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DESCRIPTION

FIELD

[0001] This invention relates to the field of transdermal indwelling medical devices, such as catheters, as well as to the field of microbial growth inhibiting solutions for flushing, locking and coating these medical devices. More specifically, the field of this invention relates to microbial growth inhibiting solutions. This invention also relates to microbial growth inhibiting solutions useful in maintaining catheter patency and preventing infection. Methods of using the microbial growth inhibiting solutions of the invention in the management and maintenance of transdermal vascular access catheters are also related to the present disclosure.

BACKGROUND

[0002] Transdermal medical devices, including vascular catheters, have become essential in the management of hospitalized or chronically ill patients. Unfortunately, vascular catheters have become the major source for hospital-acquired sepsis. Hence, the benefit derived from transdermal medical devices such as vascular catheters is often upset by infectious complications. Thrombotic occlusions of the lumen of central venous catheters ("CVC") are another complication that will often lead to the removal of catheters.

[0003] To reduce problems associated with thrombus formation, it is now common to "lock" intravascular access catheters between successive uses. Locking typically involves first flushing the catheter with saline to remove blood, medications, cellular debris and other substances from the catheter lumen. After the catheter has been flushed, a locking solution, typically heparin, is then injected to displace the saline and fill the lumen. The heparin locking solution both excludes blood from the lumen and actively inhibits clotting and thrombus formation within the lumen. To address infection, various antimicrobial substances have been combined with the locking solution in order to inhibit infection at the same time that thrombosis is being inhibited. However, problems with current and continuously emerging resistance to antimicrobial substances, as well as the over-use (and hence the increased risk of developing resistance) of antimicrobials, is an ever-growing concern.

[0004] *Staphylococcus epidermidis* and *S. aureus* account for 75% of CVC related infections. *Candida* species account for another 10% to 15% of such infections. The use of antistaphylococcal antibiotics to prevent these infections has been found to reduce CVC related bacterial infections, but only at the expense of the occurrence of higher rates of fungal (*Candida*) infections. The fibrous glycocalyx material produced by *Staphylococci* and *Candida* helps these organisms adhere and stick to catheter surfaces. These microbiological biofilm layers are made of fibrous glycocalyx material primarily polysaccharide in nature. The protective sheath provided by the glycocalyx at the infected site effectively prevents the elimination and treatment of these infections. As a result, microbial growth inhibiting solutions are needed that are effective for

reducing or eliminating glycocalyx of infectious microorganisms typically associated with catheter colonization and infection.

[0005] Transdermal vascular catheters get engulfed by a fibrin sheath that subsequently acts to cover the internal and external surfaces of a catheter. This fibrin sheath provides such organisms as *Staphylococci* and *Candida*, with an enhanced adherence capacity to the catheter surface. Unlike these particular microbes, gram-negative bacilli do not adhere well to fibrin and fibronectin. A composition that halts fibrin formation would thus be particularly useful in halting the colonization of *Staphylococci*, *Candida*, and the like, at transdermal catheter sites.

[0006] Ethylenediaminetetraacetic acid ("EDTA") is an anticoagulant used in blood collection tubes. It is also recognized as a calcium chelating agent. EDTA is also recognized to have an antibacterial and antistaphylococcal effect (alone or in combination) (Harper & Epis (1987) *Microbios.* 51:107; Said et al. (1987) *J. Med. Microbiol.* 24:267; Root et al. (1988) *Antimicrob. Agents Chemother.* 32:1627). While those investigators found EDTA to be bacteriocidal, no remedy or suggestion of how the microbial glycocalyx of a device-related infection could be eliminated was provided.

[0007] Ethylene glycol tetraacetic acid ("EGTA") is another recognized chelating agent. This agent has not been described as antimicrobial. Triethylene tetramine dihydrochloride (trientine 2HCl) ("TTH") is a recognized chelating agent that chelates copper. TTH and other chelating agents, including diethylenetriamine pentaacetic acid ("DTPA"), are similarly not recognized as having antimicrobial activity.

[0008] Although glycopeptide antibiotics (vancomycin and teicoplanin) are effective against staphylococci *in vitro* and in tissue, they are not active against adherent staphylococci embedded in a biofilm layer, such as glycocalyx. While flushing with such agents may acutely destroy these microorganisms, the risk of rapid development of tolerant and resistant strains in the patient being treated makes this a contraindicated procedure in most cases.

[0009] U.S. Patent No. 5,362,754 to Raad ("Raad I") describes compositions for use with catheters that include a tetracycline antibiotic, such as minocycline, and EDTA. Raad I teaches the use of 10-100 mg/ml of EDTA in combination with 0.001-100 mg/ml of minocycline and the more preferred combination of 20-60 mg/ml of EDTA and 2-9 mg/ml of minocycline. U.S. Pat. No. 5,688,516 also to Raad ("Raad II") in Example 10 teaches that minocycline and EDTA compositions of less than 3 mg/ml EDTA are ineffective at controlling all microbial growth. Raad II further teaches: "These studies also demonstrate the marked enhancement of *anti-Candida albicans* inhibitory activity where a ratio of minocycline to EDTA of 10:1 (10% EDTA) is used."

[0010] U.S. Patent Nos. 4,343,788 and 4,479,795 to R.V. Mustacich describe polymer compositions containing carboxylate antimicrobial agents for incorporation into catheters. U.S. Patent No. 4,392,848 to D.S. Lucas describes polymer compositions for incorporation into catheters that are permeable to carboxylate antimicrobial agents. U.S. Pat. No. 4,489,097 to R.L. Stone ("Stone") describes intravenous solutions containing carboxylate antimicrobial agents, preferably n-hexanoic and n-octanoic acids and pharmaceutically-acceptable, water-soluble salts

thereof. Stone teaches the use of these carboxylate antimicrobial agents to sterilize intravenous solutions and to maintain these intravenous solutions sterile during manipulation. Administration of Stone's solutions as described into an intravenous catheter to "lock" the catheter under a static (no flow) situation would result in rapid occlusion of the access due to backflow of blood into the device and the lack of anticoagulation characteristics of the described compositions. WO 2010/110908) discloses compositions for flushing and coating medical devices such as catheters comprising a combination of a chelating agent pref. EDTA with a C4-C9 carboxylic acid or salts thereof pref. octanoic acid and opt. a buffering agent. A method for disinfecting, for locking and/or flushing an implanted catheter using the same is also disclosed. EP 0 083 820 discloses a disinfecting solution containing 0.001-3% of C5-C12 fatty acid e.g. octanoic acid, from 0.01 to 2% of calcium chelator pref. EDTA, a water soluble salt (e.g. sodium chloride, sodium phosphate or sodium octanoate) and 0.01 to 5% of a pharmacologically acceptable buffer e.g. a citrate containing buffer.

[0011] A prophylactic agent for catheter maintenance should both inhibit/eliminate the formation of polysaccharide-rich glycocalyx and eliminate *Staphylococci* and fungi. In view of the foregoing, there is a need for improved compositions, kits and methods for flushing, locking and disinfecting catheters. Such compositions should have antimicrobial activity against a broad spectrum of microorganisms, preferably including fungi and both gram-positive and gram-negative bacteria, and preferably be effective against planktonic (free-floating) and adherent microorganisms embedded in a biofilm. The compositions should discourage the development of resistant microbes, be relatively inexpensive, nontoxic, compatible with the catheter material, safe if inadvertently infused systemically, easy to implement, require minimum or no solution, and be useful with most or all types of implanted catheters, including hemodialysis and hemofiltration catheters, IV catheters, peritoneal dialysis catheters, urinary catheters, chemotherapy catheters, and the like. At least some of these objectives are met by embodiments of the invention described hereinafter.

SUMMARY

[0012] The present invention provides a microbial growth inhibiting solution according to claim 1, a method for coating a medical device according to claim 6, a medical device coated with a microbial growth inhibiting solution according to claim 7, and a kit for locking and/or flushing an implanted catheter according to claims 9 and 11.

[0013] In an embodiment, the microbial growth inhibiting solutions include a pharmacologically acceptable carrier solution, such as water, Ringer's solution or saline pH adjusted to 5.2 or less. The microbial growth inhibiting solutions can have an in-use pH of about 6.0, or below, generally in the range of about 3.5 to about 5.8, or most preferably in the pH range of about 3.5 to about 5.2. Within this acidic pH range, proper concentrations of the carboxylate compounds in the free acid form quickly and efficiently kill a wide variety of bacteria and fungi.

[0014] In an embodiment, the chelating agents provide potent glycocalyx inhibiting potential. In addition, C₄-C₉ carboxylate antimicrobial agents of the compositions preferably have a fungicidal

effect and a unique ability to penetrate a polysaccharide-rich glycocalyx biofilm layer. The combination of the C₄-C₉ carboxylate antimicrobial agent and chelating agent can advantageously provide anticoagulant, glycocalyx inhibiting, antibacterial and antifungal agent for the prevention of thrombogenesis, microbial adherence and device-related infections.

[0015] Also described but not claimed are methods of using microbial growth inhibiting solutions including the chelating agent with the C₄-C₉ carboxylate antimicrobial agent in a variety of therapeutic applications. One such therapeutic application is for preventing catheter infections. An example of a composition to be used in the practice of these methods comprises n-octanoic acid together with a chelating agent. EDTA is an example of a chelating agent contemplated for use in these methods; however, other chelating agents would also be expected to be useful.

