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(54) Title: ANTIMICROBIAL CATHETERS

(57) Abstract: The present invention relates to catheters comprising pigments obtainable by agitating a suspension comprising one or more inorganic pigments and silver acetate, in order to reduce undesirable side effects caused by microorganisms.

# Antimicrobial Catheters

The present invention relates to catheters comprising pigments obtainable by agitating a suspension comprising one or more inorganic pigments and silver acetate, in order to reduce undesirable side effects caused by microorganisms.

Microbial contamination is an essential concern in our daily life and has a great impact for products and formulations. Especially health care facilities, such as hospitals, nursing homes or outpatient facilities are faced with microbial contamination. Nosocomial infections, that means infections that originate or occur in a hospital or hospital-like setting, are a big problem in health care facilities, as described for example by R. Platt in, The new England Journal of Medicine, 1982, 637-642. These infections are responsible for about 20000 deaths alone in the U.S. per year. Nosocomial infections are commonly acquired through exposure of patient to hospital environment, hospital personnel and invasive devices, such as catheters. Generally catheters are tubes for insertion into canals, vessels, passageways, or body cavities to facilitate a variety of functions, such as injection or withdrawal of fluids, keeping passages open, application of an incision device or delivery of an electrical charge. They are widely used and therefore stand in the focus for attempts to prevent nosocomial infections.

Several attempts have been made to reduce the number of infections caused by catheters. One common approach is the antimicrobial treatment of devices, such as catheters, wherein the devices are coated or impregnated with some bactericidal agent that is released in a sustained and controlled manner to combat the bacteria present at the site.

One method is described by N. Gatter et al. in, Zent.bl. Bakteriol. 1998, 287, 157-169 which is based on the incubation of catheters with a silver

nitrate solution. Steven K. Schmitt et al. describes in J. Clin. Microbiol., 1996, 508-511 the impregnation of catheters with silver and sulfadiazine-chlorhexidine.

The above-mentioned methods have the disadvantage that either corrosive chemicals are used or the antiseptic ability of the impregnated catheters decreases rapidly.

Therefore, there is still a demand for catheters with antimicrobial activity that are suited to reduce the number or severeness of nosocomial infections. Furthermore, catheters should show an antimicrobial activity for a long period of time without reduction of the antiseptic ability.

Surprisingly, it has been found that catheters according to the present invention can fulfil the objectives cited above. Therefore, the present invention relates to catheters comprising pigments obtainable by agitating a suspension comprising one or more inorganic pigments and silver acetate, in order to reduce undesirable side effects caused by microorganisms. Undesirable side effects caused by microorganisms are preferably nosocomial infections.

Catheters according to the present invention comprising the above-mentioned antimicrobial pigments are advantageous with respect to their ability to prevent nosocomial infections, can easily be produced, show a long term antimicrobial activity and are not limited to some types of catheters. These positive effects are achieved by using antimicrobial inorganic pigments that are included in the catheters. The antimicrobial pigments can be distributed uniformly or not uniformly inside the catheter. An example for a non-uniform distribution is the deposition of antimicrobial pigments on top of the outside walls of the catheter or the incorporation into the outside surface area of the base material of the catheter. Preferably an uniform distribution of the antimicrobial component in the catheter is aimed.

Catheters comprising uniformly distributed antimicrobial pigments can easily be prepared with existing technologies for the preparation of catheters.

There is no restriction with respect to the type of the catheter according to the present invention, that means the catheter can be for example an infusion catheter, a cardiovascular catheter, a renal catheter, a catheter for hemodynamic monitoring or a neurological catheter. Examples for the above-mentioned catheters are acorn-tipped catheter, Amplatz coronary catheter, angiographic catheter, atherectomy catheter, balloon catheter, balloon-tip catheter, bicoudate catheter, catheter bicoudé, Braasch bulb catheter, Brockenbrough transseptal catheter, Broviac catheter, cardiac catheter, cardiac catheter-microphone, Castillo catheter, central venous catheter, closed end-hole catheter, conical catheter, catheter coudé, Cournand catheter, DeLee catheter, catheter à demeure, de Pezzer catheter, directional atherectomy catheter, double-current catheter, double-lumen catheter, Drew-Smythe catheter, elbowed catheter, electrode catheter, end-hole catheter, eustachian catheter, female catheter, filiform-tipped catheter, fluid-filled catheter, Fogarty catheter, Foley catheter, Garceau catheter, Gensini coronary catheter, Gouley's catheter, Gruentzig balloon catheter, Hickman catheter, indwelling catheter, Judkins coronary catheter, Judkins pigtail left ventriculography catheter, left coronary catheter, Malecot catheter, manometer-tipped catheter, multipurpose catheter, Nélaton's catheter, NIH catheter, olive-tip catheter, pacing catheter, Pezzer's catheter, Phillips' catheter, pigtail catheter, preformed catheter, prostatic catheter, right coronary catheter, Robinson catheter, self-retaining catheter, snare catheter, Sones coronary catheter, spiral-tip catheter, Swan-Ganz catheter, Tenckhoff catheter, thermodilution catheter, toposcopic catheter, tracheal catheter, transluminal endarterectomy catheter, transtracheal catheter, transtracheal oxygen catheter, two-way catheter, ureteral catheter, urethral catheter, vertebrated catheter, whistle-tip catheter, as well as van Andel Catheter, irudynamic catheters, rectal

pressure catheters, firlit-sugar intermittent catheter, non adhesive silicone condoms catheters, pediatric nephrostomic catheter, cystostomy catheter, Joseph Urodynamics catheter, Dewan suprapubic urodynamic catheter, loop catheter, Kaye nephrostomy tamponade balloon catheter, flushing catheter, Mars laparoscopic GIFT catheter, IUI (intrauterine insemination) catheter, Fanelli cholangiography catheter, Olsen endoscopic chlangiographic catheter, TPN (total parenteral nutrition) catheter, Peripherally inserted central catheter, hemodialysis catheter, peridural catheter, madduri urethogram catheter, renal access cobra catheter, schoborg nephrostomy catheter, ventricular catheter, peritoneal catheter, atrial catheter, lumbar catheter or a winged catheter.

