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(71) Applicant(s)
The Trustees of Columbia University in the City of New York

(72) Inventor(s)
Sampath, Lester, A.;Modak, Shanta, M.

(74) Agent / Attorney
Davies Collison Cave, GPO Box 4387, Melbourne, VIC, 3001

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- (71) Applicant (for all designated States except US): **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK** [US/US]; 116th Street and Broadway, New York, NY 10027 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **MODAK, Shanta, M.** [US/US]; 184 Howland Avenue, River Edge, NJ 07661 (US). **SAMPATH, Lester, A.** [US/US]; 7 Lawrence Street, Nyack, NY 10960 (US).
- (74) Agents: **TANG, Henry** et al.; Baker Botts LLP, 30 Rockefeller Plaza, New York, NY 10112-0228 (US).
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(54) Title: **ANTIMICROBIAL MEDICAL DEVICES**

(57) **Abstract:** The present disclosure invention relates to medical devices treated with a solution comprising one or more solvents and a combination of chlorhexidine free base and a water-soluble chlorhexidine salt in a weight/weight ratio of between about 1:1 to about 1:5, preferably about 1:1.

ANTIMICROBIAL MEDICAL DEVICES

SPECIFICATION

1.0 INTRODUCTION

The present invention relates to medical devices treated with a solution
5 comprising a combination of chlorhexidine free base and a water-soluble
chlorhexidine salt, in a ratio that facilitates chlorhexidine uptake by the devices and
hence improves antimicrobial effectiveness.

2.0 BACKGROUND OF THE INVENTION

Whenever a medical device comes in contact with a patient, a risk of
10 infection is created. Thus, a contaminated examination glove, tongue depressor, or
stethoscope could transmit infection. The risk of infection dramatically increases for
invasive medical devices, such as intravenous catheters, arterial grafts, intrathecal or
intracerebral shunts and prosthetic devices, which not only are, themselves, in
intimate contact with body tissues and fluids, but also create a portal of entry for
15 pathogens.

Catheter related infections, especially blood stream infections, are
associated with increased morbidity (10 to 20 percent), prolonged hospitalization (by a
period having a mean of seven days), and increased medical costs (approximately
\$6,000 per hospitalization). According to a survey of intensive care units from 1986
20 through 1990 by the National Nosocomial Infection Surveillance System, the rate of
catheter-related blood stream infections ranged from 2.1 to 30.2 per 1,000 catheter-
days. Infections associated with central venous catheters have been reported to result
from the transcutaneous migration of the pathogens from the insertion site with the
eventual colonization of the catheter tip. In addition, intraluminal colonization has
25 been suggested to result from contaminated hubs and infusates that contribute to
catheter related blood stream infections. The longer the duration of catheterization,
the greater the susceptibility to either luminal or outer surface colonization of
catheters. Even for short term use of catheters, infections have been reported due to
contamination of the insertion sites.

A number of methods for reducing the risk of infection have been developed which incorporate anti-infective agents into medical devices. Such devices desirably provide effective levels of anti-infective agent during the period that the device is being used. Sustained release may be problematic to achieve, in that a
5 mechanism for dispensing anti-infective agent over a prolonged period of time may be required, and the incorporation of sufficient amounts of anti-infective agent may adversely affect the surface characteristics of the device. The difficulties encountered in providing effective antimicrobial protection increase with the development of drug-resistant pathogens.

10 One potential solution to these problems is the use of a synergistic combination of anti-infective agents that requires relatively low concentrations of individual anti-infective agents which may have differing patterns of bioavailability. For example, WO 97/25085 relates to medical devices comprising synergistic combinations of chlorhexidine and triclosan. United States Patent Nos. 5,616,338 and
15 5,019,096 relate to infection resistant medical devices comprising synergistic combinations of a silver salt, a biguanide (such as chlorhexidine) and a polymeric component that forms a matrix to provide a sustained release of the silver salt and biguanide.

United States Patent Nos. 5,165,952 and 5,451,424 relate to medical
20 articles with chlorhexidine both coated on and bulk distributed throughout the medical articles. When chlorhexidine is bulk distributed it adversely affects certain characteristics of the device such as tensile strength, and the high temperatures needed for extension of plastics such as polyurethane may damage the chlorhexidine.

United States Patent No. 5,089,205 relates to incorporation of
25 chlorhexidine free base or one of its salts in a medical device such as a glove by both a distribution or dipping process.

Chlorhexidine is a broad spectrum antimicrobial agent and has been used as an antiseptic for several decades with minimal risk of developing resistant microbes. When relatively soluble chlorhexidine salts, such as chlorhexidine acetate,
30 were used to impregnate catheters, the release was undesirably rapid. The duration of the antimicrobial efficacy of medical devices impregnated with chlorhexidine salts,

such as chlorhexidine acetate, is short lived. Chlorhexidine free base is not soluble in water or alcohol and cannot be impregnated in sufficient amounts because of low solubility in a solvent system.

In contrast to the present invention, none of the above-cited references
5 teach medical articles treated with a solution comprising a combination of
chlorhexidine free base and a water-soluble chlorhexidine salt, at particular ratios,
which provide improved antimicrobial effectiveness through an increased uptake of
chlorhexidine into the medical device, increased retention of chlorhexidine in the
medical device and prolonged release of chlorhexidine from the medical device, while
10 utilizing relatively low levels of chlorhexidine.

3.0 SUMMARY OF THE INVENTION

The present invention relates to medical devices treated with a solution
comprising one or more solvents and a combination of chlorhexidine free base and a
water-soluble chlorhexidine salt, in a weight/weight ratio of between about 1:1 to
15 about 1:5 (inclusive), preferably about 1:1 of chlorhexidine free base to chlorhexidine
salt. The invention further relates to methods of preparing medical devices by
exposing them, in whole or in part, to a solution comprising one or more solvents and
the above-recited combinations of chlorhexidine free base and chlorhexidine salt.