[0016] For use in maintaining catheter patency, the microbial growth inhibiting solutions may be efficaciously used with medical devices such as a central venous catheter, a peripheral intravenous catheter, an arterial catheter, a Swan-Ganz catheter, a hemodialysis catheter, an umbilical catheter, a percutaneous nontunneled silicone catheter, a cuffed tunneled central venous catheter, as well as with a subcutaneous central venous port.

[0017] Embodiments of the invention also provide medical devices, such as catheters, that are coated with microbial growth inhibiting solutions. Particular exemplary medical devices that may be prepared and coated with the solutions of the present invention are provided in the above list.

[0018] Embodiments of the present invention also provide processes for preparing coated medical devices with the compositions described herein. In an embodiment, a process comprises exposing the medical device to a microbial growth inhibiting solution for a sufficient amount of time to provide a coating on the exposed surface of the device. Where the microbial growth inhibiting solution is in a liquid form, it can be allowed to dry on the device surface to form a film.

[0019] In a preferred embodiment of the above described processes, the device is first treated with a surfactant before exposing the device to the microbial growth inhibiting solution. Such surfactants, by way of example, include tridodecylmethyl ammonium chloride and benzalkonium chloride.

[0020] Another aspect of the present invention provides a method of preparing a biofilm-resistant medical device. In one embodiment, the method comprises exposing a device with the microbial growth inhibiting solutions described herein. Any of a variety of catheters may be treated or coated according to the described method employing coating techniques well known to those of ordinary skill in the art.

[0021] While the method may be used to coat virtually any surface where glycocalyx formation is to be desirably inhibited, use of the method in preparing a microbial biofilm-resistant catheter device is particularly envisioned. By way of example, catheters that may be prepared and treated according to embodiments of the invention include a central venous catheter and a triple lumen catheter. It is anticipated that the method will provide a device resistant to polysaccharide-rich glycocalyx formation, such as that typical of *Staphylococci*.

[0022] In a preferred aspect of the described method, a biofilm-resistant medical device is prepared using the microbial growth inhibiting solution. The various concentration ranges of the C₄-C₉ carboxylate antimicrobial agents and chelating agents described above are also contemplated as useful in the compositions for coating a medical device.

[0023] In one embodiment, the method comprises preparing a microbial growth inhibiting solution of the desired combination in a biocompatible adherent coating carrier solution. The surface of the medical device of interest is then exposed to the microbial growth inhibiting solution for a period of time sufficient to allow the formation of a film or coating of the solution on the surface of the device. This may be accomplished, for example, by dipping the device in the solution. Most preferably, the device to be coated is a catheter. Such treatment provides a biofilm-resistant catheter.

[0024] Also described are methods for inhibiting glycoprotein-rich glycocalyx formation at a catheter port. One method comprises flushing the catheter periodically with a microbial growth inhibiting solution comprising a glycocalyx-inhibiting concentration of a chelating agent and a C₄-C₉ carboxylate antimicrobial agent in a pharmacologically acceptable carrier solution.

[0025] The described methods can be used to inhibit infection at virtually any tunneled or untunneled catheter. As part of a catheter maintenance regimen, the catheter most preferably is to be flushed with a composition comprising a C₄-C₉ carboxylate antimicrobial agent and a chelating agent in a pharmaceutically acceptable carrier solution. The described regimen is repeated once a week, once every 4 days, once every 2 days, once a day (about every 24 hours), twice a day, every four hours or as needed according to patient needs.

[0026] Also described are methods for eliminating microbial glycocalyx formation, particularly polysaccharide-rich (*Staphylococcal*) glycocalyx formation, at a catheter lumen. One method comprises preparing a microbial growth inhibiting solution comprising a chelating agent (e.g., EDTA, EGTA, or both) together with a C₄-C₉ carboxylate antimicrobial agent (e.g., n-butyric, n-pentanoic, n-hexanoic, n-heptanoic, n-octanoic or n-nonanoic acids and/or pharmaceutically acceptable salts thereof) in a carrier solution to provide a flushing composition, and flushing the catheter with an amount effective to inhibit microbial growth of the flushing composition.

[0027] Most preferably, the catheter will be flushed with a volume of about 3 mL of the described n-octanoic acid and EDTA solution containing about 0.5 mg/mL EDTA and about 1.15 mg/ml n-octanoic acid. The catheter can be flushed periodically at intervals of once a week, once every 4 days, once every 2 days, once a day, twice a day, every four hours, or as needed according to patient needs with about 2-3 mL of the n-octanoic acid and EDTA solution. The catheter flushing regimen may simply constitute once every time that the catheter is used or changed. In a preferred method, the catheter is to be flushed at 4 hour intervals with the herein described solutions.

[0028] The compositions describe herein preferably remain therapeutically effective for use as a catheter-flushing agent after storage at a refrigerated temperature.

[0029] The present invention in still another aspect provides a kit. Also described is a kit comprising a container, such as a syringe, holding a volume of one of the foregoing solutions containing a C₄-C₉ carboxylate antimicrobial agent and a chelating agent and an implantable catheter lumen to receive the solution. The kit may further comprise a package, such as a box, tray, tube, envelope, pouch, or the like, for holding the container. The volume of the solution in the container is typically in the range from 1 mL-20 mL, preferably from 2 mL-10 mL, usually being about 2 mL-4 mL. Optionally, the container will usually comprise a syringe, or device to permit direct introduction of the solution into the indwelling catheter.

[0030] In another embodiment, the kit comprises a container, such as a compartmentalized syringe, that comprises a plurality of compartments. For example, the container can have three compartments, where one compartment comprises a C₄-C₉ carboxylate antimicrobial agent comprising sodium caprylate; the second compartment comprises a chelating agent comprising EDTA; and the third compartment comprises a diluent, such as saline, Ringer's solution, or water pH adjusted to 5.2 or less. Kits that include a carrier adapted to receive at least two compartments constitute still another embodiment of the kit. In these embodiments, the chelating agent would be included together with the C₄-C₉ carboxylate antimicrobial agent within a compartment of the container. The second compartment would comprise a diluent, such as the ones described above. In an embodiment, the chelating agent and antimicrobial agent are included together in a first compartment of the device in dry powder form. The dry components would preferably be combined with the diluent of a second compartment to provide a solution suitable for use.

[0031] Also described is a method for disinfecting an implanted catheter that includes introducing a solution comprising a C₄-C₉ carboxylate antimicrobial agent and a chelating agent in a pharmaceutically acceptable carrier solution into a lumen of a catheter where at least a portion of the catheter is sufficiently porous to permit diffusion of the solution outwardly from the lumen to the outer surface of the catheter and into the tissues or the bloodstream surrounding the catheter to inhibit infection. The implanted catheter may be a subcutaneous or transcutaneous indwelling catheter.

[0032] The ability to inhibit or prevent infection of the implanted catheter can be improved by utilizing catheters where at least a portion of the catheter body is sufficiently porous to allow the antimicrobial locking solution to permeate the catheter body and, preferably, pass outwardly (i.e., seep, ooze, leak, diffuse) into the tissue region surrounding the catheter. The use of such porous or partially porous catheter bodies can be beneficial with many antimicrobial locking solutions, such as those taught in U.S. Patent Nos. 4,186,745; 4,767,400; 4,968,306; 5,077,281; 5,913,856; 6,949,087; 7,004,923; and U.S. Patent Publication Nos. 2006/0074388 and 2006/0253101. It will be appreciated that C₄-C₉ carboxylate antimicrobial agents have molecular weights and other qualities that enable them to readily penetrate into and through many porous materials. Exemplary porous materials for construction of the catheter body include silicone rubber, expanded PTFE (e.g., GORE-TEX®, medical membranes), TEFLON® films, natural, regenerated or semi-synthetic cellulosic materials such as cellulose acetate, cellulose diacetate, cuprophane, and the like. Such materials may be formed into the tubular catheter bodies or may be

incorporated as separate component(s) into the catheter bodies.

[0033] The described microbial growth inhibiting solutions are expected to be effective in preventing the adherence and colonization of catheter surfaces by *S. aureus*, *S. epidermidis*, and fungi, as well as effective in both treating and eliminating already formed glycocalyx formations of these infectious organisms.

[0034] It is contemplated that whenever appropriate, any embodiment of the present invention can be combined with one or more other embodiments of the present invention, even though the embodiments are described under different aspects or embodiments of the present invention. Additional features and advantages are described herein, and will be apparent from, the following Detailed Description and the figures.

BRIEF DESCRIPTION OF THE FIGURES

[0035]

Figs. 1A and 1B illustrate methods according to the present invention for locking and disinfecting a transcutaneous catheter.

Figs. 2A-2C illustrate methods according to the present invention for flushing, locking and disinfecting a subcutaneously implanted catheter.

Figs. 3A-3C illustrate methods according to the present invention for flushing, locking and disinfecting a peritoneal dialysis catheter.

Fig. 4 illustrates an embodiment of the present invention where an antimicrobial locking solution permeates into an implanted catheter body and preferably into the tissue surrounding the catheter body.

Fig. 5 illustrates a kit constructed in accordance with the principles of the present invention.

Fig. 6 shows a comparison of Na Octanoate/EDTA and Heparin by aPTT.

DETAILED DESCRIPTION

[0036] The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary

skill in the art to which this invention belongs. In the case of conflict, the present Specification will control.

Definitions

[0037] The terms below have the following meanings unless indicated otherwise.

[0038] The term "biofilm" as used herein refers to a polysaccharide-rich glycocalyx that typically accompanies microbial surface colonization.