Generally, catheters of the present invention are based on polymers. Preferably the polymer for catheters of the present invention is selected from the group comprising polyurethane, PET, polyethylene terephthalate, Vialon, silicones, PVC, polyamide, polyimide, polyacrylates, fluoropolymers, such as polytetrafluoroethylene, methacrylic acid esters, ethylene-vinyl acetate copolymer, polycarbonate, polybutylene, terephthalates, polyisoprene, polysiloxanes, propylene polymers, polyetherurethane, polyoxytetramethylene, polyvinylpyrollidone, polydimethylsiloxane, epoxy resins, polybutadiene, low density polyethylene, latex, polyethylene oxide, rubber, synthetic rubber and/or mixtures thereof.

Important constituents of the catheters according to the present invention are the antimicrobial pigments obtainable by agitating a suspension comprising one or more inorganic pigments and silver acetate. The inorganic pigments can have any known regular or irregular shape, for example the shape of platelets, spheres or needles, alone or in a mixture. Preferably the pigments are platelet-shaped or spherical.

Inorganic pigments in this sense comprise (according to DIN 55944) inorganic white pigments, inorganic coloured pigments, inorganic black

pigments such as for example Carbon Black, effect pigments and luminous pigments, but also magnesium carbonates, mica, $SiO_2$, $TiO_2$, aluminium oxide, glass, micaceous iron oxide, oxidised graphite, aluminium oxide-coated graphite, basic lead carbonate, BiOCl, bismuth subcarbonate, bismuth trioxide, barium sulphate, chromium oxide or MgO can be used in the present invention.

Preferably used are pigments selected from the group of effect pigments. Examples of effect pigments are those based on substrates which can additionally be coated with one or more layers of BiOCl and/or transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials. The substrate for the effect pigments is preferably platelet-shaped and is preferably selected from the group of natural or synthetic mica, $SiO_2$, $TiO_2$, BiOCl, aluminium oxide, glass, micaceous iron oxide, graphite, oxidised graphite, aluminium oxide-coated graphite, basic lead carbonate, barium sulphate, chromium oxide, BN, MgO, magnesium fluoride, $Si_3N_4$ and/or metals. Examples for metals are aluminium, titanium, silver, copper, bronze, alloys or gold, preferably aluminium or titanium. The metals can be passivated by inorganic treatment. Effect pigments with natural or synthetic mica, $SiO_2$, $TiO_2$, iron oxide, BiOCl, aluminium oxide and/or glass are especially preferred as substrates.

For the one or more layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials all known materials can be selected. The one or more layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials can

have a high refractive index ($n > 1.8$) or a low refractive index ($n \leq 1.8$). The metal oxides or metal oxide hydrates can be selected from any known metal oxide or metal oxide hydrate, such as for example $SiO_2$, $Al_2O_3$, $TiO_2$, ZnO, $ZrO_2$, $Ce_2O_3$, FeO, $Fe_2O_3$, $Cr_2O_3$, $SnO_2$, silicon oxide hydrate, aluminium oxide hydrate, titanium oxide hydrate and/or mixtures thereof, such as for example ilmenite or pseudobrookite. The metal can be selected from any known metal, such as for example chromium, molybdenum, aluminium, silver, platinum, nickel, copper, gold and/or alloys, preferably from aluminium and/or silver. An example for a metal fluoride is magnesium fluoride. As metal nitrides or metal oxynitrides for example the nitrides or oxynitrides of titanium, zirconium and/or tantalum can be used. Preferably the one or more layer consist of metal oxides, metal oxide hydrates, metals and/or metal fluorides, in particular metal oxides and metal oxide hydrates. Furthermore, the effect pigments can have multilayer compositions comprising materials with a high and a low refractive index. formulations according to the present invention comprising inorganic pigments based on multilayer effect pigments are characterised through an intensively lustrous appearance and an angle-dependent interference colour. Preferably the one or more layers of BiOCl and/or transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials are arranged as alternating layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials or BiOCl with a refractive index $n > 1.8$ and transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials with a refractive index $n \leq 1.8$, in particular as stack of two layers comprising one layer of a material with a high refractive index and one

layer of a material with a low refractive index, whereas one or more of these stacks can be applied to the substrate. The sequence of the layers of the material with a high refractive and the material with the low refractive index can be adapted to the material of the substrate thus incorporating the substrate into the multilayer composition.

Preferred examples for materials with a refractive index $n > 1.8$ are titanium oxide, iron oxide, iron titanate, iron, chromium, silver and/or nickel, preferably titanium oxide, iron oxide, iron titanate. Preferred examples for materials with a refractive index $n \leq 1.8$ are silicon oxide, silicon oxide hydrate, aluminium oxide, aluminium oxide hydrate, aluminium and/or magnesium fluoride. In another embodiment the transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials additionally may contain organic and/or inorganic colorants or elements as dopant. The absorption colour of the organic or inorganic colorant is combined with interference effects of the one or more layers of metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials thus producing pigments with special colour effects. Examples of organic colorants are azopigments, anthrachinonepigments, indigo- or thioindigo derivatives, diketo-pyrrolo-pyrrol pigments, perylen pigments or phthalocyanin pigments. Carbon black, Prussian blue, Turnbulls blue, Rinnmanns green, Thenards Blue and coloured metal oxide are only few examples of inorganic colorants, which can be introduced into the one or more layers. Yttrium or antimony can be used as dopant. Combinations of the materials mentioned above, for example mica platelets coated with fine particles of barium sulphate and a thin film of titanium dioxide are within the scope of the present invention.

Pigments based on all these systems combine the absorption and interference colour of the pigments with an antimicrobial activity thus

enhancing the applicability of the pigments in order to reduce undesirable side-effects caused by microorganisms, such as for example nosocomial infections. Additionally, the different types of catheters can individually be coloured, thus making the catheters distinguishable.

The outer layer of the effect pigments which can be used according to the present invention preferably comprises a transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxide, metal suboxide, metal oxide hydrate and/or mixture of these materials, most preferably a metal oxide or metal suboxide with a high refractive index. This outer layer can be additionally applied to the one or more layers or can be one of them. Preferably the outer layer is composed of $TiO_2$, titanium suboxides, $Fe_2O_3$, $SnO_2$, ZnO, $ZrO_2$, $Ce_2O_3$, CoO, $Co_3O_4$, $V_2O_5$, $Cr_2O_3$ and/or mixtures thereof, such as for example ilmenite or pseudobrookite, $TiO_2$ is in particular preferred.

Examples and embodiments of the above-mentioned materials and pigment compositions are for example described in Research Disclosure RD 471001 and RD 472005, whose specifications are herein incorporated by reference.