This invention is based, at least in part, on the discovery that devices
20 treated with combinations of chlorhexidine free base and a water-soluble
chlorhexidine salt exhibit improved antimicrobial effectiveness due to increased
uptake of chlorhexidine into the medical device, increased retention of chlorhexidine
in the medical device, and prolonged release of chlorhexidine while utilizing
relatively low levels of chlorhexidine, and, in certain non-limiting embodiments, in
25 the absence of agents other than chlorhexidine. In particular, while it had been
previously found that triclosan can be particularly useful when used in conjunction
with chlorhexidine free base, it has been further discovered that medical articles
having suitable antimicrobial properties may be prepared, according to the present
invention, without the use of triclosan. Therefore, in particular embodiments, medical
30 articles according to the present invention offer the advantage of preventing or

inhibiting infection while avoiding undesirable adverse reactions to antimicrobial agents other than chlorhexidine by allergic individuals.

4.0 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for medical articles treated with a
5 solution comprising one or more solvents and a combination of chlorhexidine free base ("CHX") and a water-soluble chlorhexidine salt, and further provides for methods of preparing medical devices by exposing the device, in whole or in part, to said solution.

While not being bound or limited by any particular theory, it is
10 believed that the combination of CHX and water-soluble chlorhexidine salt forms a soluble complex. This would explain the increased uptake of chlorhexidine into the medical device, increased retention of chlorhexidine in the medical device, and increased sustained release of chlorhexidine from the medical device while utilizing relatively low levels of chlorhexidine in the absence of agents other than
15 chlorhexidine.

The following are definitions of terms used herein unless otherwise indicated:

Water soluble chlorhexidine salts have a solubility of at least about 2.0 grams per 100 ml in water at 20°C. Examples of water soluble chlorhexidine salts
20 include chlorhexidine diacetate (also referred to herein as chlorhexidine acetate, or "CHA") and chlorhexidine digluconate (or "CHG") with CHA being preferred.

The terms "medical article" and "medical device" are used interchangeably herein. Medical articles that may be treated according to the invention are either fabricated from and/or coated or treated with biomedical polymer
25 (and hence may be referred to as "polymeric medical articles") and include, but are not limited to, catheters including urinary catheters and vascular catheters (*e.g.*, peripheral and central vascular catheters), wound drainage tubes, arterial grafts, soft tissue patches (such as polytetrafluoroethylene (PTFE) soft tissue patches, gloves, condoms, shunts, stents, tracheal catheters, wound dressings, sutures, guide wires and
30 prosthetic devices (*e.g.*, heart valves and LVADs). Medical articles that may be

treated according to the invention include soft tissue patches made of expanded PTFE ("e-PTFE"), which is commercially available from W.L. Gore under the trade name Gore-Tex. Polymeric medical articles that may be treated according to the invention also include biodegradable polymers (such as polylactic acid (PLA), polyglycolic acid (PGA) and polycaprolactone (PCL)) with PCL being preferred. Vascular catheters which may be prepared according to the present invention include, but are not limited to, single and multiple lumen central venous catheters, peripherally inserted central venous catheters, emergency infusion catheters, percutaneous sheath introducer systems and thermodilution catheters, including the hubs and ports of such vascular catheters. The present invention may be further applied to medical articles that have been prepared according to United States Patent Nos. 5,616,338 and 5,019,096 by Fox, Jr. et al. and United States Patent No. 5,772,640 by Modak et al.

The term "hydrophilic polymeric medical article" is a medical article fabricated from a hydrophilic polymer. As used herein, "hydrophilic polymer" refers to polymers that have a water absorption greater than 0.6 percent by weight (and, in preferred embodiments, less than 2 percent by weight; as measured by a 24 hour immersion in distilled water, as described in ASTM Designation D570-81) including, but not limited to biomedical polyurethanes (e.g., ether-based polyurethanes and ester-based polyurethanes, as set forth in Baker, 1987, in *Controlled Release of Biologically Active Agents*, John Wiley and Sons, pp. 175-177 and Lelah and Cooper, 1986, *Polyurethanes in Medicine*, CRC Press, Inc., Fla. pp. 57-67; polyurethanes comprising substantially aliphatic backbones such as Tecoflex™ 93A; polyurethanes comprising substantially aromatic backbones such as Tecothane™; and Pellethane™), polylactic acid, polyglycolic acid, natural rubber latex, and gauze or water-absorbent fabric, including cotton gauze and silk suture material.

The term "hydrophobic polymeric medical article" is a medical article fabricated from a hydrophobic polymer. As used herein, "hydrophobic polymer" refers to a polymer that has a water absorption of less than 0.6% (w/w) and includes, but is not limited to, silicone polymers such as biomedical silicones (e.g., Silastic Type A) or elastomers (e.g., as set forth in Baker, 1987, in *Controlled Release of Biologically Active Agents*, John Wiley and Sons, pp. 156-162), Dacron, PTFE (also

“Teflon”), expanded PTFE, polyvinyl chloride (PVC), cellulose acetate, polycarbonate, and copolymers such as silicone-polyurethane copolymers (*e.g.*, PTUE 203 and PTUE 205 polyurethane-silicone interpenetrating polymer).

The terms “treat”, “treated”, “treating”, etc., as used herein, refer to
5 coating, impregnating, or coating and impregnating a medical article with anti-infective agent. Medical articles are “treated” by exposing them, for an effective period of time, to a treatment solution, where an “effective period of time” is that period of time sufficient to introduce anti-infective qualities of the anti-infective agent to the articles. Medical articles may be dipped, soaked, or otherwise have a surface
10 coated. The term “dipped” suggests briefer exposure to the treatment solution relative to “soaking,” and preferably is for a period of time less than fifteen minutes.

Percentages recited herein refer to weight/volume (w/v), except as indicated otherwise (*e.g.*, volume/volume or “v/v”).

The term “CFU” means colony forming unit.

15 The term “about” indicates a variation within 20 percent.

The present invention provides for medical articles treated with a solution comprising one or more solvents and a combination of CHX and a water-soluble chlorhexidine salt, in a weight/weight ratio of between about 1:1 and 1:5, preferably about 1:1. Such medical articles include hydrophilic polymeric medical
20 articles as well as hydrophobic polymeric medical articles fabricated from and/or coated or treated with such a biomedical polymer. In addition, the present invention may be applied to medical articles that have been prepared according to United States Patent Nos. 5,616,338 and 5,019,096 by Fox, Jr. et al. and United States Patent No. 5,772,640 by Modak et al. Such one or more solvents may be selected from the group
25 consisting of water, reagent alcohol, ammonium hydroxide, methyl alcohol, tetrahydrofuran (“THF”), dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, and mixtures thereof.

