 90% of all cases of sepsis in intensive care. The use of central venous catheters therefore not only involves a higher risk of infection for the patients, but also causes extremely high follow-up therapy costs (subsequent treatment, extended stays in the clinic).

The problems associated with urinary tract and central venous catheters can be solved only in part by prophylactic measures such as, for example, hygienic

measures (handling of the catheters, training of the staff) or routine endoluminal antibiotic administrations.

A rational strategy for preventing polymer-associated infections consists of modifying the polymeric materials used. The aim of this modification must be to inhibit bacterial adhesion and the proliferation of already adherent bacteria, for causal prevention of foreign-body infections in this way. This can be achieved for example by incorporating a suitable antimicrobially active substance into the polymer matrix (e.g. antibiotics), provided that the incorporated active ingredient can also diffuse out of the polymer matrix in a controlled manner. An infection-resistant material ought therefore to have the following properties:

1) wide range of effects against the microorganisms relevant for infections associated with the appropriate catheter, especially coagulase-negative staphylococci such as Staphylococcus aureus for central venous catheters and enterococcal, Proteus, Klebsiella, Enterobacter species with urethral catheters

2) sufficient duration of the antimicrobial effect, the requirement being for durations of action of longer than 30 days

3) protection of the internal and external surfaces of the materials

4) polymer modification must not impair either the biocompatibility (thromogenicity, cytotoxicity) or the mechanical properties (tensile strength, modulus, hardness) of the material

Methods for producing antimicrobially modified polymers for medical applications have already been disclosed.

EP-A 0 696 604 describes aliphatic thermoplastic polyurethane-ureas which are hydrophilic owing to the urea groups but are unable to prevent bacterial adhesion and proliferation on the catheter surface. EP-A 1 067 974, EP-A 0 927 222, EP-A 1 128 724 and EP-A 1 128 723 describe antibacterially effective thermoplastic

compounds into which the active ingredients are introduced in sufficiently fine and homogeneous distribution by high viscosity processing techniques. Comparative experiments have shown that the shear forces in the extruder are, however, insufficient to achieve the required distribution of the powdered active ingredients in the silicone solid-phase rubbers employed for producing catheter tubings.

Polymer materials for medical applications which have active ingredient-containing coatings are also mentioned in EP-A 328 421. Descriptions are given of processes for producing the antimicrobially active coatings and methods for application onto the surfaces of medical devices. The coatings consist of a polymer matrix, in particular of polyurethanes, silicones or biodegradable polymers, and of an antimicrobially active substance, preferably of a synergistic combination of a silver salt (silver sulphathiazine) with chlorhexidine or an antibiotic. This publication describes combinations of various polymers, inter alia also silicones, with antibiotics. However, the difficulties of incorporating powdered active ingredients into silicone rubbers are not dealt with. The process according to the invention is not described in this publication.

European patent EP-A 0 688 564 describes active ingredient-containing silicone elastomers whose delivery rate can be controlled by the density of crosslinking. The special significance of the particle size of active ingredients in silicone elastomers and how this is achieved is not mentioned. In addition, additives which assist the release of active ingredients are described but are deliberately dispensed with in the present invention.

US publication 4 230 686 (Schöpflin et al) describes room temperature-crosslinking (RTV) silicone elastomers which comprise nonionic lipophilic active ingredients. According to this publication (column 5, lines 57 to 59), such silicone elastomers are suitable as active ingredient carriers with slow release only for lipophilic nonionic active ingredients. In addition, column 7, lines 51 to 60, describe the incorporation of the active ingredients as dry powders into the silicone elastomers. The particle size is said in this case to be chosen in such a way that as the solubility of the active

ingredient in water increases the size of the incorporated particles (4 to 400 µm) must be larger.

It was an object of the invention to provide novel silicone elastomers which are suitable for producing medical shaped articles for short-term implants, especially catheters, and efficiently prevent for a prolonged period (more than 30 days) surface colonization by microorganisms.

An additional object of the invention was to provide a process making it possible to incorporate active ingredients in fine distribution into silicone elastomers.

It has now surprisingly been found that the silicone elastomers according to the invention which comprise antiseptics, especially those selected from the group of bispyridinium alkanes, of polymeric amidobiguanides, of quaternary ammonium compounds, in particular benzalkonium chloride, and chlorhexidine, taurolidine and triclosan, with a very small particle size (about 3 µm), have brought about a very good activity against bacterial colonization on catheter surfaces over several weeks.

The invention thus firstly relates to silicone elastomers which comprise at least one antiseptic in homogeneous distribution, where the antiseptic, in particular in the form of a suspension, has an average particle size d_{50} of from 0.5 to 15 µm, preferably between 1 and 10 µm, and a particle size distribution between 0.1 to 30 µm, preferably 0.5 to 20 µm.

The invention further relates to the use of suspensions for incorporating the antiseptic into the silicone-rubber formulation, it being possible in a preferred variant for the suspending medium to be chemically incorporated into the silicone elastomer.

The invention further relates to shaped articles which are produced by crosslinking the silicone-rubber formulations according to the invention.

The invention additionally relates to the use of the silicone elastomers according to the invention for producing medical tubings, urinary bladder catheters (Foley

catheters, intermittent catheters, suprapubic and transurethral catheters), haemodialysis catheters, single- and multiple-lumen central venous catheters, peripheral catheters, thermodilution catheters, balloon catheters for percutaneous transluminal coronary angioplasty (PTCA).

The invention further relates to medical appliances, especially catheters, which can be produced from the silicone elastomers according to the invention.

The present invention further relates to a process for preparing the silicone rubbers according to the invention comprising the provision of a silicone-rubber formulation described hereinafter and the polymerization of the said silicone-rubber formulation. The present invention further relates to the silicone-rubber formulation.

The silicone-rubber formulation according to the invention comprises the following components:

A) at least one polysiloxane of the formula (I)

$$\mathbf{R^1R^2_2SiO\text{-}(SiR^3R^4O\text{-})_xSiR^1R^2_2} \qquad \mathbf{(I)}$$

in which the radicals

R^1 and R^2 may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^3 and R^4 may in each case be identical or different, expressly including each repeating unit, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, and additionally $-OSiR^2R^3R$, in which R symbolizes the continuation of the siloxane chain in analogy to formula (I) in the branching so that the polymer molecule may have branching units of the formula $SiO_{4/2}$ and $R^3SiO_{3/2}$,

R^1 and R^3 are additionally independently of one another C_1-C_{12}-alkenyl, in which case the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and the molecule has at least two olefinically unsaturated multiple bonds,

x is an integer from 2 to 15 000 and is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C,

B) optionally at least one filler having a BET specific surface area of between 50 and 500 m^2/g,

C) optionally at least one filler having a BET specific surface area below 50 m^2/g,

D) optionally at least one further auxiliary,

E) optionally at least one saturated water repellent from the group consisting of disilazanes, siloxanediols, alkoxysilanes, silylamines, silanols, acetoxysiloxanes, acetoxysilanes, chlorosilanes, chlorosiloxanes and alkoxysiloxanes,

F) optionally at least one unsaturated water repellent from the group consisting of multiply vinyl-substituted methyldisilazanes, and methylsilanols and alkoxysilanes each having unsaturated radicals from the group consisting of alkenyl, alkenylaryl, acryl and methacryl,

G) optionally at least one nonfunctional polysiloxane,

H) optionally at least one inhibitor for the hydrosilylation reaction,

I) at least one polyhydrosiloxane of the formula (II)

$$R^{21}R^{22}{}_2SiO\text{-}(SiR^{23}R^{24}O\text{-})_xSiR^{21}R^{22}{}_2 \qquad \textbf{(II)}$$

in which the substituents

R^{21} and R^{22} may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^{23} in each case expressly including each repeating unit independently of one another is hydrogen, C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, additionally -$OSiR^{23}R^{24}R$ in which R symbolizes the continuation of the siloxane chain in analogy to formula (II) in the branching so that the polymer molecule may have branching units of the formula $SiO_{4/2}$ and $R^{23}SiO_{3/2}$, where R^{23} in at least 4 of these silyldioxyl units is hydrogen so that a molecule has at least 4 crosslinking sites,

R^{24} in each case expressly including each repeating unit independently of one another is C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, additionally -$OSiR^{23}R^{24}R$ in which R symbolizes the continuation of the siloxane chain in analogy to formula (II) in the branching so that the polymer molecule may have branching units of the formula $SiO_{4/2}$ and $R^{23}SiO_{3/2}$,

x is an integer from 4 to 10 000 and is varied so that the viscosity of the polymer extends from 0.0005 to 0.1 Pas at 25°C,

J) at least one catalyst comprising an element of the platinum group,

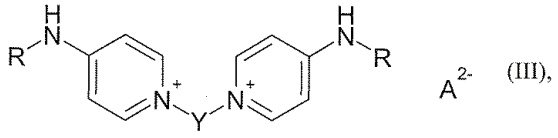
where a maximum of 3 parts by weight of metal compounds such as oxides and/or carbonates, and further salts and complex compounds, of Fe, Al, Zn, Ti, Zr, Ce or other lanthanoids are present based on 100 parts by weight of component A),

K) at least one suspension, where the suspending medium are polysiloxanes of the formula (I) and/or (II) and/or nonfunctional siloxanes G), and comprises at least one antiseptic, in particular those selected from the group of bispyridinium alkanes, of polymeric amidobiguanides, of quaternary ammonium compounds, in particular benzalkonium chloride, and chlorhexidine, taurolidine and triclosan.

