(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 199 104 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
27.01.2010 Bulletin 2010/04

(21) Application number: **01123563.7**

(22) Date of filing: **01.10.2001**

(51) Int Cl.:
B01L 3/14 *(2006.01)* ***A61B 5/00*** *(2006.01)*
A61L 33/00 *(2006.01)* ***A61L 33/06*** *(2006.01)*
A61B 5/145 *(2006.01)*

(54) Medical article having blood-contacting surface

Medizinischer Gegenstand mit blutkontaktierender Oberfläche

Article médical ayant surface en contact avec le sang

(84) Designated Contracting States:
DE FR GB IT

(30) Priority: **18.10.2000 US 691423**

(43) Date of publication of application:
24.04.2002 Bulletin 2002/17

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EP 1 199 104 B1

Printed by Jouve, 75001 PARIS (FR)

Description

Background of the Invention

[0001] 1. Field of the Invention: This invention relates to a plastic tube having a hemocompatible coating permanently affixed to a blood-contacting surface of the tube.

[0002] 2. Background: There are many applications in the medical device industry where it is desirable that a blood-contacting surface be both compatible with blood and antithrombogenic. Exemplary of such devices is blood collection tubes. Blood samples are routinely collected in glass evacuated tubes. One end of a double-ended needle is inserted into a patient's vein. The other end of the needle then punctures a septum covering the open end of the tube so that the vacuum in the tube draws the blood sample through the needle into the tube. Using this technique, a plurality of samples can be taken using a single needle puncture of the skin.

[0003] In addition, recent advancements in analytical instrumentation have made it possible to carry out a variety of hematological or chemical diagnostic procedures on very small quantities of blood, such as may be obtained by puncture of a patient's finger, earlobe or an infant's heel. Accordingly, a variety of blood sample microcollection devices have been disclosed in the art.

[0004] Plastic tubes have been proposed for blood collection. Plastic offers a number of advantages over glass such as lower breakage, less weight in shipment, and easier disposal by incineration. However, plastics are generally hydrophobic, and blood does not flow smoothly over hydrophobic surfaces. Instead, blood components, such as platelets, fibrin or clotted blood thus generally adhere tenaciously to plastic surfaces and hang up on the walls of plastic collection tubes. This is a particular problem in small diameter gravity actuated microcollection tubes during sample collection or in vacuum tubes during subsequent centrifugation. Thus, in any collection apparatus, it is highly advantageous if the collection tube has a surface which resists adherence to blood components at any stage of the collection process or any subsequent analysis procedure.

[0005] Adherence of blood components generally is not a problem with glass articles, and accordingly, one approach to overcoming this problem in plastic has been to modify the plastic surface to be more glass-like, i.e., to present a hydrophilic surface to the blood. To this end, plastic collection tubes have been treated with a gas plasma to alter the surface chemistry by introduction of heteroatoms. In another approach, the interior wall surface of the plastic tube has been modified by coating with materials such as surface-active agents, water-soluble polymers or water insoluble polymers carrying hydrophilic coatings. For example, U.S. Patent No. 6,077,235 discloses a blood collection tube in which permanent non-adherence is achieved by blending a hydrophilic-hydrophobic copolymer into the tube polymer.

[0006] While the above disclosures have improved blood flow and reduced adherence of blood components to plastic articles, the problem has not been totally solved because the coatings applied to the prior art surfaces are partially or completely removed by the blood so that the surfaces revert back to hydrophobic. There is a need for an article and method therefor which would prevent adherence without introducing any foreign material into the plasma, serum or clot until the intended medical procedure is complete.

[0007] US 5,171,264 discloses a medical article provided for blood contact. The surface of the article is coated with a hydrogel in the form of PEO star molecules. The PEO star molecules are biocompatible and demonstrate non-thrombogenic properties.

[0008] It is an object of the invention to provide a medical article in the form of a tube for taking blood samples which tube prevents adherence of blood without introducing any foreign material into the blood.

SUMMARY OF THE INVENTION

[0009] The plastic tube of the present invention is defined by Claim 1.

[0010] A method to prepare a medical article is defined, according to the invention, by Claim 8.