In a specific non-limiting embodiment, the treatment solution comprises CHX-CHA in a weight/weight ratio between about 1:1 and about 1:5,
30 preferably about 1:1 of CHX to CHA.

The present invention further provides, in a non-limiting embodiment, for methods of preparing medical devices by treating the device, in whole or in part, with a solution comprising one or more solvents and a complex formed by synergistic combinations of chlorhexidine free base and chlorhexidine acetate.

5 In non-limiting embodiments, medical articles may be treated with a solution comprising the steps of (i) placing the medical article in a solution comprising (a) a solvent selected from the group consisting of water, reagent alcohol, ammonium hydroxide, methyl alcohol, THF, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, and mixtures thereof and (b) a mixture of CHX and a water-
10 soluble chlorhexidine salt, preferably CHA, preferably in a weight/weight ratio of between about 1:1 and about 1:5; (ii) soaking the medical article in the solution for an effective period of time to allow the medical article to swell and to incorporate the anti-infective agents; (iii) removing the medical article from the solution; and (iv) drying the medical article.

15 Medical articles prepared according to the invention may be treated on an external surface, internal surface, or both. For example, and not by way of limitation, where the medical article is a catheter having a lumen, the internal (*i.e.*, luminal) surface and/or external surface of the catheter may be treated together or separately according to the invention. An open-ended catheter may be placed in a
20 treatment solution such that the internal and external surfaces are exposed to the treatment solution. Alternatively, the ends of the catheter may be sealed before being placed in the treatment solution so that only the external surface is exposed to the treatment solution. Alternatively, only the internal surface may be exposed to the treatment solution if the solution is pushed, pulled or allowed to pass through and/or
25 fill the lumen without immersing the catheter in the treatment solution.

In specific non-limiting embodiments, a catheter having a lumen may be treated with a solution comprising the steps of (i) exposing the lumen of the catheter to a solution comprising (a) a solvent selected from the group consisting of water, alcohol, ammonium hydroxide, methyl alcohol, THF, dimethylsulfoxide,
30 dimethylformamide, N-methyl-2-pyrrolidone, and mixtures thereof and (b) a mixture of CHX and a water-soluble chlorhexidine salt, preferably CHA, preferably in a molar

ratio of between about 1:1 and about 1:5; (ii) filling the lumen of the catheter with the solution by pushing, pulling, or allowing passage of the solution into the lumen for an effective period of time to allow the material surrounding the lumen of the catheter to swell and to incorporate the chlorhexidine; (iii) removing the solution from the lumen
5 of the catheter; and (iv) drying the catheter.

In the foregoing methods, the duration of exposure of the medical article or portion thereof to the treatment solution may preferably, but not by limitation, be ten seconds to one hour. The duration of exposure of the lumen of a catheter may preferably, but not by limitation, be ten seconds to two minutes. Longer
10 periods of exposure may be used provided that undesirable deterioration of the medical article does not occur.

The treatment solutions may optionally further comprise (i) an organic acid, at a concentration of between about 0.1 and about 5 percent, preferably between about 0.1 and about 2 percent; (ii) an anti-inflammatory agent, at a concentration of
15 between about 0.1 and about 5 percent, preferably between about 0.1 and about 1 percent; (iii) a hydrogel at a concentration of between about 0.5 to about 10 percent, preferably between about 1 and about 5 percent; and/or a polymer at a concentration of between about 0.1 and about 6 percent, preferably between about 0.1 and about 4 percent.

20 5.0 WORKING EXAMPLES

The following methods were used in performing experiments discussed in the following examples, unless indicated otherwise:

Method of Treatment of a Medical Article with Solution. The medical article was treated by exposing the entire medical article, or a portion thereof, to a
25 solution containing CHA alone, CHX alone or the CHX-CHA combination in various amounts in a solvent system. The medical article, or a portion thereof, was exposed by soaking the article in the solution for 100 seconds before removing the article from the solution. For articles, such as catheters, having an internal lumen, the solution was pushed into the lumen and allowed to remain for 100 seconds before removal.

Method of Determining Drug Uptake. The amount of drug uptake into the treated polymeric medical articles was determined using a spectrophotometric method after extraction in alcohol.

Method of Determining Long Term Antimicrobial Efficacy in Catheter

5 *Lumen.* In order to determine the duration of antimicrobial efficacy in catheter lumens exposed to treatment solutions, catheters were perfused for 7 days using the following continuous perfusion model. The distal lumens of catheters were connected to a peristaltic pump in a closed loop, wherein 1.5 L of 10% (v/v) trypticase soy broth in saline was constantly perfused by recycling it through each catheter lumen at a rate of
10 83 ml/hr for 7 days. On the eighth day the catheters were disconnected and used for evaluation of bacterial adherence.

Method of Evaluating Microbial Adherence to a Catheter Lumen.

After perfusion of catheters for 7 days as set forth above, the distal lumens of each catheter were filled with a 10^8 CFU/ml culture of bacteria or yeast. In the case of
15 exposure to *E. aerogenes*, *P. aeruginosa* and *C. albicans*, cultures containing 10^6 CFU/ml were used. The ends of the catheters were heat sealed and the catheters were incubated for 24 hours in an orbital shaker at 37°C. After 24 hours, the lock cultures were collected from the lumen and subcultured after serial dilution using agent inactivating media. The outer surface of the whole catheter was sterilized by wiping
20 the outer surface with an alcohol swab. Thereafter, the lumens were flushed with 20 ml trypticase soy broth to remove non-adherent bacteria. The body of the catheters were subdivided into 2 cm segments, which were further cut into 2 mm subsegments. The subsegments were placed in 4.0 ml agent inactivating media and sonicated in a 4°C water bath using an Astrasan Sonicator (Model 9T) at 60 KHz. Thereafter, 0.5
25 ml of the extract was then subcultured on a trypticase soy agar plate and incubated at 37°C for 24 hours. Colony counts were then determined.

Method of Evaluating Bacterial Adherence to PTFE Soft Tissue Patch

Disks. Polytetrafluoroethylene (PTFE) disks were soaked and agitated in 3.0 ml of media containing 50% (v/v) bovine adult serum and 50% (v/v) trypticase soy broth.
30 The media was changed on days 1, 2 and 4. On the fourth day, 10^5 CFU/ml of bacteria was added to the media. On the fifth day, the disks were removed, rinsed and

rolled on drug inactivating agar. The plates were then incubated for 24 hours at 37°C. Colony counts were determined thereafter.