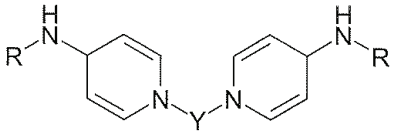
Bispyridinium alkanes

Active ingredients suitable in principle are all the active ingredients defined in Claims 1 to 4 on page 28 of DE 27 08 331 C2. The compounds from Examples 1-82 (page 5 to page 18, line 19) are preferably employed, and octenidine, its hydrochloride or very particularly preferably the dihydrochloride 1,1'-(1,10-decanediyl)bis[4-(octylamino)pyridinium] dichloride are particularly preferably employed.

These active ingredients referred to as bis[4-(substituted amino)-1-pyridinium]-alkanes are defined by the general formulae (III) and (IV)



(III),



(IV),

in which

Y is an alkylene group having 4 to 18 carbon atoms,

R is C_6-C_{18}-alkyl, C_5-C_7-cycloalkyl or phenyl which is substituted by a halogen atom, and

A is two monovalent or one divalent anion.

Y is preferably 1,10-decylene or 1,12-dodecylene, particularly preferably 1,2-dodecylene.

R is preferably n-hexyl, n-heptyl or n-octyl, particularly preferably n-octyl.

A is for example one sulphate, in each case 2 fluoride, chloride, bromide, iodide, or methanesulphonate ions, preferably in each case 2 fluoride, chloride, bromide, particularly preferably 2 chloride ions.

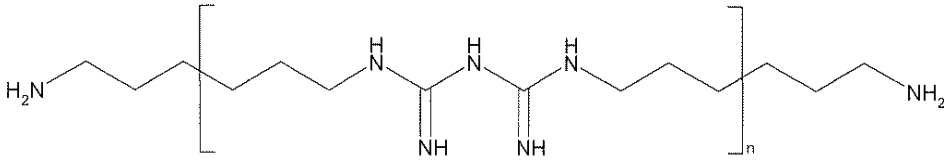
Formula (IV) designates the corresponding free bases which can be prepared by neutralization from the salts of the formula (III) by conventional methods of organic chemistry. The salts of the formula (III) are frequently depicted in the literature also in the form of the formula (V)

$$\text{formula (IV)} \times H_2A \qquad \text{(V)}$$

in which “formula (IV)” and A have the meanings indicated above. By its nature, a chemical formula is only a simplified depiction of reality. In this case, tautomers are involved, for which there is no evidence that they can be distinguished under usual conditions and temperatures. For octenidine dihydrochloride there are nevertheless in each case 2 chemical abstracts registry numbers and 2 numbers in the European inventory of existing commercial chemical substances. It is not intended to be relevant to the invention whether compounds of the formula (III) or of the formula (V) are employed or in which form they are present in the polymer composition. Salts of the formula (III) or (V) are preferably employed.

Polymeric amidobiguanide

The aminopropylbiguanides to be used according to the invention have in particular the formula VI

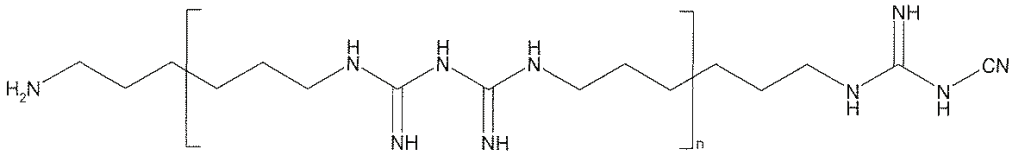


(VI)

in which n is an integer between 1 and 500, and it is also possible to use salts of compounds of the formula VI, especially the salts thereof.

The compounds of the formula VI are known. Their preparation is described for example in GB 702 268 and GB 1 152 243. In addition, these compounds are also commercially available, e.g. as Vantocil™, Cosmocil™ or as Arlagard™ E from ICI Chemicals.

The compounds of the formula VI may, depending on their mode of preparation, comprise certain proportions of a by-product of the formula VII



(VII)

or salts thereof, in which n is likewise an integer between 1 and 500. Mixtures of compounds of the formula VI with those of the formula VII can likewise be used according to the invention. The proportion of compounds of the formula VII based on the total amount of compounds of the formula VI and compounds of the formula VII is preferably less than 20 percent by weight, more preferably less than 2 to 10 percent by weight and is particularly preferably zero percent by weight.

The index n in the formulae VI and VII is preferably from 1 to 200, preferably 2 to 100, particularly preferably 2 to 50 and very particularly preferably 3 to 12. Depending on the meaning of the index n in the formulae VI or VII, the molecular weight of the aminopropylbiguanides which can be used is as low as that molecular weight of the monomers of the formula VI (n = 1), or in the range from about 600 to 1600 if oligomers are used, i.e. if n is for example 3 to 8, or else in the range from

about 50 000 to about 90 000 if n stands for distinctly higher values, e.g. for about 270 to 500.

Suitable salts are those with inorganic or organic acids, for example hydrochlorides, hydrobromides, borates, acetates, gluconates, sulphonates, maleates, ascorbates, tartrates or citrates.

The antiseptics are preferably incorporated into the silicone-rubber formulations according to the invention in a concentration appropriate for their antimicrobial activity. The antiseptics are normally used in a concentration range from 0.01 to 10.0% by weight, preferably from 0.05 to 5% by weight, particularly preferably 0.1 to 5% by weight, in the silicone elastomers.

For the purposes of the present invention, component A) is defined by at least one linear or branched polysiloxane of the general formula (I) indicated hereinbefore.

$$\mathbf{R^1R^2_2SiO\text{-}(SiR^3R^4O\text{-})_xSiR^1R^2_2} \qquad \mathbf{(I)}$$

R^1 and R^2 may in each case be identical or different, and each is preferably C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and phenyl or naphthyl which is optionally mono- or polysubstituted by F, Cl, CF_3, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or phenyl.

R^3 and R^4 may in each case be identical or different, expressly including each repeating unit, and are each preferably C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and phenyl or naphthyl which is optionally mono- or polysubstituted by F, Cl, CF_3, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or phenyl.

R^1 and R^3 are preferably in addition independently of one another also C_1-C_{12}-alkenyl, where the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and each molecule has at least two olefinically unsaturated multiple bonds.

x is preferably an integer from 2 to 15 000 and is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C.

R^2 to R^4 are particularly preferably C_1-C_{12}-alkyl.

R^1 is particularly preferably vinyl.

R^2 to R^4 are very particularly preferably methyl.

The viscosity of component A) is preferably between 0.1 and 30 000 Pas.

For the purposes of the present invention, component B) has the meaning of a filler having a BET specific surface area of between 50 and 500 m^2/g. It is expedient for these to be reinforcing fillers. Reinforcing means in this connection that the mechanical strength properties are improved, in particular tensile strength, tear propagation resistance, etc. are improved. The reinforcing fillers are expediently added in a form which positively influences or at least does not impair the electrical properties of the cured mixtures according to the invention. This is achieved for example by addition of precipitated or pyrogenic, preferably pyrogenic, silica having a BET surface area of from 50 to 500 m^2/g (the BET surface area is determined by the method of *S. Brunauer, P.H. Emmett, E. Teller, J. Am. Soc. 60, 309 (1938)).*

The fillers may be hydrophobic or hydrophilic fillers. The fillers B) may be surface-modified, i.e. made water-repellent, e.g. with organosilicon compounds. The modification can take place before or else during the compounding for the silicone-rubber formulation according to the invention.

Components E) and/or F) are preferably used for making water-repellent where appropriate with addition of water. Saturated or unsaturated disilazanes and methylsilanols, which may where appropriate also be produced from the disilazanes, in accordance with the definition of components E) or F) are preferably used for making water-repellent.