The mean diameter of platelet-shaped substrates and hence the resulting pigments can vary between 1 and 200 µm, preferably 10 and 150 $\mu$m. Depending on the desired application, the size of the pigments can accordingly optimised. The overall thickness of the pigments is in the range between 0.05 and 6 $\mu$m, in particular between 0.1 and 4.5 $\mu$m.

The thickness of the one or more layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials can vary between 3 and 300 nm, preferably between 20 and 200 nm. The

thickness of the metal layers is preferably in the range of 4 to 50 nm. By adjusting the layer thickness the intensity of the absorption colour or the interference colours and angles can be tuned.

Depending on the material of the substrate and the thereon-coated layers, inorganic pigments with variable colour, hiding strength, lustre and angle-dependent colour impressions (optically variable pigments) are obtainable.

The preparation of above described layers can result from wet chemical treatment, from sol gel processes or by chemical or physical vapour deposition (CVD/PVD). After deposition, the resulting pigments can be dried or calcined.

Examples of effect pigments described here comprise pigments like Iriodin®, Candurin®, Timiron®, Colorstream® and Xirallic® pigments from Merck KGaA, Mearlin® and Dynacolor® pigments from Engelhard Corp., Variochrom® and Paliochrom® pigments from BASF or Spectraflair® pigments from Flex Products.

In another preferred embodiment of the present invention the inorganic pigments comprise spherical particles of metal oxides, for example $SiO_2$, $TiO_2$, aluminium oxide, glass, MgO, iron oxide but also BiOCl, magnesium carbonates, graphite, oxidised graphite, aluminium oxide-coated graphite, basic lead carbonate, barium sulphate, chromium oxide, BN, magnesium fluoride, $Si_3N_4$ and/or metals. Preferably the spherical particles comprise $SiO_2$, $TiO_2$, $Al_2O_3$, ZnO, $Fe_2O_3$, FeO and/or mixtures thereof. Furthermore, the spherical particles can be coated with one or more layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials. The materials for the one or more layers of transparent, semitransparent or opaque, selectively or nonselectively

absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials can be selected from the ones described for the effect pigments.

Spherical capsules of materials described above encapsulating organic and/or inorganic compounds or materials are also suited in the sense of the definition of inorganic pigments applied here. The encapsulated compound or material can for example be selected for example from antibiotics. Capsules, which are to be used particularly preferably, have walls that can be obtained by a process for example described in the applications WO 00/09652, WO 00/72806 and WO 00/71084. Preference is given here to capsules whose walls are made of silica gel.

In one embodiment of the present invention the spherical particles are coated with one or more layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials. Layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates as an outer layer, are preferred. Particles described above can be obtained commercially, e.g. as Ronaspheres® from Merck KGaA, Darmstadt.

The mean diameter of the spherical particles or capsules can vary between 5 nm and 100 µm, preferably between 8 nm and 50 µm and most preferably from 8 nm to 5 µm. Spherical metal oxides, in particular metal oxides with UV-filtering activity, preferably have a mean diameter of 5 to 100 nm, especially of 8 to 50 nm and most preferably of 8 to 30 nm. A large surface area characterizes these particles, which therefore can advantageously be used as inorganic pigments for catheters according to the present invention.

The possibility to vary the colour of the antimicrobial pigments helps to distinguish different types of catheters by simply using different colours for different types of catheters without diminishing the antimicrobial activity of the obtained catheters.

In a further embodiment, the inorganic pigments can additionally be further coated with a protective coating layer. The protective coating layer is believed to influence the rate at which the antimicrobial component diffuses from a dispersed particle into the application matrix. The small residual porosity of the silica or alumina coating, for example, also allows the antimicrobial component to diffuse through at a slow controlled rate thus extending the duration of the antimicrobial activity. Further, the ability to adjust the dispersibility of the particulate compositions of this invention both increases their use efficiency and improves the quality of the product. The antimicrobial particles may further comprise a tertiary coating layer of a hydrous metal oxide, which is much legs agglomerated and disperse readily in polymers. For example, a tertiary coating of hydrous alumina or magnesia will raise the isoelectric point of the composition. The control of the isoelectric point between about 5.5 and about 9.5 is beneficial in facilitating the dispersion and/or flocculation at the particulate compositions during plant processing and in their end use applications. This both increases the use efficiency of the antimicrobial pigments and improves the quality in applications. Enhanced dispersibility also can be impacted by micronizing the product with small levels, e.g. 0.1 to 1 % of organic dispersion aids. Dispersion aids may be incorporated either with the antimicrobial pigments or in the process for incorporating them in catheters.

The protective coating is selected from silica, silicates, borosilicates, aluminosilicates, alumina, aluminum phosphate, or mixtures thereof. The protective coating functions as a barrier between the antimicrobial outer layer and an application matrix in which it may be incorporated, minimizing

interaction with the application matrix. This protective coating also is believed to influence the rate at which the antimicrobial component diffuses from a dispersed pigment into the catheter.

The protective protective coating layer corresponds to 0.5 to 20 % by weight based on the antimicrobial pigments, and preferably, e.g., 1 to 5 % by weight of silica or e.g., 1 to 6 % by weight of alumina in the coated antimicrobial pigment. It will be appreciated by those skilled in the art that if fine particles of a substrate are employed in carrying out the invention, the practitioner should assure total surface coverage of the first coated substrate. The protective layer of silica or alumina can be quite dense although it must be sufficiently porous to permit diffusion of the antimicrobial metal ions through the coating at a slow rate, while functioning as a barrier which limits interaction between the antimicrobial layer and the application matrix in which it is distributed. Silica is a preferred coating material because of the relative ease with which dense, uniform coatings can be obtained. Silica-coated particles my have a low isoelectric point and may tend to be difficult to disperse in organic materials. The isoelectric point represents the pH at which a particle surface carries zero electric charge. Control of the isoelectric point between 5.5 and 9.5 is beneficial in facilitating the dispersion and/or flocculation of the particulate compositions during plant processing and in their end use applications. Therefore, for particles coated with silica or related materials with a low isoelectric point, a tertiary coating of hydrous alumina or magnesia or other metal oxide may be added to raise the isoelectric point. For example, hydrous oxides of Al, Mg, Zr and the rare earths, may bring the isoelectric point into the range of 5.5 to 9.5. Hydrous alumina, typically as a mixture of boehmite (AlOOH) and amorphous alumina ($Al_2O_3H_2O$), is a preferred tertiary coating material. Isoelectric points in a preferred range of 5.5 to 8.8 can readily be obtained with alumina coatings. For higher isoelectric points, magnesia is preferred.