[0039] As used herein, a "biofilm-resistant" device or surface is a surface or device that will prevent the adherence or growth of organisms that produce polysaccharide-rich glycocalyx material. Such organisms include, but are not limited to, the *Staphylococcus aureus* and *S. epidermidis* species.

[0040] The term "glycocalyx inhibiting concentration" as used herein refers to a concentration effective to degrade, dissolve, or otherwise inhibit a polysaccharide-rich glycocalyx. By way of example, such a polysaccharide-rich glycocalyx is characteristic of established staphylococcal infections of *S. aureus* and *S. epidermidis*.

[0041] As used herein, the terms "implanted", "subdermal", "subcutaneous" and "indwelling" are used synonymously to refer to the placement of a medical device, for example, a catheter. These implanted catheters typically will have a distal end which is at least partially open to a body lumen. Most commonly, the catheters will be intravascular catheters where the distal end is implanted in or attached to a blood vessel -- usually a vein, but in some cases an artery. Exemplary intravascular catheters include hemodialysis and hemofiltration catheters, as well as intravenous catheters. Intravenous catheters can be used for a wide variety of purposes, including fluid infusion and drug delivery. Catheters attached other than to the vasculature include peritoneal dialysis catheters which are open to the peritoneal cavity and urinary catheters which open to the bladder.

[0042] The medical devices, such as catheters, which are described herein may be transcutaneously implanted or subcutaneously implanted. By "transcutaneously implanted," it is meant that the distal end of the catheter is attached to or implanted within a target body lumen and a proximal end of the catheter is located externally to the patient. An intermediate portion of the catheter will thus pass through or penetrate the patient's skin, and the proximal end of the catheter will usually have a hub to permit selective attachment of infusion tubes, syringes, solution bags, and the like. Most commonly, the proximal attachment hub will have a luer fitting. By "subcutaneously implanted," it is meant that the entire catheter is implanted beneath the skin and no portion of the catheter extends through the skin. Such subcutaneously implanted catheters are typically attached to a fully implanted hub at their proximal ends. The hub permits percutaneous access via a needle or other penetrating element.

[0043] The microbial growth inhibiting solutions of the invention are expected to be particularly

useful in preventing the formation of the "biofilm" or polysaccharide-rich glycocalyx that typically accompanies microbial surface colonization. In particular, the microbial growth inhibiting solutions are expected to be most effective in breaking down staphylococcal glycocalyx and in inhibiting its formation. This feature renders the microbial growth inhibiting solutions of the present invention particularly useful in the treatment of staphylococcal infections where a polysaccharide-rich glycocalyx has formed or may potentially be formed, as well as in the prevention and treatment of *Staphylococcus* and *Candida* infection.

[0044] Embodiments of the present invention also provide treated or coated medical devices, such as catheters, that prevent staphylococcal or fungal colonization. The coating or film provided on these devices comprises a microbial growth inhibiting solution of the present invention. Devices coated with these combinations of agents are also envisioned to be useful.

Antimicrobial Agents

[0045] The C₄-C₉ carboxylate antimicrobial agent used in any of the microbial growth inhibiting solutions and methods described herein comprises sodium caprylate and can include other non-aromatic water-soluble C₄-C₉ alkyl, alkenyl or alkynyl organic acids, or any of their water-soluble, pharmaceutically-acceptable salts. Such salts include, for example, sodium, potassium and ammonium salts. The sodium and potassium salts are preferred.

[0046] While the various carboxylate compounds exhibit different degrees of antimicrobial activity (per mole), water-soluble agents having the formula: R-COOH, wherein R = C₃-C₈ n-alkyl, as well as pharmaceutically acceptable salts thereof or a combination thereof, exhibit excellent antimicrobial activity. The n-octanoic acid and pharmaceutically-acceptable, water-soluble salts thereof are much preferred

[0047] The microbiocidal activity of the C₄-C₉ carboxylate antimicrobials is directly related to the presence of their respective free acids in solution. The concentration of free carboxylic acid in solution, as opposed to carboxylate salt (anionic) form, is a function of the solution pH. Carboxylic acid salts can be used, but only as long as the solution pH is such that a minimum lethal concentration ("MLC") of free acid is present. Accordingly, the amount of acid or acid salt used will vary somewhat with the use pH. The amount of a given acid salt or acid that will provide the MLC at a given pH will depend on the pK_a of the acid. Of course, knowing the pK_a, the MLC of the particular acid and the use pH, the amount of any C₄-C₉ acid or acid salt to be used is easily calculated from the following formula

$$pK_a = pH + \log\left(\frac{[HC_x]}{[C_x^-]}\right),$$

where [HC_x] is the concentration of free acid of chain length x and [C_x⁻] is the concentration of its anion.

[0048] The antimicrobial agent is present in an amount ranging from about 0.071 mg/ml to about 1.15 mg/ml in the microbial growth inhibiting solution. More specifically, the amount of the antimicrobial agent can be about 0.1 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 0.75 mg/mL, 1 mg/mL and

the like. It should be appreciated that any two amounts of the antimicrobial agent recited herein can further represent end points in a therapeutically preferred range of the antimicrobial agent.

Chelating Agents and Buffers

[0049] In addition to the C₄-C₉ carboxylate antimicrobial agent comprising sodium caprylate, the microbial growth inhibiting solutions and methods described herein also include a chelating agent comprising disodium ethylenediamine tetraacetic acid and a buffer comprising citrate, e.g. citrate-citric acid. Any of the microbial growth inhibiting solutions and methods described herein can also include additional chelating agents and buffers. Nonlimiting examples of suitable chelating agents and buffers that can be used in various embodiments of the present invention can be selected from Tables 1 and 2, respectively. Pharmaceutically acceptable salts (e.g., edetate calcium disodium) of any chelating agents listed in Table 1 can also be used.

Table 1. CHELATING AGENTS

Deferoxamine
Dimercaprol
EDTA
EGTA
DTPA
DMSA
Penicillamine
Dimercaptosuccinic acid

Table 2. BUFFERING AGENTS

Acetate-Acetic acid
Phosphate-Phosphoric acid
Tartrate-Tartaric acid
Malate-Malic acid
Fumarate-Fumaric acid
Malonate-Malonic acid
Barbiturate-barbituric acid

[0050] As will be appreciated by those of skill in the art, the foregoing lists are only intended to be exemplary. Other chelating agents, as well as buffers, are also expected to be useful and effective in combination with a C₄-C₉ carboxylate antimicrobial agent. These combinations formulated as a coating will preferably further include a material, such as a cationic surfactant (e.g., tridodecylmethyl ammonium chloride or benzalkonium chloride), that will enhance adherence or film forming characteristics, of the solution. As a solution for flushing or other medicinal use, the ingredients will be suspended in a carrier solution such as sterile saline, phosphate buffered saline, dextrose in water, Ringer's solution, distilled water or any other physiologically acceptable

solution pH adjusted to 5.2 or less.

[0051] In an embodiment, the amount of the chelating agent can be about 0.1 mg/mL, 0.15 mg/mL, 0.2 mg/mL, 0.25 mg/mL, 0.3 mg/mL, 0.35 mg/mL, 0.4 mg/mL, 0.45 mg/mL, 0.5 mg/mL, 0.55 mg/mL, 0.6 mg/mL, 0.65 mg/mL, 0.7 mg/mL, 0.75 mg/mL, 0.8 mg/mL, 0.85 mg/mL, 0.9 mg/mL, 0.95 mg/mL, 1 mg/mL and the like. It should be appreciated that any two amounts of the chelating agent recited herein can further represent end points in a therapeutically preferred range of the chelating agent. For example, the amounts of 0.2 mg/mL and 0.5 mg/mL can represent the individual amounts of the chelating agent as well as a preferred range of the chelating agent in the solution from about 0.2 mg/mL to about 0.5 mg/mL.

Methods of Flushing, Locking and Disinfecting a Catheter

[0052] Referring now to Figs. 1A and 1B, methods for locking an implanted venous catheter 10 will be described. The venous catheter 10 will be implanted through a patient's skin S into a vein V for infusion of the patient. When it is desired to disconnect the patient from the source of infusion, it will be necessary to lock the catheter to inhibit plugging and fouling caused by coagulation, and preferably to further inhibit or eliminate the risk of infection. Shown in Fig. 1A, a tube 12 containing an IV solution will normally be connected to the proximal hub 14 of the catheter 10. The IV line 12 will be disconnected, and the catheter 10 rinsed with a flushing solution. After flushing is completed, a locking solution of the invention is introduced to fill the inner lumen of the catheter 10, as shown in Fig. 1B. Usually, a sufficient volume of the locking solution will be introduced to completely fill the lumen of the implanted catheter 10, with minimum excess passing from distal end 16 of the catheter. The loss of excess solution into a blood vessel or most other body lumens, however, will generally not be a problem. The "column" of the solution will then occupy the inner lumen, and the proximal hub will be sealed, helping retain the solution in place. The locking solution will effectively inhibit clotting and coagulation at the distal end 16 as well as inhibit or eliminate infection throughout the catheter. When it is desired to reattach the patient to the IV source, the solution will be removed and the catheter lumen flushed.

[0053] Referring now to Figs. 2A-2C, flushing and locking of a subcutaneously implanted catheter 20 used for hemodialysis access will be described. The catheter 20 is implanted between a target blood vessel BV, typically a vein, and an implanted port 22. During hemodialysis, blood is withdrawn through the catheter 20, through the port 22 and externally through a needle N and connecting line 23 used to percutaneously access the port 22 (Fig. 2A). Alternatively, the port and catheter can be used to return treated blood to the patient.