Preferred ranges for the BET surface area of the filler B) are from 50 to 400, particularly preferably 150 to 300, m^2/g. The amount of component B) is expediently between 0 and 75 parts by weight per 100 parts by weight of component A), preferably 20 to 50 parts by weight.

For the purposes of the present invention, component C) is a filler having a BET specific surface area of below 50, preferably below 40, more preferably below 30, m^2/g. So-called "non-reinforcing fillers" which do not improve the mechanical properties, in particular the tensile strength, tear propagation resistance, etc., are expedient. Preference is given to diatomaceous earths, finely ground quartz or cristobalite, other amorphous silicas or silicates. The amount of component C) is expediently between 0 and 300 parts by weight per 100 parts by weight of component A), preferably 0 to 50 parts by weight.

For the purposes of the present invention, the term "auxiliary" according to component D) expediently includes pigments, release agents, extrusion aids and hot-air stabilizers, i.e. stabilizers against hot-air ageing. The release agents are expediently selected from the group of mould release agents such as, for example, stearyl derivatives or waxes, metal salts of fatty acids. Extrusion agents are, for example, boric acid or PTFE pastes. Hot stabilizers are, for example, metal compounds such as oxides and/or carbonates, and further salts and complex compounds, of Fe, Al, Zn, Ti, Zr, Ce or other lanthanoids and antioxidants. The amount of component D) is expediently between 0 and 10 parts by weight per 100 parts by weight of component A), excluding the presence of more than 3 parts by weight, preferably more than 2 parts by weight, of metal compounds, such as oxides and/or carbonates, and further salts and complex compounds, of Fe, Al, Zn, Ti, Zr, Ce or other lanthanoids.

The silicone-rubber formulation according to the invention preferably comprises no metal compounds such as oxides and/or carbonates and no further salts and complex compounds of Fe, Al, Zn, Ti, Zr, Ce or other lanthanoids.

For the purposes of the present invention, component E) is a saturated water repellent from the group consisting of disilazanes, siloxanediols, alkoxysilanes, silylamines, silanols, acetoxysiloxanes, acetoxysilanes, chlorosilanes, chlorosiloxanes and alkoxysiloxanes. Component E) serves to make the fillers C) and preferably B) water-repellent. The making water-repellent can moreover take place separately before the compounding or in situ during the compounding. The amount of component E) is expediently from 0 to 30 parts by weight, preferably 2 to 25, based on 100 parts by weight of B).

For the purposes of the present invention, component F) is a unsaturated water repellent from the group consisting of multiply vinyl-substituted methyldisilazanes, and methylsilanols and alkoxysilanes each having unsaturated radicals from the group consisting of alkenyl, alkenylaryl, acryl and methacryl. Component F) likewise serves to make the fillers B) and C) water-repellent. The amount of component F) is expediently from 0 to 2 parts by weight, preferably 0.01 to 1, based on 100 parts by weight of A).

The total amount of components E) and F) is preferably 5-25% by weight based on the total amount of components B) and C), preferably based on B).

For the purposes of the present invention, the term “non-functional polysiloxanes” according to component G) expediently means low molecular weight polysiloxanes which are non-functional in relation to the hydrosilylation reaction, are non-crosslinkable, are preferably trimethylsilyl end-blocked and have dimethyl-, diphenyl or phenylsilyloxy groups with degrees of polymerization of 4-1000, or which reliably make the surface of the insulators water-repellent after crosslinking to give the shaped article, as described for example in EP-A 0 057 098. The amount of component G) is expediently from 0 to 15, preferably 1 to 3, parts by weight based on 100 parts by weight of A).

For the purposes of the present invention, the term “inhibitor for the hydrosilylation reaction” according to component H) includes all inhibitors known in the art for the hydrosilylation reaction with metals of the Pt group, such as, for example, maleic

acid and its derivatives, amines, azoles, alkylisocyanurates, phosphines, phosphites and acetylenically unsaturated alcohols in which the OH group is bonded to a carbon atom adjacent to the C-C triple bond, as are described in detail for example in US 3 445 420. Component G) is preferably 2-methyl-3-butyn-2-ol or 1-ethynylcyclohexanol or (±)3-phenyl-1-butyn-3-ol. Component H) is preferably used in a proportionate amount of from 0 to 1 parts by weight based on 100 parts by weight of the total of A) to I). Component H) is preferably present in a proportionate amount of from 0.0001% to 2% by weight, particularly preferably 0.01% by weight to 2% by weight and very particularly preferably 0.05% by weight to 0.5% by weight, in each case based on the total weight of the mixture.

For the purposes of the present invention, component I) is defined by at least one polyhydrosiloxane which has at least two hydrogen atoms directly linked to different silicon atoms, according to the general formula (II) indicated hereinbefore. The following definitions apply to the radicals therein:

$$R^{21}R^{22}{}_2SiO–(SiR^{23}R^{24}O–)_xSiR^{21}R^{22}{}_2 \qquad (II),$$

R^{21} and R^{22} may in each case be identical or different, and are preferably each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl.

R^{23} is preferably in each case expressly including each repeating unit independently of one another hydrogen, C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, where R^{23} is hydrogen in at least 4 of these silyldioxyl units so that a molecule has at least 4 crosslinking sites.

R^{24} is in each case expressly including each repeating unit independently of one another C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl.

x is preferably an integer from 4 to 10 000 and is varied so that the viscosity of the polymer extends from 0.0005 to 0.1 Pas at 25°C.

The molar proportion of hydrogen atoms directly linked to a silicon atom in component I) is preferably between 0.01 and 10 mmol/g, particularly preferably between 0.5 and 9 mmol/g and very particularly preferably between 1 and 7, mmol/g.

The amount of component I) is preferably from 0.2 to 30, preferably 0.2 to 20, parts by weight based on 100 parts by weight of component A).

Component J) is a catalyst at least comprising one element of the platinum group.

Component J) is preferably a catalyst which catalyses the hydrosilylation reaction and is selected from metals of the platinum group such as Pt, Rh, Ni, Ru and compounds of metals of the platinum group, such as salts or complex compounds thereof. It is further preferred for component J) to be a catalyst comprising an element from the platinum group selected from platinum and platinum compounds, which may optionally be adsorbed on a support, and other compounds of elements of the platinum group. Platinum and platinum compounds are most preferred. Thus, Pt salts, Pt complex compounds with nitrogen, phosphorus compounds and/or alkene compounds or Pt metals on supports are preferably employed. All Pt(0) and Pt(II) compounds are preferred, and Pt-olefin complexes and Pt-vinylsiloxane complexes are preferred. Pt-Vinylsiloxane complexes, Pt-vinyldi- and tetrasiloxane complexes, which preferably have at least 2 or 4 olefinically unsaturated double bonds in the siloxane, are particularly preferred (see, for example, US 3 715 334). The term siloxane includes in this connection polysiloxanes or else polyvinylsiloxanes.

It is additionally possible for component J) also to be a product of the reaction of reactive platinum compounds with the inhibitors H).

The amount of component J) in the formulation according to the invention is preferably from 10 to 100 ppm, preferably 15 to 80 ppm and very particularly preferably 20 to 50 ppm, based on the total amount of components A) to I) and

calculated on the basis of the metal of the platinum group in component J). The silicone-rubber formulations preferably comprise 20-100 ppm Pt, based on the amount of components A) to J), in the form of Pt salts, Pt complex compounds with nitrogen compounds, phosphorus compounds and/or alkene compounds or Pt metal on supports.

The active ingredient suspension K) consists on the one hand preferably of polysiloxanes of formula (I) indicated hereinbefore as suspending agents. The definitions of the radicals therein are as follows

$$R^1R^2_2SiO-(SiR^3R^4O-)_xSiR^1R^2_2 \quad (I),$$

R^1 to R^4 are independently of one another particularly preferably each methyl and vinyl, where the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and each molecule has at least two olefinically unsaturated multiple bonds.

x is particularly preferably varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C.

The suspension K) comprises on the other hand at least one antiseptic selected from the group of bispyridinium alkanes, of polymeric amidobiguanides, of quaternary ammonium compounds, in particular benzalkonium chloride, and chlorhexidine, taurolidine and triclosan dispersed in an average particle size d_{50} of from 0.5 to 15 µm, preferably between 1 and 10 µm, and a particle size distribution between 0.1 to 30 µm, preferably 0.5 to 20 µm.

The powdered antiseptics are usually supplied in micronized form. In order to incorporate them into the silicone rubbers, they are previously suspended in a suitable medium. Care must be taken in this connection that the medium has good solubility in the silicone elastomer. Suitable for this purpose in one embodiment of the invention are commercially available silicone oils (R' and R" equal to alkyl), vinyl-terminated polydimethylsiloxanes (R' equal to vinyl; R' equal to methyl) or

polyhydrosiloxanes (R' equal to H; R' equal to methyl), which have viscosities of from 100 to 1 000 000 mPas, preferably from 100 to 500 000 mPas at 25°C. The suitability is decided by whether the active ingredient/medium mixture can be sufficiently finely homogenized in a bead mill.