Method of Determining Zones of Inhibition. Zones of inhibition were measured by seeding a specified amount of bacteria onto a trypticase soy agar plate.

5 Then, three units of a specified amount of medical article were placed on the plate. The plates were incubated at 37°C for 24 hours. The zones of inhibition were then measured for Day 1. To measure the zones of inhibition on Day 2 and subsequent days, the units of medical article were transferred onto a fresh plate of similarly prepared agar, incubated at 37°C for 24 hours and colony-free zones were measured.

10 5.1 EXAMPLE: POLYURETHANE CENTRAL VENOUS CATHETERS

Polyurethane central venous catheters, which are hydrophilic polymeric medical articles, were separated into three otherwise identical groups of catheters and separately treated with a solution that either (i) contained no antimicrobial agents; (ii) contained CHA alone, or (iii) contained a combination of CHX and CHA ("CHX-
15 CHA") in accordance with the present invention. In particular, the luminal surfaces of the catheters were separately treated with one of the following solutions:

(1) a solvent system of 80% (v/v) reagent alcohol and 20% (v/v) THF with no antimicrobial agents;

(2) 2.4% CHA in a solvent system of 80% (v/v) reagent alcohol and
20 20% (v/v) THF; and (3) 1.2% CHX and 1.2% CHA in a solvent system of 80% (v/v) reagent alcohol and 20% (v/v) THF.

The solution was exposed to the luminal surface of the catheter by pushing the solution into the lumen and allowing the solution to remain in the lumen for 100 seconds. Thereafter, the solution was removed, and the distal lumens of the
25 catheters were connected to a peristaltic pump in a closed loop, wherein 1.5 L of 10% trypticase soy broth in saline was constantly perfused by recycling it through each catheter lumen at a rate of 83 ml/hr for 7 days, according to the continuous perfusion method discussed above. On the eighth day the catheters were disconnected and the ability of bacteria to adhere to the lumens was tested as follows.

The distal lumens of each of the three groups of catheters were separately filled with 8×10^8 CFU/ml culture of *S. epidermidis*. The ends of the catheters were heat sealed and the catheters were incubated for 24 hours in an orbital shaker at 37°C. After 24 hours, the lock cultures were collected from the lumen and subcultured after serial dilution using agent inactivating media. The outer surface of the whole catheter was sterilized by wiping the outer surface with an alcohol swab. Thereafter, the lumens were flushed with 20 ml trypticase soy broth to remove non-adherent bacteria. The bodies of the catheters were subdivided into 2 cm segments, which were further cut into 2 mm subsegments. The subsegments were placed in 4.0 ml agent inactivating media and sonicated in a 4°C water bath using an Astrasan Sonicator (Model 9T) at 60 KHz. Thereafter, 0.5 ml of the extract was then subcultured on a trypticase soy agar plate and incubated at 37°C for 24 hours. Colony counts were then determined and are shown below in Table 1.

TABLE 1

Solution	Bacterial Adherence of <i>S. epidermidis</i> (CFU/cm)
80% (v/v) reagent alcohol + 20% (v/v) THF	2.2×10^4
2.4% CHA in 80% (v/v) reagent alcohol + 20% (v/v) THF	3×10^2
1.2% CHX + 1.2% CHA in 80% (v/v) reagent alcohol + 20% (v/v) THF	2

15

The luminal surfaces of catheters were also tested according to the above described techniques to evaluate the adherence of a wide variety of organisms. The luminal surfaces of catheters were separately treated with the following solutions:

- (1) a solvent system of 80% (v/v) reagent alcohol and 20% (v/v) THF with no antimicrobial agents; and

20

(2) 1.2% CHX and 1.2% CHA in a solvent system of 80% (v/v) reagent alcohol and 20% (v/v) THF.

The luminal surfaces were exposed to the respective solutions for 100 seconds. Thereafter, the solutions were removed, and the lumens were perfused
5 according to the continuous perfusion method discussed above.

On the eighth day, the catheters were disconnected and susceptibility to microbial adherence was evaluated. The distal lumens of each group of catheters were separately filled with the following amounts of bacteria (*S. aureus*, *P. aeruginosa*, and *Enterobacter*) or yeast (*C. albicans*):

- 10 (1) 8×10^8 CFU/ml culture of *S. aureus*;
(2) 8×10^6 CFU/ml culture of *P. aeruginosa*;
(3) 8×10^8 CFU/ml culture of *Enterobacter*; and
(4) 8×10^6 CFU/ml culture of *C. albicans*.

The four subgroups of lumens were prepared for evaluating microbial adherence to the
15 catheter lumens as described above. The ends of the catheters were heat sealed, incubated, subcultured, externally sterilized, flushed, subdivided, placed in inactivating media and sonicated according to the techniques set forth *supra*. Thereafter, 0.5 ml of the extract was subcultured, incubated and examined to determine the colony counts. The results are shown below in Table 2.

TABLE 2

Solution	Adherence of <i>S. aureus</i> (CFU/cm)	Adherence of <i>P. aeruginosa</i> (CFU/cm)	Adherence of <i>Enterobacter</i> (CFU/cm)	Adherence of <i>C. albicans</i> (CFU/cm)
80% (v/v) reagent alcohol + 20% (v/v) THF	1.3×10^4	$>10^5$	$>10^5$	1.7×10^4
1.2% CHX + 1.2% CHA in 80% (v/v) reagent alcohol + 20% (v/v) THF	3	9	2	26

The results shown in Table 1 demonstrate the synergistic antimicrobial effect of treating a polyurethane central venous catheter lumen with a solution comprising the mixture of CHX and CHA. Table 2 shows that articles treated with CHX and CHA exhibit an increased effectiveness across a wide variety of organisms by decreasing luminal adherence substantially more than articles treated with no antimicrobial agents.

In a further study, the luminal surface of three groups of otherwise identical polyurethane central venous catheters were separately treated with one of the following three solutions:

- (1) 2% CHA in a solvent system of 80% (v/v) ethanol and 20% (v/v) THF;
- (2) 0.625% CHX and 1.375% CHA in a solvent system of 80% (v/v) ethanol plus 20% (v/v) THF; and (3) 1% CHX and 1% CHA in a solvent system of 80% (v/v) ethanol plus 20% (v/v) THF.