[0054] When it is desired to end a hemodialysis (or hemofiltration) treatment, a flushing solution ("FS") of the invention will be introduced through the needle N (typically from a syringe which is attached to the connecting line 23) to flush the lumen, as depicted in Fig. 2B. After the flush is complete, a locking solution is injected from a container such as a syringe 26 through the line 23/port 22 and into the lumen of catheter 20 to displace the flushing solution and lock the catheter (Fig. 2C). The locking solution will remain in place within the catheter 20. Alternatively or additionally, the locking solution can be a solution of the invention.

[0055] The methods described herein may also be used to flush and lock non-vascular catheters, such as peritoneal dialysis catheters 30, as shown in Figs. 3A-3C. After a peritoneal dialysis treatment, the used dialysate is withdrawn from the catheter 30, as shown in Fig. 3A. After the dialysate has been sufficiently removed, the dialysis catheter 30 is flushed with a flushing solution FS of the invention, as shown in Fig. 3B. After flushing, the locking solution is introduced to the peritoneal dialysis catheter 30, as shown in Fig. 3C, so that it fills the lumen of the catheter, as described previously with the vascular catheters. Alternatively or additionally, the locking solution can be a solution of the invention.

[0056] Referring now to Fig. 4, the use of a locking solution can be enhanced by utilizing an implanted catheter which is formed at least partly from a porous material. When the lumen 40 of the porous catheter body 42 is filled with a solution of the invention, the solution will be able to slowly penetrate (i.e., seep) into the catheter body and outwardly into the tissue T surrounding the catheter, as shown by the arrows in Fig 4. Thus, the antimicrobial properties of the locking solution will not be entirely limited to the interior lumen of the catheter, but will also be effective on the surface of the catheter and in the tissue region immediately surrounding the catheter body. Particularly suitable materials and porosity properties for the catheter bodies have been set forth above.

[0057] Referring now to Fig. 5, kits according to the present invention will include at least a container 60, such as a syringe, for holding a volume of a locking solution of the invention and an implantable catheter lumen to receive the solution. The volume will typically be within the ranges set forth herein. The kits can further contain a package 62 to hold the container 60. The package can be any conventional medical device package, including boxes, tubes, envelopes, trays and pouches. In addition, the kit can contain instructions for use ("IFU") setting forth a method for locking and/or disinfecting an implanted catheter by introducing the solution from the container into a lumen of the implantable catheter between successive uses of the catheter.

EXAMPLES

[0058] The present invention is further defined in the following Examples. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only.

EXAMPLE 1 Evaluation of microbial growth inhibiting solutions

[0059] The following studies provided antimicrobial/antifungal testing of formulated microbial growth inhibiting solutions according to the present disclosure.

Methicillin-Resistant *Staphylococcus Aureus* ("MRSA")

[0060] A stock culture of *Staphylococcus aureus* was maintained as a frozen stock culture at -70°C until use. The bacterial testing used *Staphylococcus aureus* isolated from human blood. A cell suspension was prepared from the frozen stock culture and cultivated in tryptic soy broth ("TSB") to yield approximately 1×10^8 colony forming units ("CFU") per milliliter for MRSA. The final concentration of the inoculum solution was confirmed using plate counts.

[0061] Bacterial testing - For the test, 9.9 ml of each test solution was inoculated with 100 ul of the MRSA cell suspension to yield a final cell concentration of approximately 1×10^6 CFU/ml. This represents a 1:100 dilution of the starting 1×10^8 CFU/ml culture; the initial cell concentration was calculated based on the inoculum plate count. Each test or control solution was evaluated in triplicate. Samples were collected at T = 1 hour.

[0062] Sampling of treated organisms for growth - Each sample was serially diluted in PBS (pH 7.0) and plated in duplicate on tryptic soy agar ("TSA") plates. All plates were incubated inverted at 37°C for 24 hours. For the remaining volume of the treated sample: 1) Each sample was filtered through a 0.22 μ m filter membrane, and 2) Each filter was rinsed with 15 ml sterile water. The filter was placed directly onto a TSA plate and incubated without inversion for 24 hr at 37°C.

[0063] Analyses - The CFU/ml for each solution was logarithmically transformed (base 10). In cases where the plate counts were zero, a value of 0.5 was substituted for one of the zero counts. This substituted value was scaled, based on the dilution plated or volume filtered. The results of three experiments were averaged to determine the mean log density and the associated standard deviation was calculated. Log reductions were calculated for the cultures treated with locking solution by subtracting the mean log density at 24 hrs from that at time zero.

Pseudomonas aeruginosa

[0064] *Pseudomonas aeruginosa* (a representative gram negative bacterium) was grown to a defined log phase growth in culture. Representative samples of the culture were incubated/treated for a defined time with various vehicle (solvent) or locking solutions. Aliquots of the treated samples were plated on agar plates and colony counts performed after sufficient time for growth to assess the efficacy of the lock in killing the organisms of interest.

[0065] Bacterial strain and solution of cultures - A stock culture of *Pseudomonas aeruginosa* to be tested was maintained as a frozen stock culture at -70°C until use. The bacterial testing used *Pseudomonas aeruginosa* isolated from human blood. A cell suspension was prepared from the frozen stock culture and cultivated in TSB to yield approximately 1×10^8 CFU per milliliter for *P. aeruginosa*. For reference, a 0.5 McFarland unit will typically reflect this approximate number of organisms. The final concentration of the inoculum solution was confirmed using plate counts.

[0066] Bacterial testing - For the test, 9.9 ml of each test solution was inoculated with 100 ul of the *P. aeruginosa* cell suspension to yield a final cell concentration of approximately 1×10^6 CFU/ml. Note that this represents a 1:100 dilution of the starting 1×10^8 CFU/ml culture. The initial

cell concentration was calculated based on the inoculum plate count. Each test or control solution was evaluated in triplicate. Samples were collected at T = 1 hour. Each sample was serially diluted in PBS (pH 7.0) and plated in duplicate on TSA plates. All plates were incubated inverted at 37°C for 24 hours. For the remaining volume of the treated sample: 1) each sample was filtered through a 0.22 µm filter membrane, and 2) each filter was rinsed with 15 ml sterile water. The filter was placed directly onto a TSA plate and incubated (without inversion) for 24 hrs at 37°C.

[0067] Analyses - The CFU/ml for each solution was logarithmically transformed (base 10). In cases where the plate counts were zero, a value of 0.5 was substituted for one of the zero counts. This substituted value was scaled, based on the dilution plated or volume filtered. The results of three experiments were averaged to determine the mean log density and the associated standard deviation was calculated. Log reductions were calculated for the cultures treated with locking solution by subtracting the mean log density at 24 hrs from that at time zero.

Candida albicans

[0068] *Candida albicans* (a representative fungus/yeast) was grown to a defined log phase growth in culture. Representative samples of the culture were incubated/treated for a defined time with various vehicle (solvent) or locking solutions. Aliquots of the treated samples were plated on agar plates and colony counts performed after sufficient time for growth to assess the efficacy of the locking solution in killing the organisms of interest.

[0069] A stock culture of *Candida albicans* ATCC was maintained as a frozen stock culture at -70°C until use. The bacterial testing used *Candida albicans* ATCC # 90028 isolated from human blood. A cell suspension was prepared from the frozen stock culture and cultivated in TSB to yield approximately 1×10^8 CFU per milliliter for *C. albicans*. For reference, a 0.5 McFarland unit will typically reflect this approximate number of organisms. The final concentration of the inoculum solution was confirmed using plate counts.

[0070] Bacterial testing - For the test, 9.9 ml of each test solution was inoculated with 100 µl of the *C. albicans* cell suspension to yield a final cell concentration of approximately 1×10^6 CFU/ml. Note that this represents a 1:100 dilution of the starting 1×10^8 CFU/ml culture. The initial cell concentration was calculated based on the inoculum plate count. Each test or control solution was evaluated in triplicate. Samples were collected at T = 1 hour.

[0071] Sampling of treated organisms for growth - Each sample was serially diluted in PBS (pH 7.0) and plated on TSA plates. All plates were plated in duplicate and incubated inverted at 37°C for 24 hours. For the remaining volume of the treated sample: 1) each sample was filtered through a 0.22 µm filter membrane, and 2) each filter was rinsed with 15 ml sterile water. The filter was placed directly onto a TSA plate and incubated (without inversion) for 24 hr at 37°C.

[0072] Analyses - The CFU/ml for each solution was logarithmically transformed (base 10). In

cases where the plate counts were zero, a value of 0.5 was substituted for one of the zero counts. This substituted value was scaled, based on the dilution plated or volume filtered. The results of three experiments were averaged to determine the mean log density and the associated standard deviation was calculated. Log reductions were calculated for the cultures treated with locking solution by subtracting the mean log density at 24 hrs from that at time zero. Table 3 shows the summary of results for study 1.0 discussed above.