In a preferred variant, the suspending medium used is at least one vinyl group-terminated silicone polymer which is chemically incorporated into the silicone elastomer in the subsequent crosslinking reaction. It is thereby no longer possible for the suspending medium to be leached out into the surrounding body tissue or a body fluid on use of the silicone elastomer. For example, vinyl group-terminated silicone polymers are available as polymer VS 200 (η (25°C) = 200 mPas; vinyl group content 0.25 mmol/g), polymer VS 1000 (η (25°C) = 1000 mPas; vinyl group content 0.11 mmol/g), or polymer VS 165 000 (η (25°C) = 165 000 mPas; vinyl group content 0.015 mmol/g), from Hanse-Chemie. Comparable products are available from other suppliers such as Dow Corning (Syl-Off® 7673: η (25°C) = 425 mPas) or Wacker Silicones (Dehesive® 920; η (25°C) = 500 mPas) or (Dehesive® 924; η (25°C) = 200 mPas).

"Expressly including each repeating unit" means that, in a deviation from the exact definition of the corresponding formula, that for example in the stated repeating units of the polymers employed according to the invention, of the formula (I), each individual R^3 or R^4 which occurs x times in one molecule can be selected in each case independently from the stated definitions and their preferred ranges, i.e. the radicals occurring in one molecule may be identical or different.

C_1-C_{12}-Alkyl for the purposes of the present invention are aliphatic hydrocarbon radicals having 1 to 12 carbon atoms, which may be straight-chain or branched. Examples which may be listed are methyl, ethyl, propyl, n-butyl, pentyl, hexyl, heptyl, nonyl, decyl, isopropyl, neopentyl, and 1,2,3-trimethylhexyl.

C_1-C_{12}-Fluoroalkyl means for the purposes of the present invention aliphatic hydrocarbon radicals having 1 to 12 carbon atoms, which may be straight-chain or branched and are substituted by at least one fluorine atom.

Examples which may be listed are perfluoroalkylethylene, 1,1,1-trifluoropropyl, 1,1,1-trifluorobutyl, and trifluoropropyl is preferred.

Substituted phenyl means for the purposes of the present invention phenyl radicals which are unsubstituted or mono- or polysubstituted by F, Cl, CF_3, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_7-cycloalkyl, C_2-C_6-alkenyl or phenyl; phenyl is preferred.

Polymerization of the silicone-rubber formulations according to the invention to give the silicone rubbers according to the invention can take place in principle at any temperature customary for this purpose. The polymerization preferably takes place at or in the neighbourhood of room temperature (20 to 25°C).

It is known from the literature, e.g. the product brochure "Die platinkatalysierte Additionsvernetzung mit Elastosil R plus" from Wacker, that inter alia amines impair the activity of the platinum catalyst in crosslinking.

However, it has surprisingly been found that the platinum catalyst retains its activity in the platinum-catalysed crosslinking of the silicone-rubber formulations according to the invention despite the presence of amine groups. The mechanical properties found for silicone rubbers prepared from the silicone-rubber formulations according to the invention were the same as for antiseptic-free comparison specimens.

To prepare the silicone rubbers according to the invention, it is possible in principle to use, apart from the silicone-rubber formulations which are described above and undergo platinum-catalysed crosslinking at room temperature, also heat-vulcanizable (HV) formulations which are vulcanized at temperatures of about 200°C with vulcanization catalysts on the basis such as benzoyl peroxide or di-p-chlorobenzoyl peroxide and require a thermal aftertreatment. Such silicone elastomers can be produced as described in US Patents 2 541 137 or 3 002 951.

In addition, so-called single-component silicone-rubber formulations which are cured at room temperature on exposure to atmospheric humidity without further addition

are used to prepare the silicone rubbers according to the invention. These single-component formulations comprise mainly organopolysiloxanes having two terminal acyloxy, such as, for example, acetoxy, groups which hydrolyse on exposure to atmospheric humidity with formation of trifunctional siloxane units and act in the polymer as crosslinkers with formation of elastomers.

The silicone rubbers which undergo platinum-catalysed crosslinking at room temperature are preferred in the present invention because the active ingredients employed might be chemically changed in the case of HV silicone-rubber systems at the required high vulcanization temperature and with use of peroxide catalysts. In addition, the catalyst residues which remain in the elastomer in the case of HV silicone-rubber systems might be responsible for toxic reactions in the body.

The acetic acid eliminated from usual moisture-curing silicone-rubber formulations as byproduct of the vulcanization at room temperature on exposure to atmospheric humidity may undergo unwanted side reactions with the active ingredient employed.

In a preferred embodiment, the invention further relates to the silicone-rubber formulations described above in which

- the polysiloxane A) is a polysiloxane of the formula (I)

$$\mathbf{R^1R^2_2SiO\text{-}(SiR^3R^4O\text{-})_xSiR^1R^2_2} \qquad \mathbf{(I)}$$

in which the radicals

R^1 and R^2 may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^3 and R^4 may in each case be identical or different, expressly including each repeating unit, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl,

R^1 and R^3 are additionally independently of one another C_1-C_{12}-alkenyl, in which case the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and the molecule has at least two olefinically unsaturated multiple bonds,

x is an integer from 2 to 15 000 and is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C,

- a filler B) having a BET specific surface area of between 50 and 400 m^2/g is used,

- the polyhydrosiloxane I) corresponds to the formula (II)

$$\mathbf{R^{21}R^{22}_2SiO\text{-}(SiR^{23}R^{24}O\text{-})_xSiR^{21}R^{22}_2} \qquad \mathbf{(II)}$$

in which the substituents

R^{21} and R^{22} may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^{23} in each case expressly including each repeating unit independently of one another is hydrogen, C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, where R^{23} is hydrogen in at least 4 of these silyldioxyl units so that a molecule has at least 4 crosslinking sites,

R^{24} in each case expressly including each repeating unit independently of one another is C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl,

x is an integer from 4 to 10 000 and is varied so that the viscosity of the polymer extends from 0.0005 to 0.1 Pas at 25°C,

- the catalyst from the platinum group J) is a catalyst which catalyses the hydrosilylation reaction and is selected from metals of the platinum group such as Pt, Rh, Ni, Ru, and compounds of metals of the platinum group, such as salts or complex compounds thereof,

- the suspending medium used for the suspension K) is at least one polysiloxane of the formula (I) according to A) in which the substituents R^1 to R^4 are each methyl and vinyl radicals, so that the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and the molecule has at least two olefinically unsaturated multiple bonds, and x is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C,

and the suspension K) comprises at least one antiseptic selected from the group of bispyridinium alkanes, of polymeric amidobiguanides, of quaternary ammonium compounds, in particular benzalkonium chloride, and chlorhexidine, taurolidine and triclosan, which comprises in each case an average particle size d_{50} of from 0.5 to 15 µm, preferably between 1 and 10 µm, and a particle size distribution between 0.1 and 30 µm, preferably 0.5 to 20 µm.

Embodiments which are preferred, particularly preferred or very particularly preferred are those which make use of the parameters, compounds, definitions and explanations which are specified as preferred, particularly preferred or very particularly preferred.

However, the general definitions, parameters, compounds and explanations mentioned in the description, or definitions, parameters, compounds and explanations mentioned in preferred ranges, may also be combined with one another, that is to say between the respective ranges and preferred ranges, as desired.

Polymeric additives such as polyvinylpyrrolidone or polyethylene glycol can in principle be admixed with the silicone rubbers up to a concentration of 5% by weight. In a preferred embodiment, such additives influencing the release to the surface are dispensed with.

The suspension K) is produced by using conventional dissolvers which are employed as bead mill. Active ingredient, suspending medium and beads are put into the temperature-controlled vessel. In addition to the total volume, 1/3 glass beads are also added. Instead of glass beads, it is also possible to use other grinding beads, e.g. made of zircon oxide.

The concentration of the active ingredient in the suspension K) is from 10 to 40% by weight, preferably 15 to 35% by weight. The material for grinding can be heated to up to 100°C in order to adjust the viscosity suitable for the grinding. However, the lowest possible temperature is always to be preferred in order to carry out the processing of the active ingredient under conditions which are as mild as possible.

The suspensions K) are incorporated into the silicone-rubber matrix, for example, on a roll mixer. Their viscosity must not be too low for this purpose because they flow away too easily. The risk associated with pastes which are too viscous is that they cannot be incorporated homogeneously into the silicone rubber.