The solution was pushed into the lumen and allowed to remain for 100 seconds.

The amount of uptake of chlorhexidine in the catheters was determined using a spectrophotometric method after extraction with alcohol.

In order to determine the amount of drug retention and antimicrobial efficacy, the catheters were perfused for 6 days with 1.500 L of saline per day. The treated catheters were then studied on Day 1 and Day 6 after perfusion to determine the amount of drug retention. The chlorhexidine in the catheter after perfusion was determined using a spectrophotometric method after extraction with alcohol. The antibacterial activity was measured on Day 6 after perfusion by counting the CFU/cm of *S. epidermidis*. Table 3 shows results of the uptake, drug retention and antibacterial activity of the treated catheters.

TABLE 3

Solution	Uptake ($\mu\text{g}/\text{cm}$)	Retention of Drug ($\mu\text{g}/\text{cm}$)		Antibacterial Activity (CFU/cm) <i>S. epidermidis</i> Day 6
		Day 1	Day 6	
2% CHA in 80% (v/v) Ethanol + 20% (v/v) THF	44	34	8	10^2
0.625% CHX + 1.375% CHA in 80% (v/v) Ethanol + 20% (v/v) THF	70	43	22	0
1% CHX + 1% CHA in 80% (v/v) Ethanol + 20% (v/v) THF	80	45	26	0

These results demonstrate the synergistic antimicrobial effect of treating a polyurethane central venous catheter lumen with a solution comprising a mixture of CHX and CHA.

5.2 EXAMPLE: URINARY CATHETERS

Hydrophilic urinary catheters were separated into two otherwise identical groups, and the whole catheters (*i.e.*, external and luminal surfaces of the catheter) were treated with a solution containing either:

- 5 (1) 4% CHA in a solvent system of 85% (v/v) THF and 15% (v/v) methanol; or
- (2) 2% CHX plus 2% CHA in a solvent system of 85% (v/v) THF and 15% (v/v) methanol.

The catheters of each group were soaked in the respective solution for
10 30 minutes to one hour. Thereafter, the catheters were removed from the solution.

The amount of uptake of chlorhexidine was determined using a spectrophotometric method after extraction with alcohol, which results are shown below in Table 4.

The two groups of catheters were separately exposed to cultures of
15 *P. aeruginosa* and *C. albicans* in order to study the antimicrobial efficacy of the medical article. Trypticase soy agar plates were seeded with 0.3 ml of 10^8 CFU/ml of *P. aeruginosa* and *C. albicans*, respectively. Thereafter, a 0.5 cm length of urinary catheter was placed on each plate with three units per plate. The plates were then incubated for 24 hours at 37°C. After 24 hours, the zones of inhibition were measured
20 for Day 1. To measure the zones of inhibition for Day 2 to Day 6, the process was repeated upon transferring the units to fresh agar plates similarly prepared. The results are shown in Table 4.

TABLE 4

Solution	Uptake ($\mu\text{g}/\text{cm}$)	Antimicrobial Efficacy (Zone of Inhibition (mm)) <i>P. aeruginosa</i> Day						Antimicrobial Efficacy (Zone of Inhibition (mm)) <i>C. albicans</i> Day					
		1	2	3	4	5	6	1	2	3	4	5	6
4% CHA in 85% (v/v) THF + 15% (v/v) Methanol	123	15	11	10	9	0	0	11	9	0	0	0	0
2% CHX + 2% CHA in 85% (v/v) THF + 15% (v/v) Methanol	380	16	13	11	10	10	10	12	11	11	10	9	6

These results demonstrate the synergistic antimicrobial effect of
 5 treating the urinary catheters with a solution comprising a mixture of CHX and CHA.

5.3 EXAMPLE: PTFE SOFT TISSUE PATCHES

Disks cut from PTFE soft tissue patches, which are hydrophobic
 polymeric medical articles, were treated with a solution that contained CHA alone and
 a solution that contained a CHX-CHA complex in accordance with the present
 10 invention. Groups of disks having a 1 mm thickness were treated for one hour with
 one of the following solutions:

- (1) 0.4% CHA in a solvent system of 70% (v/v) THF and 30% (v/v)
 methanol; or
- (2) 0.2% CHX and 0.2% CHA in a solvent system of 70% (v/v) THF
 15 and 30% (v/v) methanol.

The amount of uptake of chlorhexidine in the PTFE disks was
 determined using a spectrophotometric method after extraction with alcohol, and the
 results are shown below in Table 5.

The two groups of disks were separately exposed to cultures of *P. aeruginosa* and *S. epidermidis* in order to study their antimicrobial efficacy.

Trypticase soy agar plates were seeded with 0.3 ml of 10^8 CFU/ml of *P. aeruginosa* and *C. albicans*, respectively. Thereafter, 0.5 cm diameter disks were placed on each
 5 plate with three units per plate. The plates were then incubated for 24 hours at 37°C. After 24 hours, the zones of inhibition were measured for Day 1. The process was repeated upon transferring the disks to fresh agar plates similarly prepared for Day 2 to Day 6. The zones of inhibition are shown in Table 5.

10

Table 5

Solution	Uptake ($\mu\text{g}/\text{cm}$)	Antimicrobial Efficacy (Zone of Inhibition (mm)) <i>P. aeruginosa</i> Day				Antimicrobial Efficacy (Zone of Inhibition (mm)) <i>S. epidermidis</i> Day			
		1	2	3	4	1	2	3	4
0.4% CHA in 70% (v/v) THF + 30% (v/v) Methanol	450	8	5	0	0	12	10	9	9
0.2% CHX + 0.2% CHA in 70% (v/v) THF + 30% (v/v) Methanol	840	12	8	8	7	15	13	12	11

These results demonstrate the synergistic effect of treating PTFE soft tissue patches with a solution comprising a mixture of CHX and CHA.

Bacterial adherence on PTFE soft tissue patch disks treated with CHA
 15 alone, CHX alone, or a mixture of CHA and CHX were studied. 2 mm thick disks were separated into four groups and separately treated with one of the following solutions:

- (1) a solvent system of 70% (v/v) THF and 30% (v/v) methanol with no antimicrobial;
- 20 (2) 0.4% CHA in a solvent system of 70% (v/v) THF and 30% (v/v) methanol;

(3) 0.4% CHX in a solvent system of 70% (v/v) THF and 30% (v/v) methanol; and

(4) 0.2% CHX and 0.2% CHA in a solvent system of 70% (v/v) THF and 30% (v/v) methanol.