In an alternative embodiment of the invention, alumina may be selected as the protective coating and a further coating may not be needed to adjust the isoelectric point. When alumina is used as the protective coating, the isoelectric point of the resulting pigment typically will be in the preferred range.

In a preferred embodiment, the inorganic pigment is BiOCl, bismuth subcarbonate, bismuth trioxide or barium sulphate. Therefore, catheters according to the present invention preferably comprise antimicrobial BiOCl, bismuth subcarbonate, bismuth trioxide or barium sulphate, obtainable by agitating a suspension comprising BiOCl, bismuth subcarbonate, bismuth trioxide or barium sulphate and silver acetate. Catheters comprising antimicrobial BiOCl, bismuth subcarbonate, bismuth trioxide or barium sulphate are especially preferred because BiOCl, bismuth subcarbonate, bismuth trioxide or barium sulphate show high radiopacity resulting in clear visibility and a sharp contrast image under X-ray or fluoroscope. This helps to pinpoint the location of the catheter or to position it. Especially preferred is BiOCl. Suitable BiOCl can be prepared by hydrolysis of bismuth salts in an acidic aqueous system in the presence of excess chloride ions and is commercially available, for example as Biron® Powders from Merck KGaA, Darmstadt.

The pigments, especially BiOCl, included in catheters according to the present invention can be obtained in a simple way. A preferred process for the production of the pigments includes the agitation of a suspension comprising one or more inorganic pigments and silver acetate as antimicrobial component. The process is based on a process described by A. Goetz, E. C. Y. Inn in "*Reversible Photolysis of Ag Sorbed on Collodial Metal Oxides*" in *Rev. Modern Phys.* **1948**, *20*, 131-142.
The preparation can be performed in water, ethanol, methanol, 1-propanol, 2-propanol and/or mixtures thereof, preferably water is used. The

preparation temperature can vary between 10 and 60°C, preferably between 20 and 45°C and is most preferably held at 37°C.

The suspension is agitated from 4 up to 24 hours, preferably from 7 to 20 hours, and most preferably from 17 to 18 hours.

Similar pigments with antimicrobial activity can be obtained by substituting silver acetate by other antimicrobial compounds, such as for example silver salts, for example silver halogenide, silver nitrate, silver sulfate, silver oxide, silver benzoate, silver carbonate, silver citrate, silver lactate, silver salicylate, but also copper oxides, copper sulfide, copper nitrate, copper carbonate, copper sulfate, copper halogenides, copper carboxylates, zinc oxide, zinc sulfide, zinc silicate, zinc acetate, zinc chloride, zinc nitrate, zinc sulfate, zinc gluconate, zinc citrate, zinc phosphate, zinc propionate, zinc salicylate, zinc lactate, zinc oxalate, zinc iodate, zinc iodide or combinations thereof. Silver acetate, silver oxide, copper sulfate, zinc acetate are the most preferably used.

The amount of the antimicrobial compound is in the range of 0.001 to 10% by weight, preferably 0.005 to 5% by weight, preferably 0.01 to 2% by weight, and most preferably 0.5% by weight, based on the inorganic pigment.

The resulting pigments with antimicrobial activity can be separated using any method known for a person skilled in the art. Preferably the product is filtrated or filtrated with suction and washed with water. Additionally the silver treated pigments can be further washed with organic solvents, such as acetone, to remove residual water. The pigments can be dried. Preferably the antimicrobial pigments are dried in an oven, most preferably at a temperature below 50°C, or by using a vacuum pump or a continuous flash evaporator, most preferably by evaporation of the solvents in vacuum.

In a further embodiment the inorganic pigments are further coated with a protective coating layer. Usable materials for the protective coating layer are mentioned above. Any method known for a person skilled in the art can be used to coat the pigments with the protective coating layer, preferably the coating is performed wet-chemically. In the case of a silica coating, active silica is added to the agitated aqueous suspension heated to a temperature between 60 and 90°C, while maintaining the pH of the suspension in the range of 6 to 11. The procedure is described in detail in U.S. Pat. No. 2,885,366, the teachings of which are incorporated herein by reference. Active silica, a low molecular weight form of silica, such as silicic acid or polysilicic acid, may be added to the suspension, or formed in situ as by the continuous reaction of an acid with an alkali silicate. Potassium silicate is generally preferred since the potassium ion has little tendency to coagulate active silica. The bulk commodity is also more stable, which is advantageous from the standpoint of shipping and storing. The silica content of the coated composition is between 0.5 and 20 % by weight and most commonly it is between 1 and 5 % by weight.

During the silica deposition it is desirable to maintain substantially uniform conditions in the reaction zone to minimize precipitation of free silica gel. This is preferably accomplished by maintaining good agitation and introducing the reactants in a manner that does not allow local over-concentration. The pH is allowed to fall gradually to about 6 as the process is completed and the slurry is then cured to permit completion of the deposition of silica onto the surface of the antimicrobial pigments. The curing step consists of holding the slurry at temperatures between 60 and 90°C, preferably between 75 and 90°C, for from about one-half to two hours, preferably about one hour, while maintaining the pH of the agitated slurry between 6 and 7.5.

Alternatively, the pigments may be coated with alumina. This is accomplished by the addition, to the agitated aqueous suspension of the

antimicrobial particles heated to between 60 and 90°C, of an alkali aluminate solution or other soluble aluminum salt, e.g., aluminate nitrate while maintaining the pH in the range 6 to 11 by the concurrent addition of acid or base, as required. Sodium aluminate is preferred, because it is commercially available as a solution, such as Vining's Solution. It is desirable to increase the density of the amorphous alumina phase in the coating by the addition of polyvalent anions selected from the group consisting of sulfate, phosphate and citrate. As in the case of the silica coating a small residual porosity is necessary to allow the antimicrobial species to diffuse through the protective coating. The alumina content of the coated composition is between 0.5 and 20 % by weight and preferably between 1 and 6 % by weight. The concentration of polyvalent anion in the suspension is about 0.5 % by weight based on the alumina used to coat the particles.

The product is then recovered as a dry powder, consisting of antimicrobial pigments coated with silica, alumina or silica/alumina, by filtration or centrifugation combined with aqueous washing to remove soluble salts. A vacuum rotary-type filter is particularly suitable since washing can be carried out without removing the product from the filter. The thus obtained pigments can be introduced in catheters. To accomplish this, any method known to a person skilled in the art can be used.

Preferably, a process for the preparation of catheters according to the present invention comprises the steps

a) agitating a suspension comprising one or more inorganic pigments and silver acetate and
b) mixing the pigment a) with further base materials suitable for catheters.