The suspensions K) according to the invention therefore ought to have viscosities of from 10 000 mPas to 2 000 000 mPas at room temperature. Those preferably suitable for use for the process according to the invention have viscosities at 25°C of from 20 000 to 1 000 000 mPas, particularly preferably from 50 000 to 500 000 mPas.

The active ingredients in the suspension K) according to the invention usually have an average particle size d_{50} of from 0.5 to 15 µm, preferably between 1 and 10 µm, and a particle size distribution between 0.1 to 30 µm, preferably 0.5 to 20 µm.

In addition, the suspensions K) produced in this viscosity range remain stable for several weeks and do not sediment. It is possible to dispense with additional dispersion aids.

Components A) + F) + K) and I) ought preferably to be present in the active ingredient-containing silicone-rubber mixtures according to the invention in a ratio of amounts such that the molar ratio of hydrogen directly linked to a silicon atom (SiH) in component I) to unsaturated radicals in components A), F) and K) is between 0.1 and 20, preferably between 0.8 and 10 and very particularly preferably between 1 and 5.

The silicone-rubber formulations according to the invention consist of components A) to K), with components B) to H) being optionally present. The silicone-rubber formulation according to the invention preferably comprises component G) in addition to the necessary components A), I), J) and K).

In the rubber formulations according to the invention it is possible for ingredients A), polysiloxanes of the formula (I), and I), polyhydrosiloxanes of the formula (II), to be present completely or partly in component K), of the suspension, as suspending medium. Also included here according to the invention are formulations without separate further components A) and/or I).

The invention further relates to a process for producing the silicone-rubber formulations according to the invention, which is characterized in that initially components A) to J) are combined and mixed, and K) is then added and incorporated.

The suspension K) is added to the silicone-rubber compositions on a roll mixer, in a kneader or on an extruder. In a preferred embodiment, in the case of 2-component systems the two components are premixed and then the active ingredient suspension is added.

The silicone-rubber formulations according to the invention are preferably produced by adding the water repellents E) and F) which are optionally used, and optionally water, to component A), and incorporating component D) (filler) at temperatures of from 20 to 160°C under a nitrogen atmosphere, and thus making the filler D) water-repellent by reaction with components E) and F). Subsequently, excess reaction products E) and F), and volatile reaction products therefrom (such as silanols, alcohols and water) are removed (preferably by heating at 150 to 170°C, where appropriate in vacuo). In the case of a two-component formulation, either component H) and I) or alternatively J) is metered into the resulting, preferably cooled mixture. If components C), D) and G) are required, they are metered after removal of the volatile components E) and F). In the case of the single-component formulation, H), I) and J) are metered in, the inhibitor H) being metered in first.

Conventional mixers are used, such as, for example, internal mixers, screw mixers, kneaders, preferably kneaders.

The crosslinkable silicone-rubber compositions according to the invention may moreover be 1-, 2- or else multicomponent systems. Multicomponent systems are for example those which comprise H), I) and J) separately.

The following examples serve to illustrate the invention without having a limiting effect.

Examples

Raw materials:

Silicone solid rubbers for urine catheters

A 50:50 A/B 2K platinum-catalysed solid silicone-rubber system 3097/PA from Degania was used to produce the silicone Foley catheter shaft.

A component: vinyl group-terminated polydimethylsiloxane; comprises ingredients A), B) and J).

B component: polyhydrosiloxane; comprises ingredients B), G) and I).

The ratios of the amounts of ingredients A), B); G), I) and J) are adjusted in the A/B components so that the silicone elastomer has a shore A hardness of 65.

Silicone solid rubbers for specimen plates

A 1K platinum-catalysed addition-crosslinked solid silicone rubber Addisil 160 from GE Bayer Silicones was used for the laboratory test to produce specimen plates.

Suspending medium

Polymer VS 1000: vinyl group-terminated polydimethylsiloxane from Hanse-Chemie; viscosity (at 25°C) = 1000 mPas; vinyl content: 0.11 mmol/g

Active ingredients

Octenidine dihydrochloride was purchased from PCAS, Turku, Finland, as a white powder with an average particle diameter of 15 µm in a purity of > 98.5%.

Vantocil hydrochloride (PHMB) was purchased from Avecia as a pale yellow crystalline powder. It was ground before use, producing a colourless powder with an average particle size of 16 µm.

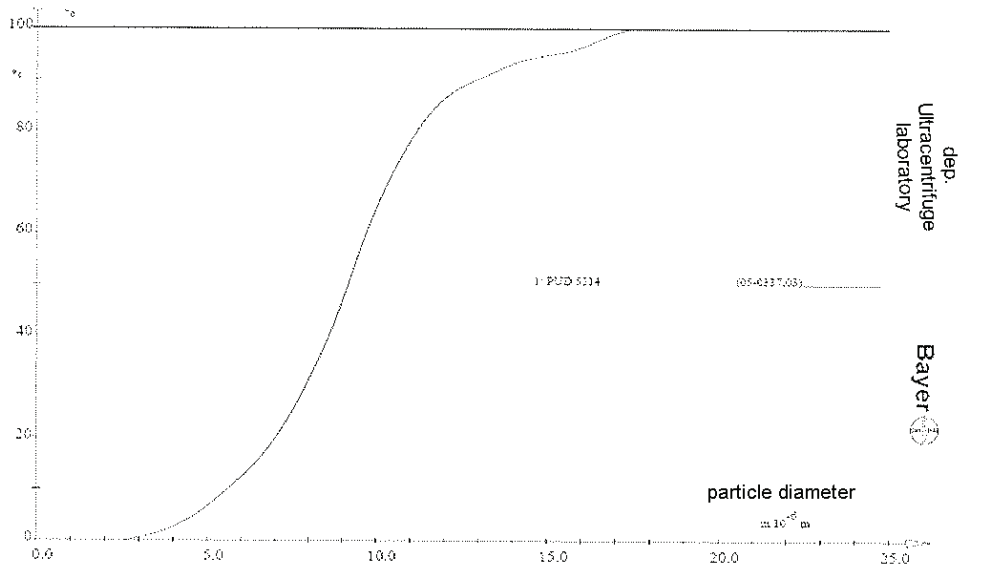
<u>Examples 1-2</u>

Production of the active ingredient suspension in polymer VS 1000:

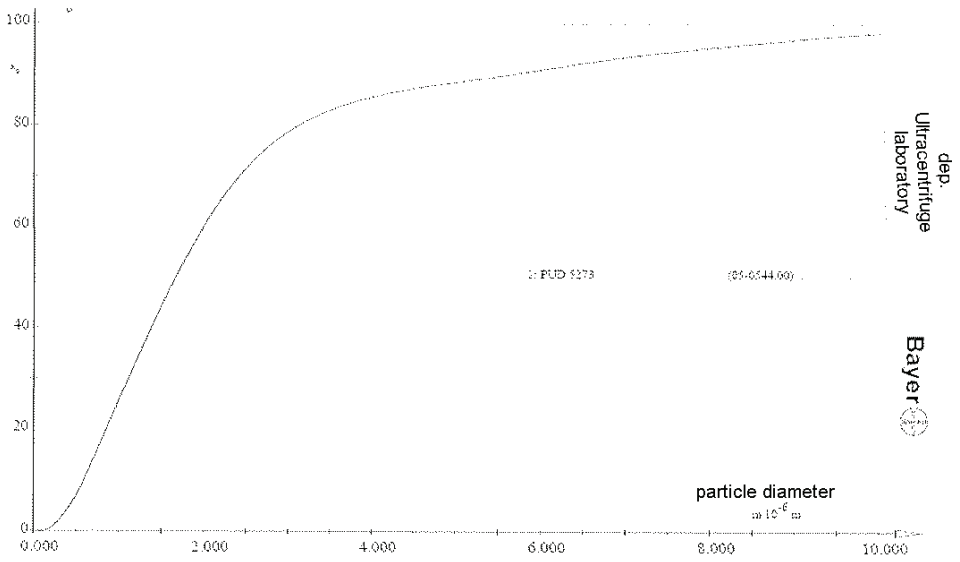
A Dispermat F 105 dissolver from VMA Getzmann was used to produce the suspension. A plastic disc was used as grinding tool. The temperature of the temperature-controlled vessel was controlled using a thermostat from Julabo HC.

45 g of vinyl-terminated silicone polymer VS 1000, 15 g of active ingredient (see table) and 20 ml of zircon oxide beads with a diameter of about 2.8 mm are weighed into a 250 ml temperature-controlled vessel. The temperature of the vessel is controlled at 25°C and the dissolver is introduced. The material to be ground is mixed at 8000/min for 20 minutes. The zircon oxide beads are then removed. A creamy white paste is obtained. The average particle diameter was determined.