Table 3: Summary of Study 1.0

Solution	Disodium EDTA Mg/mL	Citrate Buffer mM	Sodium Caprylate mg/mL	D5W 1/4NS	<i>Candida albicans</i>	MRSA	<i>Pseudomonas aeruginosa</i>
					ATCC #90028 CFU*	ATCC #700699 CFU*	ATCC #27853 CFU*
1	0.0625	1.5	0.071		TNTC	TNTC	486
2	0.125	3	0.143		TNTC	TNTC	50
3	0.25	6	0.287		TNTC	TNTC	243
4				QS	TNTC	TNTC	TNTC
5	0.5	12	0.575		0	0	1
6	1.0	24	1.15		0	40	0
7		48			TNTC	TNTC	84
Positive Control					1.8X10 ⁷	1.19X10 ⁸	1.27X10 ⁸

Final pH: 5.0
 Reported values are average of three samples
 *CFU: Colony forming units
 TNTC: Too numerous to count

Table 4: Study 2.0 Concentration Summary

Solution Final pH: 4.8	Lot #	Disodium EDTA mg/mL	Citrate Buffer mM	Sodium Caprylate mg/mL
1	0906301	0.5	25	0
2	0906302	0.5	25	1.15

Table 5: Summary of Study 2.0

Solution	<i>Staph aureus</i> Antibiotic Sensitive	<i>Staph epidermidis</i>	<i>Enterococcus faecalis</i> VRE, Antibiotic Resistant	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Serratia marcescens</i>
	ATCC #6538 CFU*	ATCC #12228 CFU*	ATCC #700802 CFU*	ATCC #8739 CFU*	ATCC #BAA-1705 CFU*	ATCC #8100 CFU*
1	7.3X10 ⁵	4.5X10 ⁵	1.9X10 ⁶	1.58X10 ⁶	7.0X10 ⁵	3.3X10 ⁶
2	0	0	0	0	13	0
Positive Control	2.9X10 ⁸	1.2X10 ⁸	2.9X10 ⁸	1.4X10 ⁸	1.1X10 ⁸	2.9X10 ⁸

Reported values are average of three samples

*CFU: Colony forming units

TNTC: To numerous to count

[0073] The protocols for *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* VRE, *Escherichia coli*, *Klebsiella pneumoniae*, and *Serratia marcescens* were similar or identical except for the microorganism tested. It is clear from study 1.0 that sodium caprylate at a concentration of 0.575 mg/mL and disodium EDTA at a concentration of 0.5 mg/mL pH adjusted to 5.0 with a citrate buffer was effective for a 7-8 log reduction of major medically important microorganisms. In addition, sodium caprylate and disodium EDTA at a concentration as low as 0.0625 mg/mL pH was effective for a 6-7 log reduction of at least one medically important microorganism (e.g., *Pseudomonas aeruginosa*). Overall, study 1.0 demonstrated that the microbial growth inhibiting solutions having a C₄-C₉ carboxylate antimicrobial agent and a chelating agent were synergistic at concentrations of 1 mg/mL chelating agent or lower.

[0074] As shown in Tables 4-5 (study 2.0), disodium EDTA in a citrate buffer at the reported concentration resulted in a 2 log reduction but was not capable of complete kill of the tested organisms. However, the addition of 1.15 mg/mL of sodium caprylate to the base disodium EDTA citrate buffer resulted in an 8 log reduction of test organisms.

[0075] From studies 1.0 and 2.0, the effective concentrations of the chelating agent evaluated were well below previously reported concentrations and at a concentration that could greatly reduce the potential risk of sudden cardiac death associated at higher dosages. In addition, the evaluated microbial growth inhibiting solutions were capable of maintaining intravenous catheters in the "Locked" no flow state at the composition proposed as demonstrated in Fig. 6.

[0076] At concentrations of microorganisms one might expect to see in indwelling intravenous access devices, it was concluded that the microbial growth inhibiting solutions having concentrations of chelating agents according to the invention were capable of maintaining these devices and effectively reducing or eliminating the microorganisms as a source of systemic infection.

[0077] It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art.

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

- 5 **1.** Opløsning til inhibering af mikrobiel vækst, omfattende et C₄-C₉-carboxylat-antimikrobielt middel, der omfatter natriumcaprylat, en buffer, der omfatter citrat, og et chelateringsmiddel, der omfatter dinatriumethylendiamintetraeddikesyre, hvor dinatriumethylendiamintetraeddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,0625 mg/ml til ca. 1 mg/ml, citratbufferen er til stede i en mængde fra ca. 1,5 til ca. 24 mM, og det natriumcaprylat-holdige antimikrobielle middel er til stede i en mængde fra ca. 0,071 mg/ml til ca. 1,15 mg/ml.
- 10
- 2.** Opløsning til inhibering af mikrobiel vækst ifølge krav 1, hvor dinatriumethylendiamintetraeddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,1 mg/ml til ca. 1 mg/ml.
- 15
- 3.** Opløsning til inhibering af mikrobiel vækst ifølge krav 1, hvor dinatriumethylendiamintetraeddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,25 mg/ml til ca. 0,5 mg/ml.
- 20
- 4.** Opløsning til inhibering af mikrobiel vækst ifølge krav 1, yderligere omfattende en farmakologisk acceptabel bæreropløsning.
- 5.** Opløsning til inhibering af mikrobiel vækst ifølge krav 4, hvor den farmakologisk acceptable bæreropløsning omfatter saltvandsopløsning, Ringers opløsning eller vand, der er pH-justeret til 5,2 eller mindre.
- 25
- 6.** Fremgangsmåde til coating af en medicinsk indretning, hvilken fremgangsmåde omfatter:
- at udsætte den medicinske indretning for en opløsning til inhibering af mikrobiel vækst i et tidsrum, der er tilstrækkeligt til at tilvejebringe en coating på den eksponerede overflade af indretningen, hvor opløsningen til inhibering af mikrobiel vækst omfatter et C₄-C₉-carboxylat-antimikrobielt middel, der omfatter natriumcaprylat, en buffer, der omfatter citrat, og et chelateringsmiddel, der omfatter dinatriumethylendiamintetraeddikesyre, og hvor dinatriumethylendiamintetraeddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,0625 mg/ml til ca. 1 mg/ml, citratbufferen er til stede i en mængde fra ca. 1,5 til ca.
- 30
- 35

24 mM, og det natriumcaprylat-holdige antimikrobielle middel er til stede i en mængde fra ca. 0,071 mg/ml til ca. 1,15 mg/ml.

5 **7.** Medicinsk indretning, der er coatet med en opløsning til inhibering af mikro-
biel vækst omfattende et C₄-C₉-carboxylat-antimikrobielt middel, der omfatter
natriumcaprylat, en buffer, der omfatter citrat, og et chelateringsmiddel, der
omfatter dinatriummethyldiamintetraeddikesyre, hvor dinatriummethyldiamin-
tetraeddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,0625
10 24 mM, og det natriumcaprylat-holdige antimikrobielle middel er til stede i en
mængde fra ca. 0,071 mg/ml til ca. 1,15 mg/ml.

15 **8.** Medicinsk indretning ifølge krav 7, hvor den medicinske indretning er ud-
valgt fra gruppen af indretninger bestående af et centralt venekateter, et peri-
fært intravenøst kateter, et arteriekateter, et Swant-Ganz-kateter, et hæmodia-
lysekateter, et umbilikalt kateter, et perkutant ikke-tunneleret silikonekateter,
et tunneleret centralt venekateter med muffe og en subkutan central veneport.

20 **9.** Kit til låsning og/eller skylning af et implanteret kateter, hvilket kit omfatter:
en beholder, der indeholder en volumen af en opløsning til inhibering af mikro-
biel vækst omfattende et C₄-C₉-carboxylat-antimikrobielt middel, der omfatter
natriumcaprylat, en buffer, der omfatter citrat, og et chelateringsmiddel, der
omfatter dinatriummethyldiamintetraeddikesyre, hvor dinatriummethyldiamin-
tetraeddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,0625
25 mg/ml til ca. 1 mg/ml, citratbufferen er til stede i en mængde fra ca. 1,5 til ca.
24 mM, og det natriumcaprylat-holdige antimikrobielle middel er til stede i en
mængde fra ca. 0,5 mM til ca. 8 mM; og
en implanterbar kateterlumen, der modtager opløsningen til inhibering af mi-
krobiel vækst.

30

10. Kit ifølge krav 9, hvor beholderen omfatter en sprøjte.

11. Kit til låsning og/eller skylning af et implanteret kateter, hvilket kit omfatter:

en beholder med et første kammer indeholdende et C₄-C₉-carboxylat-antimikrobielt middel, der omfatter natriumcaprylat, og et chelateringsmiddel i pulverform, der omfatter dinatriummethyldiamintetraæddikesyre, og et andet kammer indeholdende en farmakologisk acceptabel bæreropløsning, 5 hvor dinatriummethyldiamintetraæddikesyre-chelateringsmidlet er til stede i en mængde fra ca. 0,0625 mg/ml til ca. 1 mg/ml, og det natriumcaprylat-holdige antimikrobielle middel er til stede i en mængde fra ca. 0,071 mg/ml til ca. 1,15 mg/ml, når de er blandet med den farmakologisk acceptable bæreropløsning, og hvor det første kammer eller det andet kammer yderligere omfatter en citratbuffer, som er til stede i en mængde fra ca. 1,5 til ca. 24 mM. 10