5 In order to determine the bacterial adherence to the PTFE, three disks of 1 cm diameter from patches in each treatment group were soaked and agitated in 3.0 ml of media containing 50% (v/v) bovine adult serum and 50% (v/v) trypticase soy broth. The media was changed on days 1, 2 and 4. On the fourth day, 10^5 CFU/ml of *S. aureus* was added to the media. On the fifth day after agitation in
10 media, the disks were removed, rinsed and rolled on to plates of drug inactivation agar. The plates were then incubated for 24 hours at 37°C. Thereafter, the colony counts were determined, and the amount of antimicrobial present in the disks was determined by extracting the antimicrobial from the disk with alcohol, followed by spectrophotometric measurement. The results are shown in Table 6.

15

TABLE 6

Solution	Drug levels ($\mu\text{g}/\text{disk}$)	Bacterial Adherence of <i>S. aureus</i> (CFU/cm) Day 5
70% (v/v) THF + 30% (v/v) methanol	0	$>10^5$
0.4% CHA in 70% (v/v) THF + 30% (v/v) methanol	264	8×10^2
0.4% CHX in 70% (v/v) THF + 30% (v/v) methanol	361	1×10^2
0.2% CHA + 0.2% CHX in 70% (v/v) THF + 30% (v/v) methanol	360	60

These results demonstrate the synergistic effect of treating PTFE soft tissue patches with a solution comprising a mixture of CHX and CHA.

5.4 EXAMPLE: POLYURETHANE CENTRAL VENOUS CATHETERS

In a further study of the drug retention properties of polyurethane central venous catheters treated with a solution containing a combination of CHX and
5 CHA ("CHX-CHA") in accordance with the present invention, the outer surfaces of otherwise identical catheters were treated with (i) CHA and silver sulfadiazine ("AgSD"), and (ii) CHX-CHA and AgSD. In particular, the ends of the catheters were sealed and the outer surfaces of the catheters were impregnated by dipping the closed catheters for 5 seconds in one of the following solutions:

- 10 (1) 3.5% CHA + 0.75% AgSD + 3% 93A + 1% 60D;
(2) 2% CHA + 1.5% CHX + 0.75% AgSD + 3% 93A + 1% 60D; and
(3) 2% CHA + 1.5% CHX + 0.75% AgSD + 2.5% 93A + 2% 60D.

The treated catheters were then tested for drug retention at various times using an in vitro agar tract model (method A) or an in vivo rat subcutaneous
15 model (method B).

Method A: The bodies of the treated catheters were subdivided into 4 cm segments and implanted into 12.5 ml culture medium of 0.5 agar + 0.03 trypticase soy broth ("TSB") + 20% bovine adult serum ("BAS") + 0.5% Parmalat in a 15 ml culture tube. The catheter segments were transferred to fresh medium on day 8, 26,
20 33, and 40 to simulate in vivo drug clearance. The drug levels were determined at day 8, 14, 22 and 50.

Method B: The bodies of the treated catheters were subdivided into 4 cm segments and implanted under the skin of the test rats. The catheter segments were removed at day 8, 14 and 22 for determination of drug level.

25 In order to determine the drug level, 1 cm segments of the catheters were extracted with 2 ml dichloromethane. Thereafter, 4 ml of 50% reagent alcohol were added to remove the chlorhexidine from the dichloromethane layer. The results were read spectrophotometrically at 251 nm to determine the concentrations. The drug levels in, measured in µg/cm, were determined over time and are shown for those
30 catheters tested under method A in Table 7 below and for those catheters tested under method B in Table 8 below.

TABLE 7

SOLUTION	CHLORHEXIDINE RETENTION ($\mu\text{g}/\text{cm}$) <u>Method A (in vitro)</u>				
	Day 0	Day 7	Day 14	Day 22	Day 50
3.5 % CHA + 0.75 % AgSD + 3% 93A + 1% 60D	431	173	123	96	89
2% CHA + 1.5% CHX + 0.75% AgSD + 3% 93A + 1% 60D	426	256	214	161	113
2% CHA + 1.5% CHX + 0.75% AgSD + 2.5% 93A + 2% 60D	444	328	257	236	158

5

TABLE 8

SOLUTION	CHLORHEXIDINE RETENTION ($\mu\text{g}/\text{cm}$) <u>Method B (in vivo)</u>			
	Day 0	Day 7	Day 14	Day 22
3.5 % CHA + 0.75% AgSD + 3% 93A + 1% 60D	431	145	144	103
2% CHA + 1.5% CHX + 0.75% AgSD + 3% 93A + 1% 60D	426	301	259	195
2% CHA + 1.5% CHX + 0.75% AgSD + 2.5% 93A + 2% 60D	444	345	308	263

- These results demonstrate that the drug levels of catheters treated with
- 10 CHX-CHA and AgSD have a significantly higher drug retention under either testing method than catheters treated with similar drug levels of CHA alone with AgSD. Further, it is observed that changing the polymer component of the treatment solution containing CHX-CHA from 3% 93A + 1% 60D to 2.5% 93A + 2% 60D enhanced the effectiveness of the drug retention.

Catheters were prepared for evaluating bacterial adherence to the outer surfaces of each of the three groups of catheters described above. Catheters from each of the three groups were separately implanted according to either the agar tract model (method A) or the rat subcutaneous model (method B) described above and infected with *Staphylococcus aureus* at various time intervals. Bacterial adherence was determined 7 days after infection. Under method A, the medium was changed at day 8, 26, 33 and 40, as stated previously, and infected at day 14, 29 and 44 with 20 μ l of a 1×10^7 cfu/ml of *S. aureus* suspension. Under method B, each catheter segment was infected with a 25 μ l of a 1×10^8 cfu/ml of *S. aureus* suspension on day 21. The body of the catheters were subdivided into 1 cm subsegments, placed in a 4.0 ml drug inactivating media, and sonicated in a 4°C water bath using an Astrasan Sonicator (Model 9T) at 60 KHz. Thereafter, 0.5 ml of the extract was then subcultured on a trypticase soy agar plate and incubated at 37°C for 24 hours. Colony counts were then determined. The results of the colony counts under methods A and B are shown in Table 9 by day of infection.