	Active ingredient	**Concentration**	**Average particle size d_{50}**
Example 1	octenidine dihydrochloride	25% by weight	1.7 µm
Example 2	PHMB	25% by weight	9.2 µm



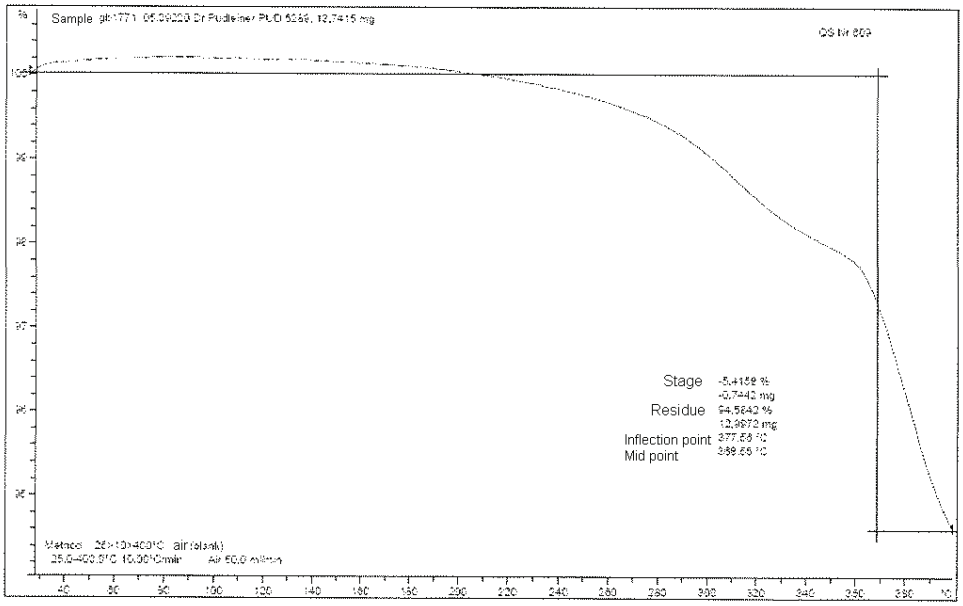
Ultracentrifuge particle size distribution of the PHMB suspension from Example 2



Ultracentrifuge particle size distribution of the octenidine dihydrochloride suspension from Example 1

Example 3

The thermal stability of the octenidine dihydrochloride suspension from Example 1 was determined by thermogravimetric analysis (TGA).



TGA curve of the suspension from Example 1

The suspension is thermally stable up to at least 200°C, so that the crosslinking reaction to be carried out at 170°C after mixing into the silicone rubber can take place without problems of stability of the active ingredient or of the suspending medium.

Examples 4-7

The solid silicone rubber Addisil 160 was put onto a roll mixer from Vogt (2 rolls; roll diameter 80 mm, roll width 280 mm; operating width 200 mm) with cooling at room temperature. The front rotating roll was operated at 16.5 min^{-1}, and the rear roll at 20 min^{-1}. The active ingredients were subsequently mixed in by adding the amounts, indicated in the table, of the active ingredient suspension from Example 1 or 2 into the roll gap, and continuing the mixing until the suspension was homogeneously incorporated. The active ingredient-containing silicone rubber was then removed as sheet about 2 mm thick from the roll.

	Silicone rubber Addisil 160 in g	**Octenidine dihydrochloride suspension based on Polymer VS 1000 Amount of suspension**	**Active ingredient concentration**
Example 4	96	4 g suspension from Example 1	1% by weight
Example 5	92	8 g suspension from Example 1	2% by weight

	Silicone rubber Addisil 160 in g	**PHMB suspension based on Polymer VS 1000 Amount of suspension**	**Active ingredient concentration**
Example 6	96	4 g suspension from Example 2	1% by weight
Example 7	92	8 g suspension from Example 2	2% by weight

The respective boards were then heated at 170°C for 2 hours for curing (crosslinking).

Example 8

Active ingredient distribution

It is possible by scanning electron micrographs coupled to EDX to visualize specifically, by chlorine detection, only the active ingredient particles in the silicone elastomer matrix. Figures 1 and 2 show scanning electron micrographs of the silicone elastomer specimen plates from Example 6 (1% by weight PHMB) and Example 7 (2% by weight PHMB) (PHMB active ingredient particles appear pale). The films show that the active ingredient is distributed homogeneously and as very fine particles about 1 to 5 µm in size in the silicone elastomer matrix.

Example 9

Continuity of the surface protection of the PHMB-containing silicone elastomer plates

The elution tests were carried out with the active ingredient-containing silicone elastomer boards from Examples 6 and 7, which were cut into pieces 1 cm^2 in size. The samples each weighed about 2.1 g and had a surface area of about 22 or 25 cm^2. 16 ml of demineralized water were used as elution medium. The elution medium was replaced by new water in each case after 1 h, 4 h, 8 h, 24 h, 48 h, 120 h and 360 hours (15 days), and the active ingredient content in the solutions was determined.

Hours	Specimen from Example 6 [µg/g*cm^2]	Specimen from Example 7 [µg/g*cm^2]
1.00	0.810	2.19
4.00	0.980	2.36
8.00	1.150	2.53
24.00	1.320	2.70
48.00	1.490	2.87
120.00	1.660	3.20
360.00	1.830	3.43

During the investigation there is diffusion of the active ingredient to the surface of the sample body, thus ensuring continuous protection of the surface against colonization by bacteria and yeasts.

Example 10

Continuity of the surface protection of the octenidine dihydrochloride-containing silicone elastomer plates

The elution tests were carried out with the boards from Examples 4 and 5 which were cut into pieces 1 cm^2 in size. The samples each weighed about 2.0 g and had a surface area of about 35 cm^2. 16 ml of demineralized water were used as elution medium. The elution medium was replaced in each case by new water after 1 h, 4 h, 8 h, 24 h, 48 h, 120 h and 360 hours (15 days), and the active ingredient content in the solutions was determined.

Hours	Specimen from Example 4 [µg/g*cm^2]	Specimen from Example 5 [µg/g*cm^2]
1.00	**1.72**	**0.01**
4.00	**2.33**	**0.02**
8.00	**2.61**	**0.03**
24.00	**3.59**	**0.04**
48.00	**4.04**	**0.05**
120.00	**4.05**	**0.06**
360.00	**4.27**	**0.07**

During the investigation there is diffusion of the active ingredient to the surface of the sample body, thus ensuring continuous protection of the surface against colonization by bacteria and yeasts.

The samples release small amounts of active ingredient over 15 days, the amount being far away from a pharmacologically effective dose.

Example 11

Microbiological assessment of the samples from Examples 4 to 5

Test plates with a diameter of about 5 mm were cut out of the active ingredient-containing silicone elastomer boards of Examples 4 and 5 and sterilized by gamma radiation. The sterile test plates were used to carry out the following microbiological tests.

1. Method

The antibacterial effect was investigated with the aid of the agar diffusion test.

1.1. Test plates

18 ml of NCCLS-compliant Mueller-Hinton agar (Merck KGaA Darmstadt/Lot ZC217935 430) were poured into 9 cm-diameter Petri dishes.

1.2. Bacterial suspension

A suspension with a McFarland density of 0.5 in 0.85% NaCl solution was prepared from an overnight culture of the test strain on Columbia blood agar. A “colony pool” of 3 to 4 colonies dabbed with an inoculating loop was used for the suspension.

1.3. Test mixture

A sterile cotton swab is dipped in the suspension. The excess liquid is squeezed out on the edge of the glass. The swab is used to inoculate the Mueller-Hinton agar plate uniformly in three directions at an angle of 60° in each case. The material samples are then placed on the test plate. The test plates were incubated at 37°C for 24 hours. The antibacterial effect of the samples was assessed on the basis of zones of inhibition.

2.2. Test strains

The test strains selected were representatively Gram-negative rods, an MRSA (Staphylococcus aureus MRSA 1150-93) and a Candida species (Candida albicans ATCC 14053).

3. Results

A zone of inhibition was detectable with the samples of Examples 4 and 5. The active ingredient in the silicone material thus prevents bacterial growth.

The effect on the yeast-like fungus Candida albicans is particularly noteworthy.

Figures 3 and 4 document the result of the tests. In these, Figure 3 shows the zones of inhibition for Candida albicans ATCC 14053 with the samples from Example 4 (5217) and 5 (5219), and Figure 4 shows the zones of inhibition for Staphylococcus aureus MRSA 1150-93 with the samples from Example 4 (5217) and 5 (5219).