[0011] In this disclosure the term hydrogel is used to designate a crosslinked polymeric coating on the substrate surface, and the term hydrophilic polymer is used to designate the material which upon crosslinking gives the hydrogel.

[0012] A preferred article is an evacuated polyethylene terephthalate (PET) blood collection tube fitted with a puncturable stopper, and the preferred hydrogel is polyvinyl pyrrolidone (PVP) bound to the inside wall surface of the tube by electron beam or gamma irradiation.

[0013] The hydrogel coating becomes lubricious by absorption of water when in contact with blood, and thereby prevents blood components from adhering to the article. Because the hydrogel is permanently affixed to the article surface, it cannot be washed away by contact with the blood. Further, the coating is applied without use of any environmentally unfriendly solvents, many of which cause plastics to become cloudy and may interfere with visual or instrumental observation of the contents. Finally the article may be sterilize by the radiation used to crosslink the polymer and bind the resulting hydrogel to the substrate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Fig 1 is a perspective view of a typical blood collection tube with puncturable stopper; and

Fig 2 is a longitudinal sectional view of a blood microcollection tube of the invention with mating lip por-

tion.

DETAILED DESCRIPTION

[0015] While this invention is satisfied by embodiments in many different forms, there will herein be described in detail preferred embodiments of the invention with the understanding that the present disclosure is to be considered as exemplary of the principles of the invention and is not intended to limit the invention to the embodiments illustrated and described. The scope of the invention is defined by the appended claims.

[0016] The invention will henceforth be described. It is to be understood that, while the invention is herein disclosed in terms of the preferred blood collection tube, the collection tube may equally well be used for collection of any other body fluid.

[0017] While the tube may be dimensioned to take a blood sample of any volume, preferred tubes are standard size as known in the art. Thus the tube may be a gravity actuated microcollection tube of conventional size, generally 40-50 mm long and 5-10 mm internal diameter. On the other hand, vacuum actuated containers designed for larger samples are generally 50 to 150 mm long and 10-20 mm in diameter. Representative conventional microcollection tubes are fully described in US Patent Nos. 4,967,763 and 5,288,466, and conventional vacuum blood collection tubes are disclosed in US Patent Nos. 4,985,026 and 4,856,533.

[0018] The drawings illustrate a vacuum blood collection tube with stopper and a gravity actuated microcollection tube with mating lip with no intention of limiting the invention to the designs shown. As is fully appreciated by one skilled in the art, the design of the collection tube and stopper is not critical, and the herein described hydrogel coating to prevent adhesion of blood components, clot and fibrin may be imparted to tubes of any design falling under the scope of claim 1.

[0019] Fig 1 illustrates a blood collection assembly which includes a tube 10 having an open end 12, a closed end 14 and a stopper 16 in open end 12. Tube 10 has a bottom wall 18 and a side wall 20 which, together with stopper 16, enclose an interior volume 22 of the tube which preferably is evacuated. Stopper 16 is preferably puncturable and extends into and presses against the inside wall surface 24 of side wall 20 to maintain stopper 16 in place. Puncturable stoppers for evacuated sample collection tubes are standard in the art and may be made of any suitable material, such as KRATON™ (trademark of Shell Corp. for styrene-butadiene copolymer).

[0020] Fig 2 illustrates a typical microcollection assembly 50 of the invention including collection tube 52 and lip 54 to aid in directing a blood sample from a lance wound into the tube. While the drawing shows the tube and lip to be separate, they may equally well be a single integral unit consequent to the molding process and be configured to mate in sealing engagement with a closure or cap (not shown) after sample taking. Inside wall 60 of tube 52, and preferably lip 54, have thereon permanently affixed hydrogel coating 62.

[0021] Suitable tube polymers for receiving the hydrogel coating are, for example, polyolefins such as polyethylene polytetrafluoroethylene and polypropylene (PP), polyesters such as PET, polystyrene, polyurethane, polyvinylchloride, polyacrylic and mixtures or copolymers thereof. PP is preferred for microcollection tubes and PET is preferred for evacuated collection tubes.