The amount of the so treated inorganic pigment and therefore of the antimicrobial pigment in the catheters is in the range between 0.001 and

60% by weight, preferably between 0.01 and 50% by weight and most preferably between 5 and 40% by weight, based on the catheters.

Mixing the antimicrobial pigment with further base materials suitable for catheters can be done by any method known to the person skilled in the art. In the case of polymers, the antimicrobial pigments may be incorporated into the molten polymer by known extrusion methods. The molten polymer may comprise further additives for processing or the additives may be introduced together with the antimicrobial pigment. Suitable additives are known to the person skilled in the art and can be selected in accordance to the desired application.

There are several alternative methods that can be used for incorporating the antimicrobial agent into the polymeric material. For example, the resin pellets can be compounded with the antimicrobial pigment using a twin screw compounder; the starting ingredients can be pelletized together using a twin screw machine; and the resin pellets can be compounded with the antimicrobial pigment using an extruder/compounder machine. Compounding the antimicrobial pigment and extruding in a single process step is preferred, because the resulting material will have a higher durometer. These methods of compounding the antimicrobial agent into the resin result in the antimicrobial pigment being uniformly distributed and incorporated into the polymeric matrix. When using the twin screw compounder, the resin pellets, antimicrobial pigment and other ingredients, such as fillers and pigments, can also be fed into the compounder at a suitable rate. In the compounder, the ingredients are melted, blended and then extruded into strands. The strands may be pelletized and dried prior to further processing. The homogeneous pellets of polymer and antimicrobial pigment, prepared as described above, may be remelted and molded or extruded into the desired shape of the catheter.

Catheters according to the present invention may additionally comprise antiseptics and/or disinfectants. Examples for antiseptics and/or disinfectants are hexachlorophene, cationic bisguanides, for example chlorhexidine, cyclohexidine, iodine and iodophores, for example povidoneiodine, para-chloro-meta-xylenol, triclosan, furan medical preparations, for example nitrofurantoin or nitrofurazone, methenamine, aldehydes, such as for example glutaraldehyde or formaldehyde and/or alcohols.

Furthermore, catheters according to the present invention may additionally comprise antibiotics. Antibiotics in this sense mean all known antibiotics, for example selected from the group of Beta-lactam, Vancomycin, Macrolides, Tetracyclines, Quinolones, Fluoroquinolones, Nitrated compounds (as for instance Nitroxoline, Tilboquinol or Nitrofurantoin), Aminoglycosides, Phenicols, Lincosamids, Synergistins, Fosfomycin, Fusidic acid, oxazolidinones, Rifamycins, Polymixynes, Gramicidins, Tyrocydine, Glycopeptides, Sulfonamides or Trimethoprims. Formulation comprising combinations of antimicrobial pigments and antibiotics are advantageous with respect to the resistance of several microorganisms against certain antibiotics. A combination of antibiotics with antimicrobial pigments according to the present invention helps to overcome the resistance by simply decreasing the number of microorganisms that have not been affected by the antibiotics.

Catheters according to the present invention may additionally comprise anti-inflammatory agents. Anti-inflammatory agents include steroidal and non-steroidal anti- inflammatory agents. Examples of non-steroidal anti-inflammatory drugs include aminoarylcarboxylic acid derivatives such as enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefanamic acid, niflumic acid, talniflumate, terofenamate and tolfenamic acid; arylacetic acid derivatives such as acemetacin, alclofenac, amfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac,

fenclofenac, fenclorac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac, isoxepac, lonazolac, metiazinic acid, oxametacine, proglumetacin, sulindac, tiaramide, tolmetin and zomepirac; arylbutyric acid derivatives such as bumadizon, butibufen, fenbufen and xenbucin; arylcarboxylic acids such as clidanac, ketorolac and tinoridine; arylpropionic acid derivatives such as alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, miroprofen, naproxen, oxaprozin, piketoprofen, pirprofen, pranoprofen, protizinic acid, suprofen and tiaprofenic acid; pyrazoles such as difenamizole and epirizole; pyrazolones such as apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenybutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone and thiazolinobutazone; salicylic acid and its derivatives such as acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamine o-acetic acid, salicylsulfuric acid, salsalate and sulfasalazine; thiazinecarboxamides such as droxicam, isoxicam, piroxicam and tenoxicam; others such as $\epsilon$-acetamidocaproic acid, s-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole and tenidap; and pharmaceutically acceptable salts thereof.

Examples of steroidal anti-inflammatory agents (glucocorticoids) include 21-acetoxyprefienolone, aalclometasone, algestone, amicinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone,

diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumehtasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol priopionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methyolprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortal, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and pharmaceutically acceptable salts thereof.

Catheters according to the present invention may additionally comprise analgesic agents. Analgesic agents include narcotic, non-narcotic analgesics and local anesthetic agents. Narcotic analgesic agents include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethlythiambutene, ethylmorphine, etonitazene, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, lofentanil, meperidine, meptazinol, metazocine, methadone hydrochloride, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenazocine, pheoperidine, piminodine, piritramide, proheptazine, promedol, properidine,

propiram, propoxyphene, rumifentanil, sufentanil, tilidine, and pharmaceutically acceptable salts thereof.

Non-narcotic analgesics include aceclofenac, acetaminophen, acetaminosalol, acetanilide, acetylsalicylsalicylic acid, alclofenac, alminoprofen, aloxiprin, aluminum bis(acetylsalicylate), aminochlorthenoxazin, 2-amino-4-picoline, aminopropylon, aminopyrine, ammonium salicylate, amtolmetin guacil, antipyrine, antipyrine salicylate, antrafenine, apazone, aspirin, benorylate, benoxaprofen, benzpiperylon, benzydamine, bermoprofen, brofenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bucetin, bufexamac, bumadizon, butacetin, calcium acetylsalicylate, carbamazepine, carbiphene, carsalam, chloralantipyrine, chlorthenoxazin(e), choline salicylate, cinchophen, ciramadol, clometacin, cropropamide, crotethamide, dexoxadrol, difenamizole, diflunisal, dihydroxyaluminum acetylsalicylate, dipyrocetyl, dipyrone, emorfazone, enfenamic acid, epirizole, etersalate, ethenzamide, ethoxazene, etodolac, felbinac, fenoprofen, floctafenine, flufenamic acid, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, ibufenac, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isonixin, ketoprofen, ketorolac, p-lactophenetide, lefetamine, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, methotrimeprazine, metofoline, miroprofen, morazone, morpholine salicylate, naproxen, nefopam, nifenazone, 5' nitro-2' propoxyacetanilide, parsalmide, perisoxal, phenacetin, phenazopyridine hydrochloride, phenocoll, phenopyrazone, phenyl acetylsalicylate, phenyl salicylate, phenyramidol, pipebuzone, piperylone, prodilidine, propacetamol, propyphenazone, proxazole, quinine salicylate, ramifenazone, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sulfamipyrine, suprofen, talniflumate, tenoxicam, terofenamate, tetradrine, tinoridine, tolfenamic acid, tolpronine, tramadol, viminol, xenbucin, zomepirac, and pharmaceutically acceptable salts thereof.