Example 12

Microbiological assessment of the samples from Examples 6 to 7

Test plates with a diameter of about 5 mm were cut out of the active ingredient-containing silicone elastomer boards of Examples 6 and 7 and sterilized by gamma radiation. The sterile test plates were used to carry out the following microbiological tests.

1. Method

The antibacterial effect was investigated with the aid of the agar diffusion test.

1.1. Test plates

18 ml of NCCLS-compliant Mueller-Hinton agar (Merck KGaA Darmstadt/Lot ZC217935 430) were poured into 9 cm-diameter Petri dishes.

1.2. Bacterial suspension

A suspension with a McFarland density of 0.5 in 0.85% NaCl solution was prepared from an overnight culture of the test strain on Columbia blood agar. A “colony pool” of 3 to 4 colonies dabbed with an inoculating loop was used for the suspension.

1.3. Test mixture

A sterile cotton swab is dipped in the suspension. The excess liquid is squeezed out on the edge of the glass. The swab is used to inoculate the Mueller-Hinton agar plate

uniformly in three directions at an angle of 60° in each case. The material samples are then placed on the test plate. The test plates were incubated at 37°C for 24 hours. The antibacterial effect of the samples was assessed on the basis of zones of inhibition.

2.2. Test strains

The test strains selected were representatively ATCC strains of three Gram-negative rods, a Staphylococcus aureus, an MRSA strain and a Candida species.

3. Results

gram - rods	35218	Eschericia coli ATCC 35218
	35659	Proteus mirabilis ATCC 35659
	27853	Pseudomonas aeruginosa ATCC 27853
gram + cocci	29213	Staphylococcus aureus ATCC 29213
	0134 - 93	Staphylococcus aureus MRSA 0134 - 93
yeast-like fungus	14053	Candida albicans ATCC 14053

The antibacterial effect of the samples was detectable by means of the zones of inhibition. Figures 5 to 8 document the results. Figure 5 shows the zones of inhibition for Escherichia coli ATCC 35218 with the samples from Example 6 (5289) and 7 (5291). Figure 6 shows the zones of inhibition for Staphylococcus aureus MRSA 0134-93 with the samples from Example 6 (5289) and 7 (5291). Figure 7 shows the zones of inhibition for Candida albicans ATCC 14053 with the samples from Example 6 (5289) and 7 (5291). Figure 8 shows the zones of inhibition for Staphylococcus aureus ATCC 29213 with the samples from Example 6 (5289) and 7 (5291).

Example 13

The active ingredient suspension from Example 1 was mixed into the A/B 2 K platinum-catalysed addition-crosslinking silicone-rubber system supplied by Degania

on a calender kneader, and the octenidine dihydrochloride-containing silicone rubber was then further processed to Foley catheter shafts with 1% by weight octenidine dihydrochloride.

Example 14

Continuity of the surface protection of the octenidine dihydrochloride-containing silicone elastomer Foley catheter shafts.

The elution tests were carried out with the shafts from Example 13, which were cut into pieces 2 cm long. The samples each weighed about 2.0 g and had a surface area of about 33 cm^2. 16 ml of simulated urine of the following composition was used as elution medium

Urea	1.94%
NaCl	0.84%
$MgSO_4$, heptahydrate	0.11%
$CaCl_2$	0.06%

The elution medium was replaced in each case after 1 h, 4 h, 8 h, 24 h, 48 h, 120 h and 360 hours (15 days), and the active ingredient content in the solutions was determined.

	Foley catheter shaft from Example 13	
Lot	5050419	
Octenidine 2 × HCl conc.	1%	
Weight:	1.93	g
Surface	33.35	cm^2
1 h	0.44	mg/l
4 h	0.540	mg/l
8 h	0.710	mg/l
24 h	1.150	mg/l
48 h	1.460	mg/l
120 h	1.610	mg/l
360 h	2.050	mg/l

Diffusion of the active ingredient to the surface of the sample body takes place during the investigation and thus ensures continuous protection of the surface colonization with bacteria and yeasts.

The samples release small amounts of active ingredient over 15 days, the amount being far away from a pharmacologically effective dose.

Example 15

Biocompatibility tests as specified in DIN ISO 10993-5 (1999), EN 30993-5 (1994)

The catheter shafts from Example 13 were for this purpose extracted non-sterile at 37°C and 5% pCO_2 in extraction medium (DMEM including antibiotics without FCS) for 24 h. The surface-volume ratio was 1 cm^2/ml of extraction medium. After

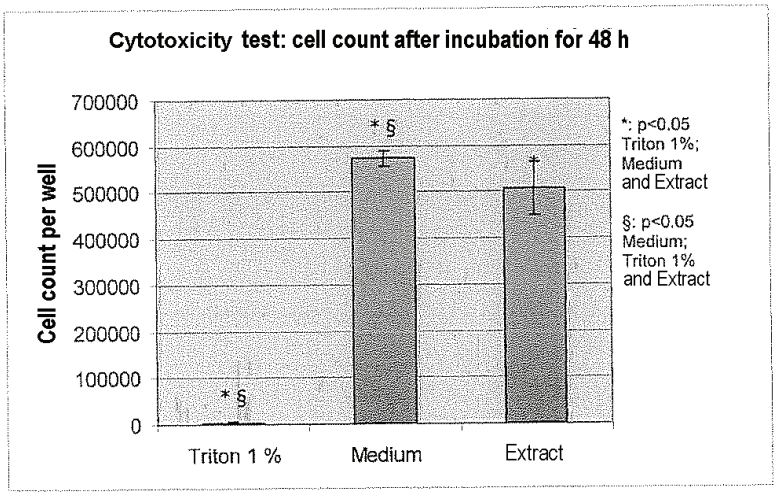
completion of the extraction, the extraction medium was sterilized by filtration and supplemented with sterile FCS (final concentration: 10% FCS in the extraction medium). The FCS-supplemented extraction medium was put sterile on precultured L 929 mouse fibroblast cells and incubated at 37°C, 5% pCO_2 for 48 h. The extract was subjected to quadruplicate parallel testing.

Triton X 100 was added to the L929 cells used as toxic positive control (final concentration 1%). Cell culture medium served as non-toxic negative control.

After the 48-hour incubation, the release of lactate dehydrogenase (LDH) in the cell culture supernatant was measured by a photometric method. The cells were then subjected to alkaline lysis and the protein content was measured by the Bradford method.

The cells were fixed and stained with methylene blue to determine the cell count. After acidic extraction of the methylene blue, the dye content was ascertained by photometry and the extinction was compared with a standard curve in order to determine the cell count on the basis of the dye concentration.

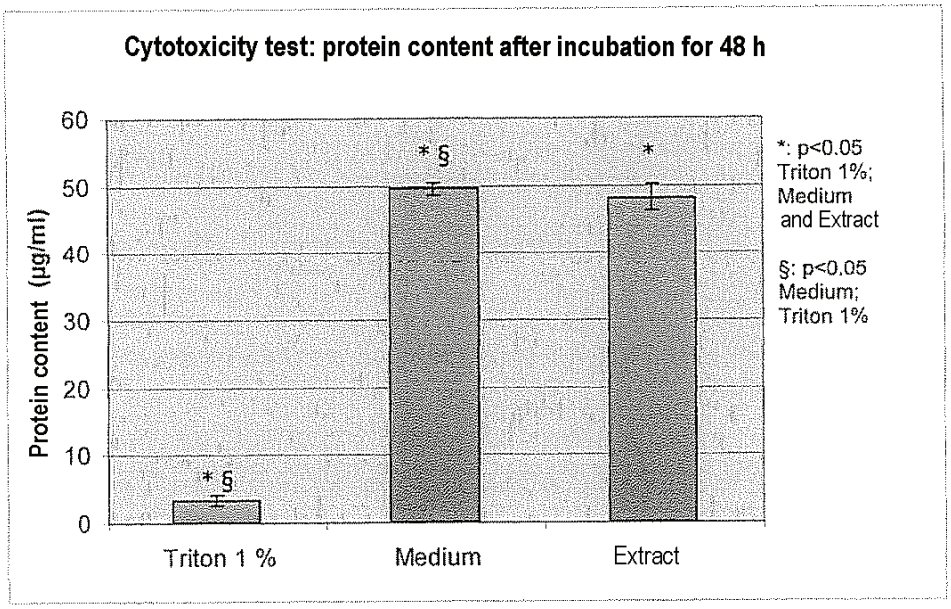
Cell count:



The value of the positive control was 0.5% of the negative control value and is thus in the valid range below 35% relative to the culture medium control.

Values of cell counts for extracts which were more than 19% below the value of the cell count for the negative control are regarded as cytotoxic. This is not the case in the present extract of the sample from Example 13. The material extract shows no cytotoxic reaction.