12. Kit ifølge krav 11, hvor beholderen omfatter en implanterbar kateterlumen.

13. Kit ifølge krav 11, hvor beholderen omfatter en sprøjte.

DRAWINGS

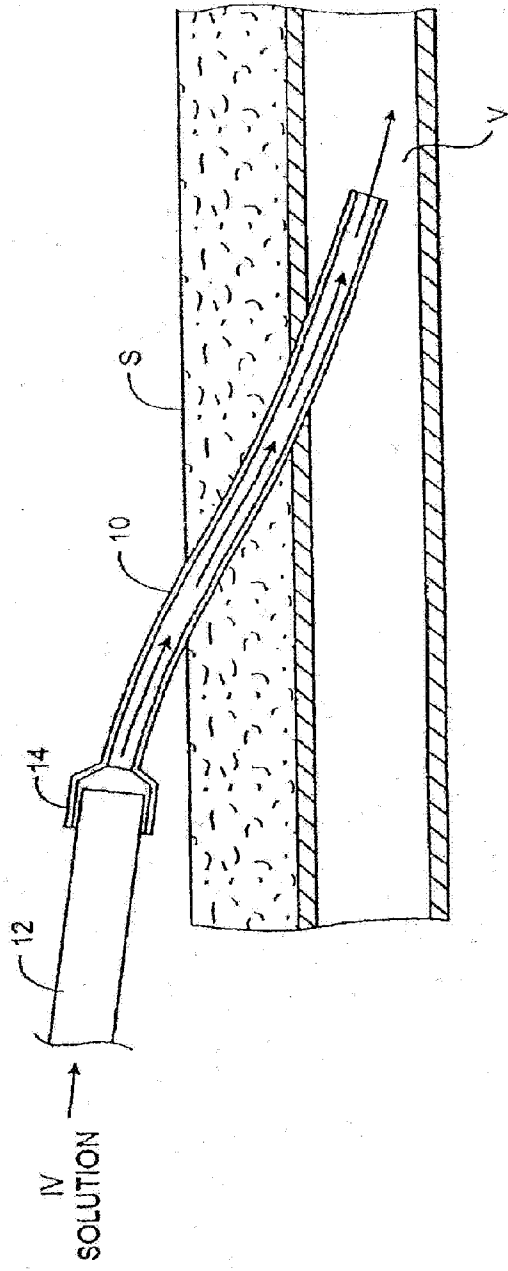


FIG. 1A

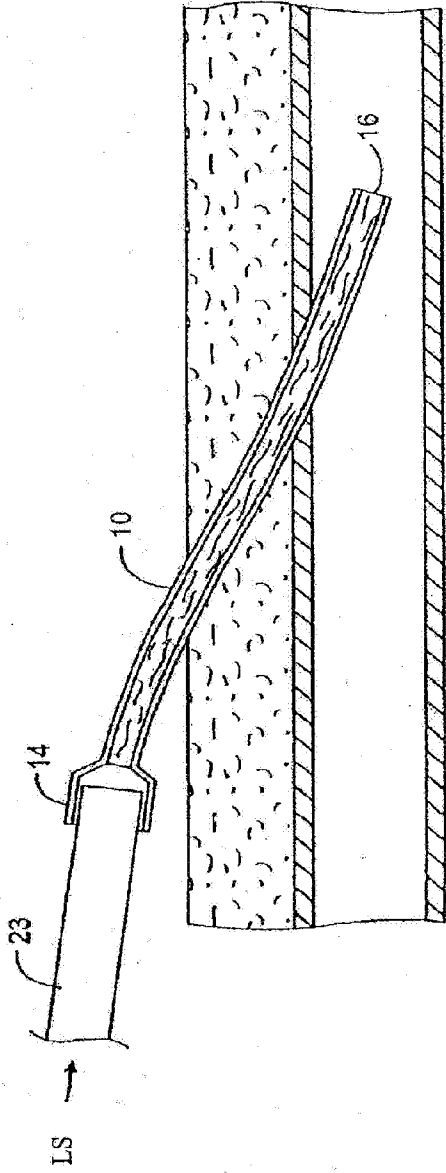