Local anesthetic agents include amucaine, amolanone, amylocaine hydrochloride, benoxinate, benzocaine, betoxycaine, biphenamine, bupivacaine, butacaine, butaben, butanilicaine, butethamine, butoxycaine, carticaine, chloroprocaine hydrochloride, cocaethylene, cocaine, cyclomethycaine, dibucaine hydrochloride, dimethisoquin, dimethocaine, diperadon hydrochloride, dyclonine, ecgonidine, ecgonine, ethyl chloride, beta-eucaine, euprocin, fenalcomine, fomocaine, hexylcaine hydrochloride, hydroxytetracaine, isobutyl p-aminobenzoate, leucinocaine mesylate, levoxadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octacaine, orthocaine, oxethazaine, parethoxycaine, phenacaine hydrochloride, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine hydrochloride, pseudococaine, pyrrocaine, ropavacaine, salicyl alcohol, tetracaine hydrochloride, tolycaine, trimecaine, zolamine, and pharmaceutically acceptable salts thereof.

Catheters according to the present invention may additionally comprise antispasmodic agents. Antispasmodic agents include alibendol, ambucetamide, aminopromazine, apoatropine, bevonium methyl sulfate, bietamiverine, butaverine, butropium bromide, n-butylscopolammonium bromide, caroverine, cimetropium bromide, cinnamedrine, clebopride, coniine hydrobromide, coniine hydrochloride, cyclonium iodide, difemerine, diisopromine, dioxaphetyl butyrate, diponium bromide, drofenine, emepronium bromide, ethaverine, feclemine, fenalamide, fenoverine, fenpiprane, fenpiverinium bromide, fentonium bromide, flavoxate, flopropione, gluconic acid, guaiactamine, hydramitrazine, hymecromone, leiopyrrole, mebeverine, moxaverine, nafiverine, octamylamine, octaverine, oxybutynin chloride, pentapiperide, phenamacide hydrochloride, phloroglucinol, pinaverium bromide, piperilate, pipoxolan hydrochloride, pramiverin, prifinium bromide, properidine, propivane, propyromazine, prozapine, racefemine, rociverine, spasmolytol, stilonium iodide,

sultroponium, tiemonium iodide, tiquizium bromide, tiropramide, trepibutone, tricromyl, trifolium, trimebutine, n,n-1trimethyl-3,3-diphenyl-propylamine, tropenzile, trospium chloride, xenytropium bromide, and pharmaceutically acceptable salts thereof

One major advantage of catheters according to the present invention is, that they can be used for the inhibition of the growth and progeny of microorganisms. Microorganisms in the latter sense are for example bacteria (Eubacteria and Archae), yeasts and/or fungi. Examples of microorganisms described herein are microorganisms selected for example from the family of Enterobacteriaceae like for instance Enterobacter and more especially Enterobacter cloaceae, Klebsiella and more especially Klebsiella pneumoniae , Escherichia Coli, Serratia and more especially Serratia marcescens, Proteus and more especially Proteus mirabilis; but also Pseudomonas and especially Pseudomonas aeruginosa, Acinetobacter and especially Acinetobacter baumannii, Clostridum and especially Clostridium perfringens, Propionibacterium species, Bacteroides and especially Bacteroides fragilis group, staphylococcus and especially Staphylococcus aureus, coagulase-negative staphylococci, Staphylococcus epidermidis, Enterococcus species, viridans streptococci, Streptococcus and especially Streptococcus pneumoniae, group A Streptococci, group B Streptococci, corynebacterium species, Listeria monocytogenes, Lactobacillaceae and especially Lactobacillus species, Stenotrophomonas and especially Stenotrophomonas maltophilia, Haemophilus influenzae, Candida albicans, Crvptococcus neoformans, Torulopsis and especially Torulopsis glabrata, Aspergillus and especially Aspergillus niger, Mycobacterium and especially Mycobacterium avium complex, Mycobacterium tuberculosis or allied microorganisms.

Therefore, a method for reducing the level of micro-organisms in a zone of biological fluid in proximity to a surface of a catheter, the method comprising incorporating pigments obtainable by agitating a suspension

comprising one or more inorganic pigments and silver acetate into the catheter or depositing them on top of the catheter, and bringing the catheter into contact with said biological fluid, is also inside the scope of the present invention.

The antimicrobial activity of the pigments in catheters according to the present invention can be shown by tests known for a person skilled in the art, for example similar to those described by N. Gatter et al. in Zent.bl. Bakteriol. 1998, 287, 157-169 or by Steven K. Schmitt et al. in J. Clin. Microbiol., 1996, 508-511.

The entire disclosure of all applications, patents and publications, cited above are hereby incorporated by reference.

The present invention is more illustratively demonstrated but not limited by means of the following examples.

**Examples:**

**A) Synthesis of the antimicrobial pigment**

10 g Biron® pigments (BiOCl, Merck KGaA, Darmstadt) are homogenized with 0.5 g silver oxide. 42 ml of deionized water is added to the mixture and stirred for 16 hours at 37-40°C. The suspension is filtered off and washed several times with deionized water, then with acetone. The product is dried at 40°C under reduced pressure.

**B) Production of polymer pellets containing silver treated-BiOCl.**

A mixture of 25 wt % ([Biron/ (0,5% $Ag_2O$)] powder, 70 wt % High Density Poly Ethylene and 5 wt % hydrocarbon wax Licowax PE 520 is gently

mixed and introduced into a single screw extruder via a hopper and is then extruded through a cylindrical die. The material is finally cooled and cut into pellets.