TABLE 9

SOLUTION	BACTERIAL ADHERENCE (cfu/cm) (<i>S. aureus</i>)				
	<u>Method A (in vitro)</u>			<u>Method B (in vivo)</u>	
	Day 14	Day 21	Day 44	Day 14	Day 21
3.5 % CHA + 0.75% AgSD + 3% 93A + 1% 60D	3	11	390	0	10
2% CHA + 1.5% CHX + 0.75% AgSD + 3% 93A + 1% 60D	0	6	2	0	6
2% CHA + 1.5% CHX + 0.75% AgSD + 2.5% 93A + 2% 60D	0	7	59	0	9

These results demonstrate that under methods A and B all of the groups of catheters were effective up to the 21st day post implantation. However, at 44 days post infection the catheters treated with CHA-CHX and AgSD in accordance with the

present invention had significantly lower colonization than the catheters with similar drug levels of CHA and AgSD without combination with CHX. Further, it is observed that changing the polymer component of the treatment solution containing CHX-CHA from 2.5% 93A + 2% 60D to 3% 93A + 1% 60D resulted in even lower
 5 colonization.

5.5 EXAMPLE: EXPANDED PTFE SOFT TISSUE PATCHES

In a further study of the drug retention properties and bacterial adherence of soft tissue patches, disks cut from expanded PTFE soft tissue patches were separately treated with one of the following solutions containing the specified
 10 amounts of CHA, CHX-CHA complex in accordance with the present invention, silver carbonate ("Ag₂CO₃"), triclosan ("TC") and/or polycaprolactone ("PCL") in a solvent system containing ammonium hydroxide ("NH₄OH"), methyl alcohol ("MetOH"), and tetrahydrofuran ("THF"):

- (1) 0.4 % CHA + 0.2 % Ag₂CO₃ in 20 % (v/v) NH₄OH + 10% (v/v) MetOH + 70% (v/v) THF;
 15
- (2) 0.4% CHA + 0.1% Ag₂CO₃ + 1% PCL (w/v) in 10% (v/v) NH₄OH + 10% (v/v) MetOH + 80% (v/v) THF;
- (3) 0.2 % CHA + 0.2% CHX + 0.2% Ag₂CO₃ in 10% (v/v) NH₄OH + 10% (v/v) MetOH + 80% (v/v) THF;
- (4) 0.2 % CHA + 0.2% CHX + 0.1% Ag₂CO₃ + 1% (w/v) PCL in 10% (v/v) NH₄OH + 10% (v/v) MetOH + 80% (v/v) THF;
 20
- (5) 0.2% CHA + 0.2% TC + 0.2% Ag₂CO₃ in 20% (v/v) NH₄OH + 10% (v/v) MetOH + 70% (v/v) THF;
- (6) 0.1% CHA + 0.1% CHX + 0.2% TC + 0.2% Ag₂CO₃ in 20% (v/v) NH₄OH + 10% (v/v) MetOH + 70% (v/v) THF;
 25
- (7) 0.1% CHA + 0.1% CHX + 0.2% TC + 0.1% Ag₂CO₃ in 20% (v/v) NH₄OH + 10% (v/v) MetOH + 70% (v/v) THF;
- (8) 0.1% CHA + 0.1% CHX + 0.2% TC + 0.1% Ag₂CO₃ + 1% (w/v) PCL in 10% (v/v) NH₄OH + 10% (v/v) MetOH + 80% (v/v) THF;

(9) 0.4% CHA + 0.2% TC in 20% (v/v) NH_4OH + 10% (v/v) MetOH + 70% (v/v) THF; or

(10) 0.2% CHA + 0.2% CHX + 0.2% TC in 20% (v/v) NH_4OH + 10% (v/v) MetOH + 70% (v/v) THF.

5 Groups of disks having a 1 mm thickness were treated for one hour with one of the above solutions. The amount of drug uptake was determined using a spectrophotometric method after extraction with alcohol. The results are shown below in Table 10.

10 In order to determine the bacterial adherence to the expanded PTFE soft tissue patches, six 1 cm² pieces 1 mm thick expanded PTFE soft tissue repair material from each treatment group were soaked in media containing 50% (v/v) BAS and 50% (v/v) TSB, incubated at 37°C and agitated on a shaker at 50 RPM. At each 7 day interval, the patches were removed, rinsed and placed in fresh media consisting of 50% (v/v) BAS and 50% (v/v) TSB infected with 10⁵ cfu of *Staphylococcus aureus*,
 15 which is available from the American Type Culture Collection, ATCC # 10390. After each 24 hour period of incubation at 37°C and shaking at 50 RPM, the patches were removed, blotted, rinsed twice and pushed across the surface of D/E drug inactivating agar to semi quantitatively determine the number of adherent organisms. Patches with greater than 100 cfu/cm² were considered colonized. The results are shown in Table
 20 10 below.

TABLE 10

SOLUTION		μg chlorhexidine/cm ²	μg TC/cm ²	μg Total Drug/cm	Duration of Activity (days)
	Control	0	0	0	0
(1)	0.4 % CHA + 0.2 % Ag_2CO_3 in 20 % NH_4OH + 10% MetOH + 70% THF	226	—	226	<7
(2)	0.4% CHA + 0.1% Ag_2CO_3 + 1% PCL in 20% NH_4OH + 10% MetOH + 70% THF	373	—	373	<7

(3)	0.2 % CHA + 0.2% CHX + 0.2% Ag ₂ CO ₃ in 20% NH ₄ OH + 10% MetOH + 70% THF	307	—	307	>7 <14
(4)	0.2 % CHA + 0.2% CHX + 0.1% Ag ₂ CO ₃ + 1% PCL in 20% NH ₄ OH + 10% MetOH + 70% THF	400	—	400	>7 <14
(5)	0.2% CHA + 0.2% TC + 0.2% Ag ₂ CO ₃ in 20% NH ₄ OH + 10% MetOH + 70% THF	74	168	242	>7 <14
(6)	0.1% CHA + 0.1% CHX + 0.2% TC + 0.2% Ag ₂ CO ₃ in 20% NH ₄ OH + 10% MetOH + 70% THF	118	155	273	<7
(7)	0.1% CHA + 0.1% CHX + 0.2% TC + 0.1% Ag ₂ CO ₃ in 20% NH ₄ OH + 10% MetOH + 70% THF	209	244	453	>7 <14
(8)	0.1% CHA + 0.1% CHX + 0.2% TC + 0.1% Ag ₂ CO ₃ + 1% PCL in 20% NH ₄ OH + 10% MetOH + 70% THF	128	140	268	>21
(9)	0.4% CHA + 0.2% TC + in 20% NH ₄ OH + 10% MetOH + 70% THF	433	158	591	<7
(10)	0.2% CHA + 0.2% CHX + 0.2% TC + in 20% NH ₄ OH + 10% MetOH + 70% THF	515	215	730	>7 <14