FIG. 1B

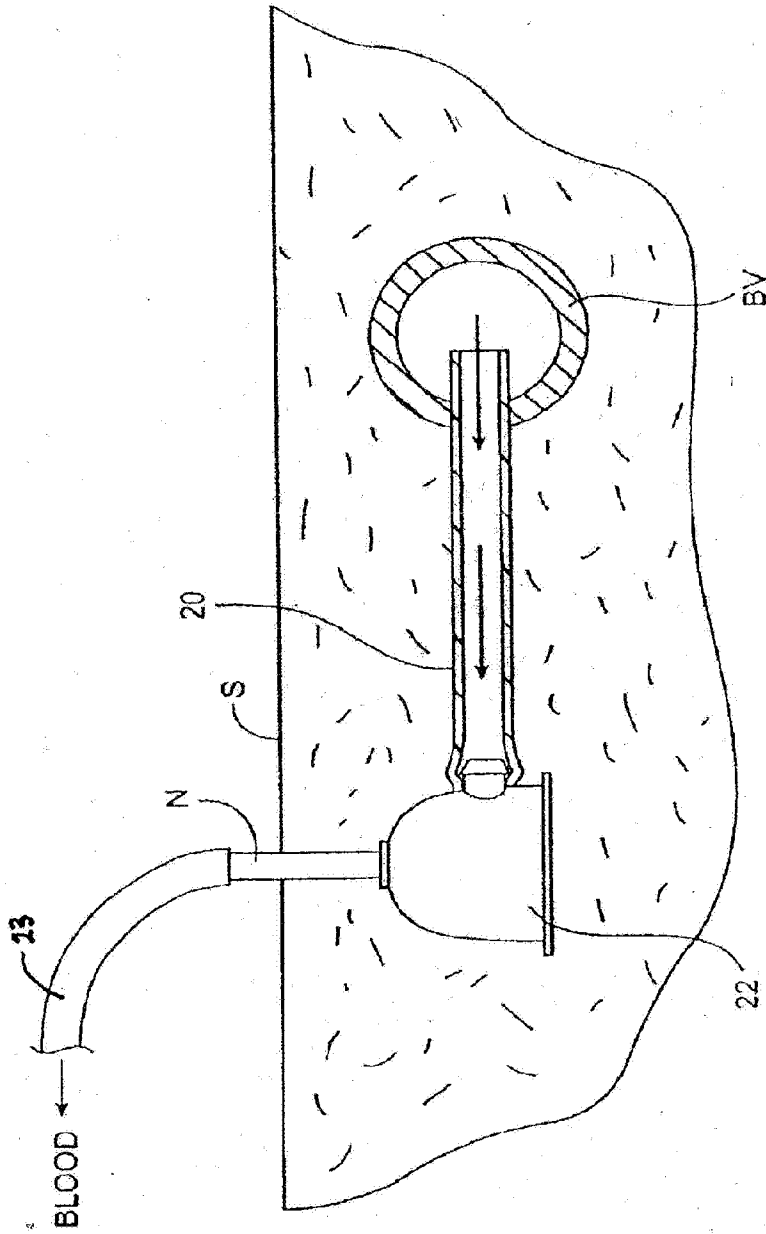


FIG. 2A

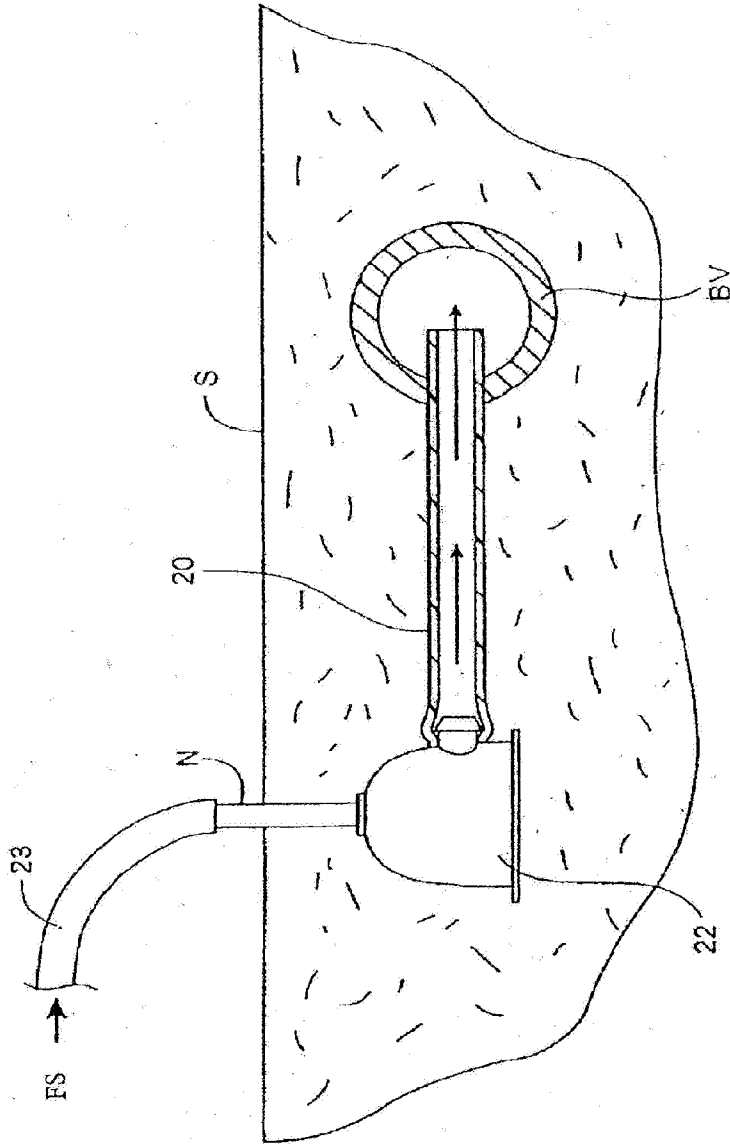


FIG. 2B

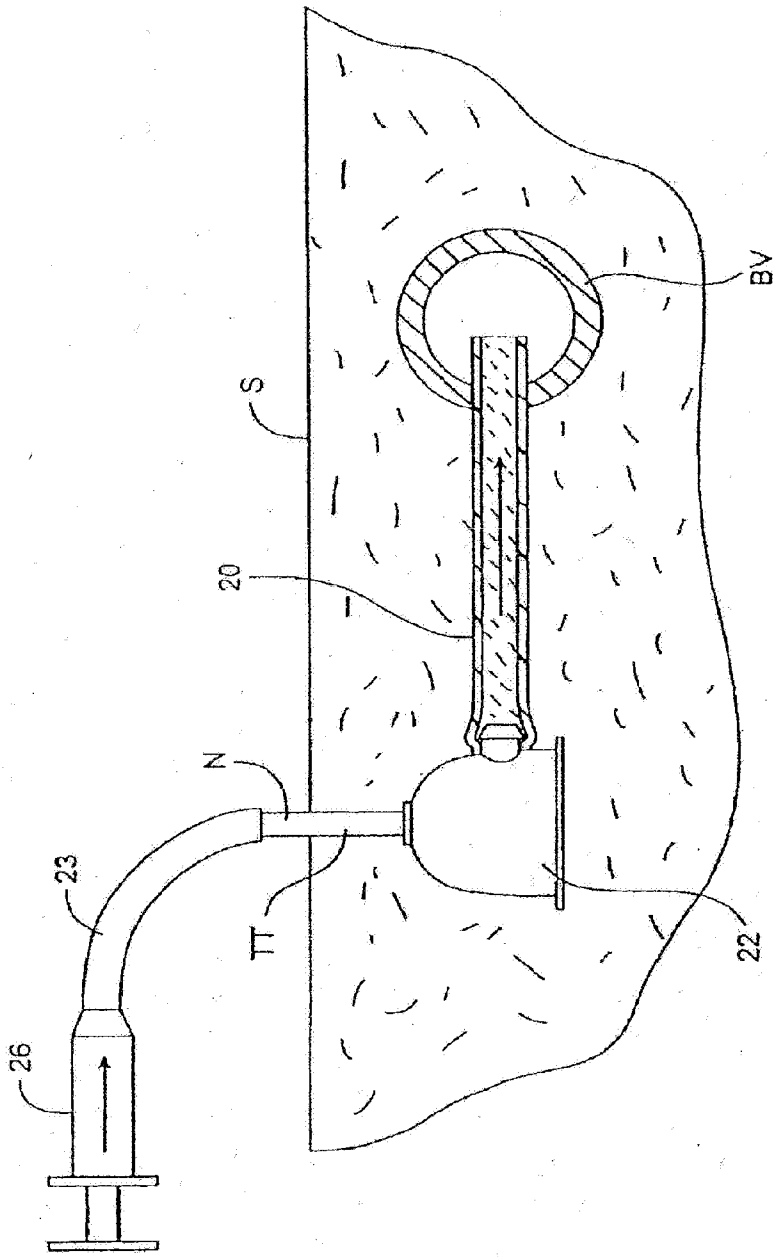


FIG. 2C

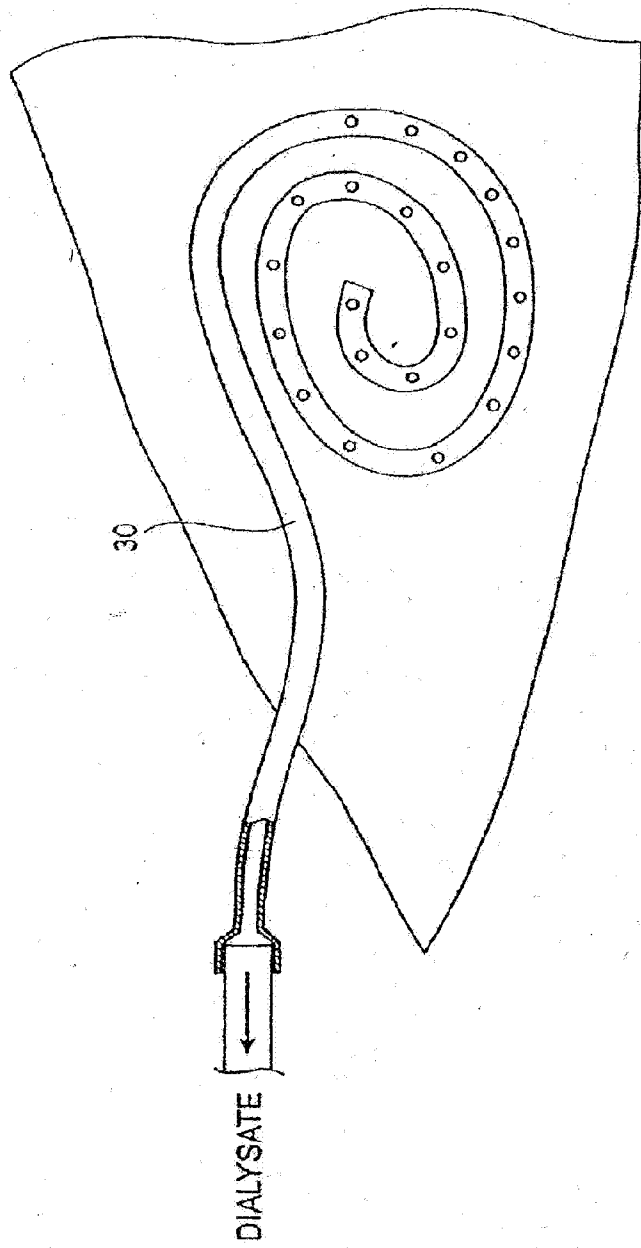


FIG. 3A