Anti-microbial investigations

A standard procedure (given by the European Pharmacopeia 5th Edition) to measure the anti-microbial activity of substances is used. A suspension of test organisms ($10^5$ to $10^6$ germs/ml) is inoculated into a recipient containing already the substance to be tested. Samples of the inoculated suspension are taken and the number of germs is measured thanks to the Agar plates method. Decrease in germ number is performed at t=0, t=24h after the inoculation, t=48h after the inoculation, t=7days after the inoculation.

Sterile water containing 50% w/w of treated and untreated pellets is each investigated.

Results are given in the following tables in log of the reduction i.e. (log Inoculum – log germ count at t)

Abbreviations:

P= Polyethylene pellets

AgION: commercial sample of silver zeolithe

***Table 1: P.aeruginosa* counts in log of the reduction**

| | P + 25% pure BiOCl | P + 25% BiOCl/ **0,1%Ag2O** | P +25% BiOCl/ **0,5%Ag2O** | P + 25% BiOCl/ **1,2%Ag2O** | Commercial cuttings of antimicrobial catheter (Bardex) | P+15%BiOCl + 10%AgION |
|---|---|---|---|---|---|---|
| Inoculum | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ |
| 0 | -0,4 | 0 | 0,2 | 0,7 | 0 | -0,1 |
| 24 h | 1,0 | 1,9 | >4,0 | >4,0 | 0,9 | >4,0 |
| 48 h | 2,5 | 3,7 | >4,0 | >4,0 | 3,3 | >4,0 |
| 7 d | >4,0 | >4,0 | >4,0 | >4,0 | >4,0 | >4,0 |

***Table 2: E. coli* counts in log of the reduction**

| | P + 25% pure BiOCl | P + 25% BiOCl/ **0,1%Ag2O** | P +25% BiOCl/ **0,5%Ag2O** | P + 25% BiOCl/ **1,2%Ag2O** | Commercial cuttings of antimicrobial catheter (Bardex) | P+15%BiOCl + 10%AgION |
|---|---|---|---|---|---|---|
| Inoculum | $1,0.10^5$ | $1,0.10^5$ | $1,0.10^5$ | $1,0.10^5$ | $1,0.10^5$ | $1,0.10^5$ |
| 0 | -0,4 | 0,2 | 0,5 | 0,7 | -0,4 | 0,2 |
| 24 h | 1,3 | 2,7 | >4,0 | >4,0 | 0,1 | >4,0 |
| 48 h | 2,8 | 4,0 | >4,0 | >4,0 | 1,5 | >4,0 |
| 7 d | >4,0 | >4,0 | >4,0 | >4,0 | 3,1 | >4,0 |

***Table 3: S. aureus* counts in log of the reduction**

| | P + 25% pure BiOCl | P + 25% BiOCl/ **0,1%Ag2O** | P +25% BiOCl/ **0,5%Ag2O** | P + 25% BiOCl/ **1,2%Ag2O** | Commercial cuttings of antimicrobial catheter (Bardex) | P+15%BiOCl + 10%AgION |
|---|---|---|---|---|---|---|
| Inoculum | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ |
| 0 | -0,3 | -0,3 | 0 | -0,3 | -0,1 | 0,4 |
| 24 h | 0,2 | >4,0 | >4,0 | >4,0 | >4,0 | 3,1 |
| 48 h | 1,5 | >4,0 | >4,0 | >4,0 | >4,0 | 4,0 |
| 7 d | >4,0 | >4,0 | >4,0 | >4,0 | >4,0 | >4,0 |

***Table 4: C. albicans* counts in log of the reduction**

| | P + 25% pure BiOCl | P + 25% BiOCl/ **0,1%Ag2O** | P +25% BiOCl/ **0,5%Ag2O** | P + 25% BiOCl/ **1,2%Ag2O** | Commercial cuttings of antimicrobial catheter (Bardex) | P+15%BiOCl + 10%AgION |
|---|---|---|---|---|---|---|
| Inoculum | $1,5.10^5$ | $1,5.10^5$ | $1,5.10^5$ | $1,5.10^5$ | $1,5.10^5$ | $1,5.10^5$ |
| 0 | -0,3 | -0,2 | 0,9 | -0,2 | -0,40 | -0,2 |
| 24 h | -0,2 | 1,4 | >4,2 | 1,6 | -0,5 | 2,6 |
| 48 h | -0,3 | 1,5 | >4,2 | 2,7 | -0,5 | 2,8 |
| 7 d | -0,2 | 1,6 | 4,5 | >4,2 | >4,0 | >4,2 |

***Table 5: A. niger* counts in log of the reduction**

| | P + 25% pure BiOCl | P + 25% BiOCl/ **0,1%Ag2O** | P +25% BiOCl/ **0,5%Ag2O** | P + 25% BiOCl/ **1,2%Ag2O** | Commercial cuttings of antimicrobial catheter (Bardex) | P+15%BiOCl + 10%AgION |
|---|---|---|---|---|---|---|
| Inoculum | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ | $1,1.10^5$ |
| 0 | 0,1 | -0,2 | 0,1 | 0,1 | -0,3 | 0,1 |
| 24 h | 0,1 | -0,2 | 2,1 | 2,1 | -0,4 | 2,0 |
| 48 h | -0,1 | 0 | >4,0 | >4,0 | -0,6 | 2,8 |
| 7 d | 0,1 | 0,7 | >4,0 | >4,0 | -0,7 | 4,0 |

**C) Manufacturing of a Urine collection system:**

A single-layer matrix polymer structure is formed from a mixture containing 80 wt % of Elvax® 460, an ethylene vinyl acetate copolymer having a 18 wt % vinyl acetate content available from DuPont, and 20 wt % of BiOCl according to example A as a radio- opacifying agent, The BiOCl and EVA copolymer are precompounded at 177°C, for example, in a Haake twin screw extruder. The resulting mixture is then compounded at 102°C using a Haake twin screw extruder at a reduced shear rate (<30% of full screw power). About 6-8 inches of the length of extruded rod (instead of 6-8 feet of extruded length, which is more typical) is guided through a chilled water bath, followed by air-drying. The compounded resin is then extruded into 6 Fr. tubes using a Davis Standard 1" single screw extruder at 108°C. Shear rate is controlled by keeping the screw rate under 16 rpm. The take-off rate is about 18 feet/min. As above, the extruded tube is subjected to a brief water cooling step, followed by air cooling.

## Claims

1. Catheters comprising pigments obtainable by agitating a suspension comprising one or more inorganic pigments and silver acetate.

2. Catheters according to claim 1, characterized in that they are used to reduce undesirable side-effects caused by microorganisms.

3. Catheters according to claim 2, characterized in that the undesirable side effects caused by microorganisms are nosocomial infections.