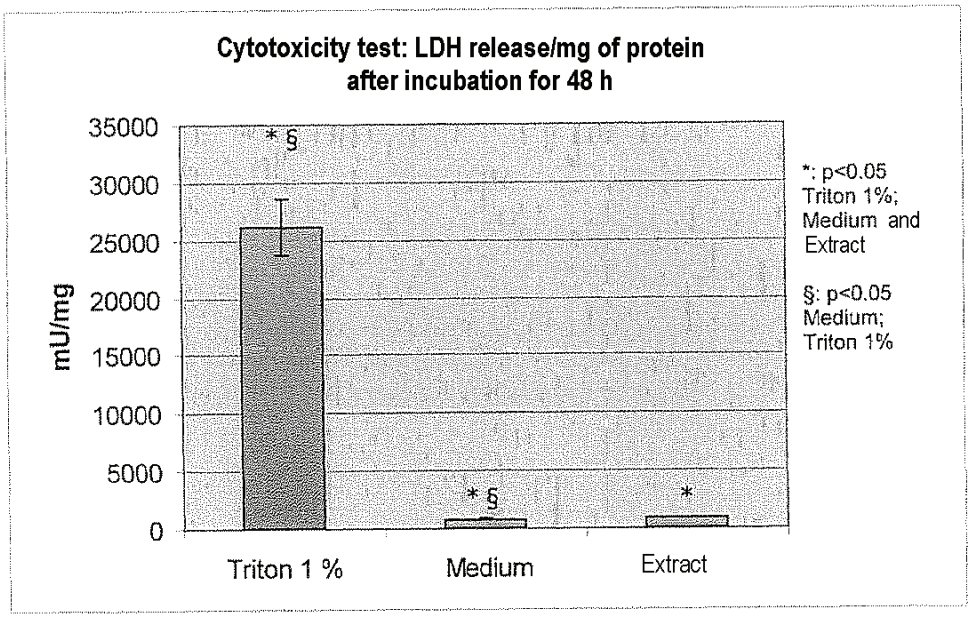
Protein content:



The value of the positive control is 6.8% of the negative control value and is thus in the valid range below 35% relative to the culture medium control.

Protein levels in extracts which are more than 19% less than the level of the protein content in the negative control are regarded as cytotoxic. This is not the case in the present extract of the sample from Example 13. The material extract shows no cytotoxic reaction.

LDH release:



In contrast to Triton X 100 in the cell culture medium, the specific LDH activity is increased more than 31-fold compared with the negative control (medium).

The sample from Example 13 has no cytotoxic effect.

Claims

1. Silicone elastomers which comprise at least one antiseptic in homogeneous distribution, where the antiseptic has an average particle size d_{50} of from 0.5 to 15 µm, preferably between 1 and 10 µm, and a particle size distribution of from 0.1 to 30 µm, preferably from 0.5 to 20 µm.

2. Silicone elastomers according to Claim 1, characterized in that the antiseptic is selected from the group consisting of bispyridinium alkanes, polymeric amidobiguanides, quaternary ammonium compounds, in particular benzalkonium chloride, and chlorhexidine, taurolidine and triclosan.

3. Catheter comprising silicone elastomers according to Claim 1 or 2.

4. Silicone-rubber formulation comprising

A) at least one polysiloxane of the formula (I)

$$\mathbf{R^1R^2_2SiO\text{-}(SiR^3R^4O\text{-})_xSiR^1R^2_2} \qquad \mathbf{(I)}$$

in which the radicals

R^1 and R^2 may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^3 and R^4 may in each case be identical or different, expressly including each repeating unit, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, and additionally -$OSiR^2R^3R$, in which R symbolizes the continuation of the siloxane chain in analogy to formula (I) in the branching so that the polymer molecule may have branching units of the formula $SiO_{4/2}$ and $R^3SiO_{3/2}$,

R^1 and R^3 are additionally independently of one another C_1-C_{12}-alkenyl, in which case the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and the molecule has at least two olefinically unsaturated multiple bonds,

x is an integer from 2 to 15 000 and is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C,

I) at least one polyhydrosiloxane of the formula (II)

$$\mathbf{R^{21}R^{22}{}_2SiO\text{-}(SiR^{23}R^{24}O\text{-})_xSiR^{21}R^{22}{}_2} \qquad \mathbf{(II)}$$

in which the substituents

R^{21} and R^{22} may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^{23} in each case expressly including each repeating unit independently of one another is hydrogen, C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, additionally -$OSiR^{23}R^{24}R$ in which R symbolizes the continuation of the siloxane chain in analogy to formula (II) in the branching so that the polymer molecule may have branching units of the formula $SiO_{4/2}$ and $R^{23}SiO_{3/2}$, where R^{23} in at least 4 of these silyldioxyl units is hydrogen so that a molecule has at least 4 crosslinking sites,

R^{24} in each case expressly including each repeating unit independently of one another is C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, additionally -$OSiR^{23}R^{24}R$ in which R symbolizes the

continuation of the siloxane chain in analogy to formula (II) in the branching so that the polymer molecule may have branching units of the formula $SiO_{4/2}$ and $R^{23}SiO_{3/2}$,

x is an integer from 4 to 10 000 and is varied so that the viscosity of the polymer extends from 0.0005 to 0.1 Pas at 25°C,

J) at least one catalyst comprising an element of the platinum group,

where a maximum of 3 parts by weight of metal compounds such as oxides and/or carbonates, and further salts and complex compounds, of Fe, Al, Zn, Ti, Zr, Ce or other lanthanoids are present based on 100 parts by weight of component A),

K) at least one suspension, where the suspending medium are polysiloxanes of the formula (I) and/or (II) and/or nonfunctional siloxanes G), and comprises at least one antiseptic, in particular those selected from the group consisting of chlorhexidine, octenidine, PHMB, quats, taurolidine and triclosan.

5. Silicone-rubber formulation according to Claim 4, in which

- the polysiloxane A) is a polysiloxane of the formula (I)

$$\mathbf{R^1R^2_2SiO\text{-}(SiR^3R^4O\text{-})_xSiR^1R^2_2} \qquad \mathbf{(I)}$$

in which the radicals

R^1 and R^2 may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^3 and R^4 may in each case be identical or different, expressly including each repeating unit, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl,

R^1 and R^3 are additionally independently of one another C_1-C_{12}-alkenyl, in which case the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and the molecule has at least two olefinically unsaturated multiple bonds,

x is an integer from 2 to 15 000 and is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C,

- a filler B) having a BET specific surface area of between 50 and 400 m^2/g is used,

- the polyhydrosiloxane I) corresponds to the formula (II)

$$\mathbf{R^{21}R^{22}_2SiO\text{-}(SiR^{23}R^{24}O\text{-})_xSiR^{21}R^{22}_2} \qquad \mathbf{(II)}$$

in which the substituents

R^{21} and R^{22} may in each case be identical or different, and are each C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl, and optionally substituted phenyl or naphthyl,

R^{23} in each case expressly including each repeating unit independently of one another is hydrogen, C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl, where R^{23} is hydrogen in at least 4 of these silyldioxyl units so that a molecule has at least 4 crosslinking sites,

R^{24} in each case expressly including each repeating unit independently of one another is C_1-C_{12}-alkyl, C_1-C_{12}-fluoroalkyl and optionally substituted phenyl or naphthyl,

x is an integer from 4 to 10 000 and is varied so that the viscosity of the polymer extends from 0.0005 to 0.1 Pas at 25°C,

- the catalyst from the platinum group J) is a catalyst which catalyses the hydrosilylation reaction and is selected from metals of the platinum group such as Pt, Rh, Ni, Ru, and compounds of metals of the platinum group, such as salts or complex compounds thereof,

- the suspending medium used for the suspension K) is at least one polysiloxane of the formula (I) according to A) in which the substituents R^1 to R^4 are each methyl and vinyl radicals, so that the polymer comprises from 0.0002 to 3% by weight of vinyl groups, and the molecule has at least two olefinically unsaturated multiple bonds, and x is varied so that the viscosity of the polymer extends from 0.1 to 1000 Pas at 25°C,

and the suspension K) comprises at least one antiseptic selected from the group consisting of chlorhexidine, octenidine, PHMB, quats, taurolidine and triclosan which comprises in each case an average particle size d_{50} of from 0.5 to 15 µm, preferably between 1 and 10 µm, and a particle size distribution between 0.1 and 30 µm, preferably 0.5 to 20 µm.

6. Process for preparing silicone elastomers according to Claim 1 or 2 comprising the provision of a silicone-rubber formulation according to Claim 5 or 6 and the polymerization of the said silicone-rubber formulation.