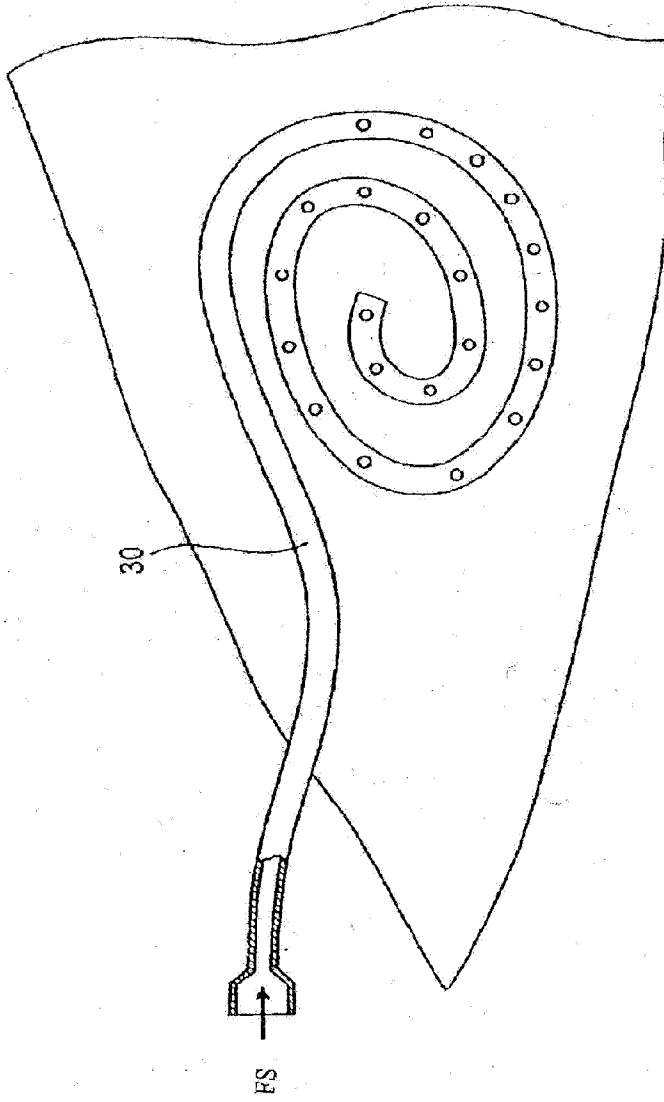


FIG. 3B

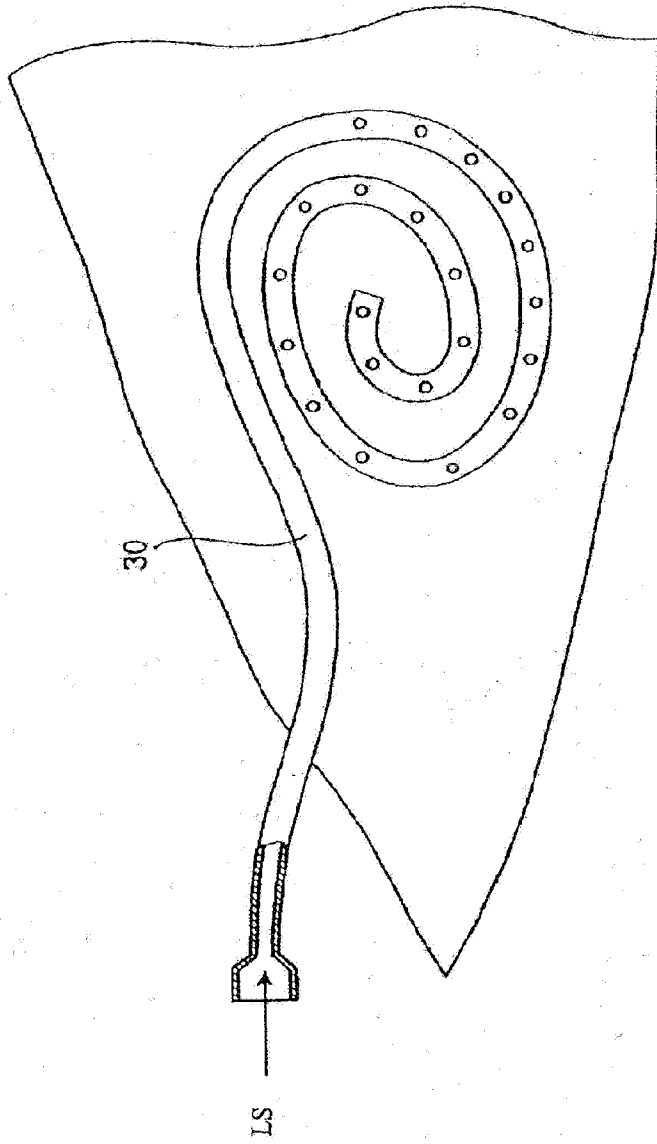


FIG. 3C

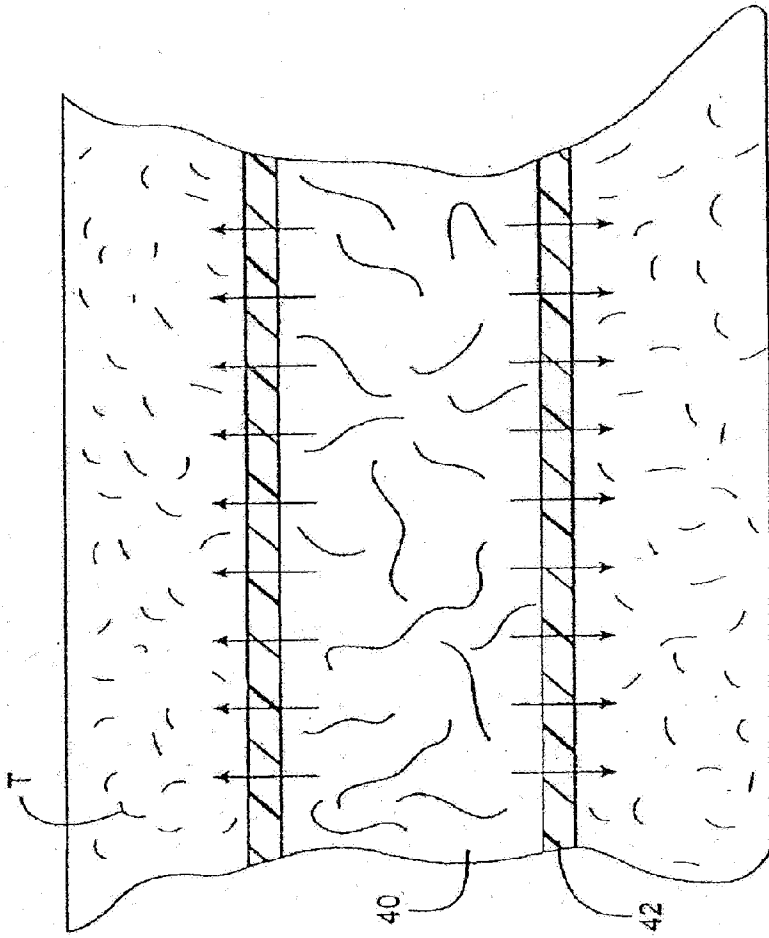
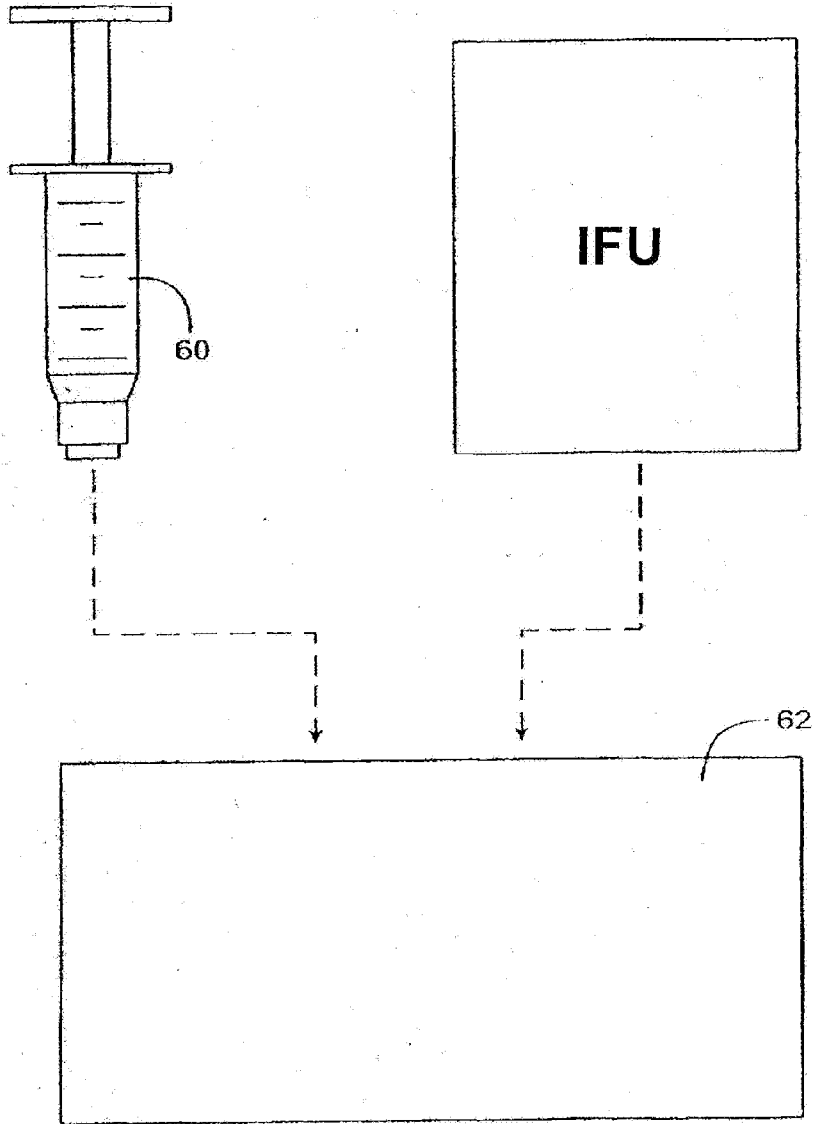


FIG. 4

FIG. 5



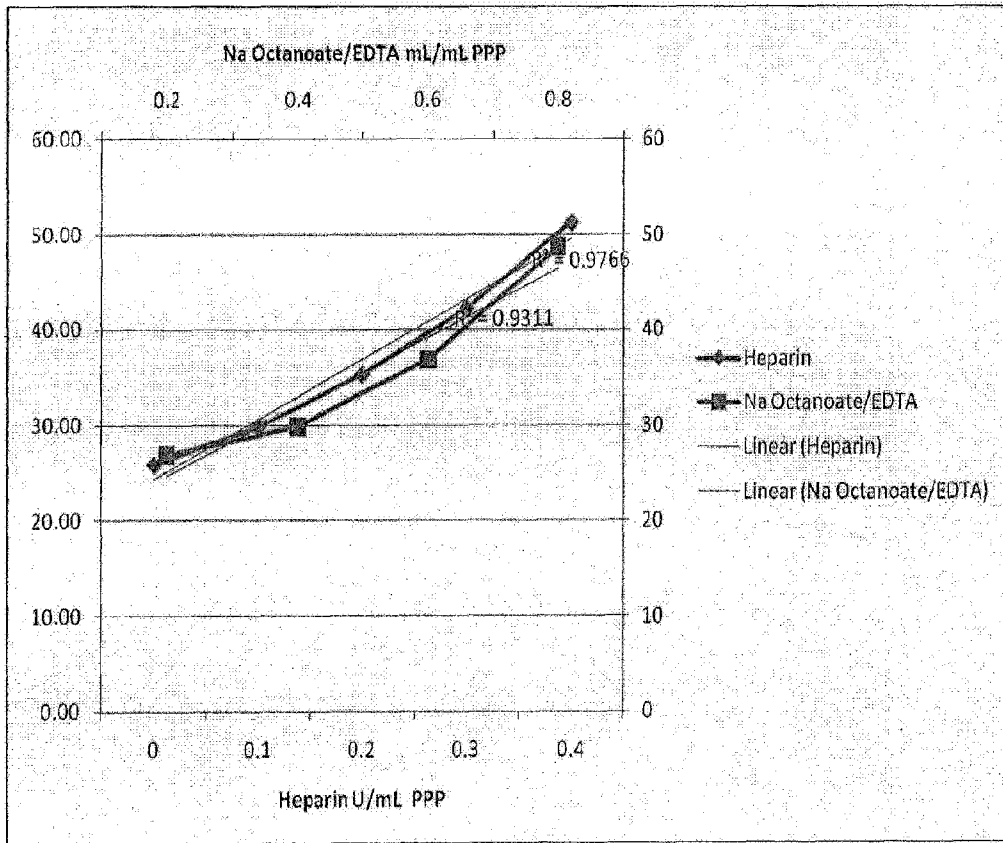


Fig. 6