4. Catheters according to one or more of claims 1 to 3, characterized in that the catheter is an infusion catheter, a cardiovascular catheter, a renal catheter, a catheter for hemodynamic monitoring or a neurological catheter.

5. Catheters according to one or more of claims 1 to 4, characterized in that they are based on polymers.

6. Catheters according to claim 5, characterized in that the polymer is selected from the group comprising polyurethane, PET, polyethylene terephthalate, Vialon, silicones, PVC, polyamide, polyimide, polyacrylates, fluoropolymers, methacrylic acid esters, ethylene-vinyl acetate copolymer, polycarbonate, polybutylene, terephthalates, polyisoprene, polysiloxanes, propylene polymers, polyetherurethane, polyoxytetramethylene, polyvinylpyrollidone, polydimethylsiloxane, epoxy resins, polybutadiene, low density polyethylene, latex, polyethylene oxide, rubber, synthetic rubber and/or mixtures thereof.

7. Catheters according to one or more of claims 1 to 6, characterized in that the inorganic pigment is platelet-shaped, spherical or needle-shaped.

8. Catheters according to one or more of claims 1 to 7, characterized in that the inorganic pigments are inorganic white pigments, inorganic coloured pigments, inorganic black pigments, effect pigments, luminous pigments, magnesium carbonates, mica, $SiO_2$, $TiO_2$, aluminium oxide, glass, micaceous iron oxide, oxidised graphite, aluminium oxide-coated graphite, basic lead carbonate, BiOCl, bismuth subcarbonate, bismuth trioxide, barium sulphate, chromium oxide or MgO.

9. Catheters according to one or more of claims 1 to 8, characterized in that the effect pigments are based on substrates.

10. Catheters according to claim 9, characterized in that the substrates are selected from the group of natural or synthetic mica, $SiO_2$, $TiO_2$, BiOCl, aluminium oxide, glass, micaceous iron oxide, graphite, oxidised graphite, aluminium oxide coated graphite, basic lead carbonate, barium sulphate, chromium oxide, BN, MgO, magnesium fluoride, $Si_3N_4$, and/or metals.

11. Catheters according to claim 9 or 10, characterized in that the substrates additionally are coated with one or more layers of BiOCl and/or transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials.

12. Catheters according to claim 11, characterized in that the one or more layers of BiOCl and/or transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides,

metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials are arranged as alternating layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials or BiOCl with a refractive index n > 1.8 and transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials with a refractive index n $\leq$ 1.8.

13. Catheters according to claims 11 or 12, characterized in that the outer layer of the inorganic pigment comprises a transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxide, metal suboxide, metal oxide hydrate and/or mixture of these materials.

14. Catheters according to one or more of claims 11 to 13, characterized in that the transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials additionally contain organic and/or inorganic colorants or elements as dopant.

15. Catheters according to one or more of claims 1 to 14, characterized in that the inorganic pigment comprises spherical particles or spherical capsules of metal oxides, BiOCl, magnesium carbonates, graphite, oxidised graphite, aluminium oxide-coated graphite, basic lead carbonate, barium sulphate, BN, magnesium fluoride, $Si_3N_4$ and/or metals.

16. Catheters according to claim 15, characterized in that the spherical particles or capsules are coated with one or more layers of transparent, semitransparent or opaque, selectively or nonselectively absorbing or nonabsorbing metal oxides, metal suboxides, metal oxide hydrates, metals, metal nitrides, metal oxynitrides, metal fluorides and/or mixtures of these materials.

17. Catheters according to one or more of claims 1 to 16, characterized in that the inorganic pigments are additionally coated with a protective coating layer.

18. Catheters according to claim 17, characterized in that the protective coating is selected from silica, silicates, borosilicates, aluminosilicates, alumina, aluminum phosphate, or mixtures thereof.

19. Catheters according to one or more of claims 1 to 18, characterized in that the inorganic pigment is BiOCl, bismuth subcarbonate, bismuth trioxide or barium sulphate.

20. Catheters according to one or more of claims 1 to 19, characterized in that the silver acetate is substituted by silver halogenide, silver oxide, silver nitrate, silver sulfate, silver carbonate, silver citrate, copper oxides, copper sulfide, copper nitrate, copper carbonate, copper sulfate, copper halogenides, copper carboxylates, zinc oxide, zinc sulfide, zinc silicate, zinc acetate, zinc chloride, zinc nitrate, zinc sulfate, zinc gluconate, zinc citrate, zinc phosphate, zinc propionate, zinc salicylate, zinc lactate, zinc oxalate, zinc iodate, zinc iodide or combinations thereof.

21. Catheters according to one or more of claims 1 to 20, characterized in that he amount of the inorganic pigment in the catheters is in the range between 0.001 and 60% by weight, based on the catheters.

22. Catheters according to one or more of claims 1 to 21, characterized in that they additionally comprise antiseptics and/or disinfectants.

23. Catheters according to one or more of claims 1 to 22, characterized in that they additionally comprise antibiotics.

24. Catheters according to claim 23, characterized in that the antibiotics are selected from the group of Beta-lactam, Vancomycin, Macrolides, Tetracyclines, Quinolones, Fluoroquinolones, Nitrated compounds, Aminoglycosides, Phenicols, Lincosamids, Synergistins, Fosfomycin, Fusidic acid, oxazolidinones, Rifamycins, Polymixynes, Gramicidins, Tyrocydine, Glycopeptides, Sulfonamides or Trimethoprims.

25. Catheters according to one or more of claims 1 to 24, characterized in that they additionally comprise anti-inflammatory agents.

26. Catheters according to one or more of claims 1 to 25, characterized in that they additionally comprise analgesic agents.

27. Catheters according to one or more of claims 1 to 26, characterized in that they additionally comprise antispasmodic agents.

28. Process for the preparation of catheters according to one or more of claims 1 to 27 comprising the steps

a) agitating a suspension comprising one or more inorganic pigments and silver acetate and

b) mixing the pigment a) with further base materials suitable for catheters.

29. A method for reducing the level of micro-organisms in a zone of biological fluid in proximity to a surface of a catheter, the method comprising incorporating pigments obtainable by agitating a suspension comprising one or more inorganic pigments and silver acetate into the catheter or depositing them on top of the catheter, and bringing the catheter into contact with said biological fluid.

30. Method according to claim 29, characterized in that the micro-organisms are selected from the group of Eubacteria and Archae bacteria, yeasts and/or fungi.