These results demonstrate the synergistic effect of treating expanded PTFE soft tissue patches with a mixture of CHX and CHA, particularly when comparing the significant improvement in chlorhexidine retention and increased

duration of efficacy for patches from groups (3), (4), and (10), when compared with groups (1), (2), and (9), respectively.

Table 10 further demonstrates the advantages of higher chlorhexidine uptake using PCL in the treatment solution of the patches of groups (2) and (4) when compared with the patches of groups (1) and (3), respectively. PCL also provides an advantage of significantly increasing duration of efficacy as evidenced by comparing the patches of group (8) with group (7), which demonstrates a three-fold increase in the duration of activity from less than 14 days to greater than 21 days despite lower total drug levels. PCL is also advantageous to use, when compared with other biodegradable polymers, because it does not affect the flexibility and softness of the resulting e-PTFE patch.

Various publications are cited herein, which are hereby incorporated by reference in their entireties.

CLAIMS

1. An antimicrobial medical article prepared by treating a polymeric medical article, for an effective period of time, with a solution consisting essentially of one or more solvents and a mixture of chlorhexidine free base and a water-soluble chlorhexidine salt, wherein the weight/weight ratio of chlorhexidine free base and the water-soluble chlorhexidine salt in the solution is between 1:1 to 1:5.
2. The antimicrobial medical article of claim 1, wherein the ratio is 1:1.
3. The antimicrobial medical article of claim 1, wherein the solvent is selected from the group consisting of water, alcohol, tetrahydrofuran, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, and mixtures thereof.
4. The antimicrobial medical article of claim 3, wherein the solvent is a mixture of between 10 and 30 percent (volume/volume) tetrahydrofuran and 70 and 90 percent (volume/volume) ethanol.
5. The antimicrobial medical article of claim 7, wherein the solvent is a mixture of 20 percent (volume/volume) tetrahydrofuran and 80 percent (volume/volume) ethanol.
6. The antimicrobial medical article of claim 3, wherein the solvent is a mixture of between 75 and 95 percent (volume/volume) tetrahydrofuran and 5 and 25 percent (volume/volume) methanol.
7. The antimicrobial medical article of claim 6, wherein the solvent is a mixture of about 85 percent (volume/volume) tetrahydrofuran and 15 percent (volume/volume) methanol.

8. The antimicrobial medical article of claim 1, wherein the article is a hydrophilic polymeric medical article.

9. The antimicrobial medical article of claim 8, wherein the article
5 is a catheter.

10. The catheter of claim 9, wherein the catheter has a lumen which is treated, for an effective period of time, with the solution consisting essentially of one or more solvents and the mixture of chlorhexidine free base and water-soluble
10 chlorhexidine salt.

11. The medical article of claim 8, wherein the water-soluble chlorhexidine salt is chlorhexidine diacetate.

12. The catheter of claim 9, wherein the water-soluble chlorhexidine salt is chlorhexidine diacetate.
15

13. The catheter of claim 10, wherein the water-soluble chlorhexidine salt is chlorhexidine diacetate.
20

14. The antimicrobial medical article of claim 1, wherein the article is a hydrophobic polymeric medical article.

15. The antimicrobial medical article of claim 14, wherein the
25 article is expanded polytetrafluoroethylene.

16. The antimicrobial medical article of claim 14, wherein the article is a polytetrafluoroethylene soft tissue patch.

17. An antimicrobial medical article prepared by treating a
30 polymeric medical article, for an effective period of time, with a solution consisting essentially of

- (1) one or more solvents;
- (2) a mixture of chlorhexidine free base and a water-soluble chlorhexidine salt; and
- (3) one or more of (i) an organic acid, at a concentration of between 0.1 and 5 percent; (ii) an anti-inflammatory agent, at a concentration of between 0.1 and 5 percent; or (iii) a hydrogel at a concentration of between 0.5 to 10 percent, wherein the weight/weight ratio of chlorhexidine free base and the water-soluble chlorhexidine salt in the solution is between 1:1 to 1:5.

10 18. The antimicrobial medical article of claim 17, wherein the concentration of organic acid in the solution is between 0.1 and 2 percent.

 19. The antimicrobial medical article of claim 17, wherein the concentration of anti-inflammatory agent is between 0.1 and 1 percent.

15 20. The antimicrobial medical article of claim 17, wherein the concentration of hydrogel in the solution is between 1 and 5 percent.

 21. A method of preparing a medical article comprising the steps of

20 (i) placing the medical article in a solution consisting essentially of (a) a solvent selected from the group consisting of water, reagent alcohol, tetrahydrofuran, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, and mixtures thereof; and (b) a mixture of chlorhexidine free base and a water-soluble chlorhexidine salt, wherein the weight/weight ratio of chlorhexidine

25 free base and water-soluble chlorhexidine salt in the solution is between 1:1 to 1:5;

 (ii) soaking the medical article in the solution for an effective period of time to allow the medical article to swell;

 (iii) removing the medical article from the solution; and

 (iv) drying the medical article.

30

22. A method of preparing a catheter having a lumen comprising the steps of

(i) exposing the lumen of the catheter to a solution consisting essentially of (a) a solvent selected from the group consisting of water, reagent
5 alcohol, tetrahydrofuran, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone, and mixtures thereof; and (b) a mixture of chlorhexidine free base and a water-soluble chlorhexidine salt, wherein the weight/weight ratio of chlorhexidine free base and water-soluble chlorhexidine salt in the solution is between 1:1 to 1:5;

(ii) filling the lumen of the catheter with the solution for an
10 effective period of time to allow the lumen of the catheter to swell;

(iii) removing the solution from the lumen of the catheter; and

(iv) drying the catheter.