[0022] Suitable hydrophilic polymers are polyvinyl alcohol, poly vinyl acetate, polyvinyl pyrrolidone (PVP), polyhydroxyalkyl acrylate, polysterene sulfonate and copolymers or combinations thereof.

[0023] For the most preferred hydrophilic polymer, PVP, the molecular weight may be 25,000 to 2,500,000, preferably 60,000 to 2,500,000, most preferably, 900,000 to 2,500,000.

[0024] The blood collection tube of the invention may be prepared by coating the substrate with the hydrophilic polymer in water solution by any conventional method such as spraying, dipping or filling and aspirating onto the inside wall surface of the tube. In a preferred method, the hydrophilic polymer is dissolved in water at a concentration of about 2-30, preferably about 5-10% by weight, and the viscous solution applied to the substrate by wiping with an applicator sponge adapted to receive a continuous supply of the solution for an easily-automated process.

[0025] The coating on the substrate may then be partially dried by any convenient procedure which maintains the even coating, such as by a current of air or in an oven. The quantity of water rendering on the substrate after drying is not critical, and may conveniently be about 1 to 20, preferably about 2 to 10% by weight of the polymer.

[0026] After partial drying, the coating of hydrophilic polymer on the substrate is crosslinked to obtain the hydrogel by irradiation. A dose of about 0.25 to 1.5 Mrad, preferably about 1.0 to 1.2 Mrad is generally sufficient to effect crosslinking of the PVP and bind the hydrogel to the substrate. Higher doses of radiation may be used but are generally unnecessary for permanent binding and are less economical.

[0027] Irradiation is conveniently carried out by electron beam or gamma radiation from a Cobalt 60 source.

[0028] The tube having the hydrogel bound thereto may be further processed into a standard blood collection tube by closing the open end with a puncturable septum and reducing the pressure to whatever degree of evacuation is needed to give the desired blood draw.

[0029] If it is desired to sterilize the blood collection tube, the sterilization step may also be accomplished with a 1-2 Mrad dose of radiation. It will be apparent to one skilled in the art that all three disclosed irradiation steps, i.e., crosslinking, binding and sterilizing, may be combined into one step by the proper sequence of manufacturing steps.

[0030] Any additive useful in blood analysis, including

both procoagulants and anticoagulants, may be present in the blood collection assembly. In this way, the assembly, by proper selection of additive, may be used across the entire spectrum of blood collection devices. A representative, but not exhaustive list of suitable procoagulants are particulate clot activators such as silica particles and enzyme clot activators, such as elagic acid, fibrinogen and thrombin. If plasma is needed for analysis, an anticoagulant is generally provided to inhibit coagulation during centrifugation. Suitable anticoagulants are chelators such as oxalates, citrates, and EDTA or enzymes such as heparin.

[0031] The tube may contain a conventional thixotropic gel which, on centrifugation, migrates to the interface between the serum and the cells and serves for separation of the layers.

[0032] The plastic blood collection tube of the invention may also be treated by any conventional methodology to enhance its resistance to the passage of moisture or gas which would reduce tube vacuum and affect the blood draw volume. While not wishing to be limited thereby, one commonly used procedure for conferring gas and moisture impermeability is to apply a coating of siliceous material, such as SiOx, to the outside of the tube.

Example 1

[0033] Eighty g of PVP (K120 ISP Wayne, N.J.) and 720 g of deionized water were mixed and the viscous solution was applied to the interior wall of 16 x 100 mm PET tubes using a 14 mm foam disc attached to a rod to give an even thin coating on the tube walls. The coated tubes were exposed to electron beam radiation from a 3.0 MeV Van de Graaff electron accelerator at doses of 0.12, 0.55, 1.0 and 4.7 Mrads to crosslink the PVP and bind it to the tube surfaces.

[0034] To ascertain the permanence of the coating, the irradiated tubes were extracted for 1 hour with water at 37°C, and the extracts were found to be free of dissolved PVP, showing the PVP to be bound to the surface.

[0035] The coated and irradiated tubes were converted to blood collection tubes by adding a conventional clot activator and serum separating gel, fitting with puncturable stoppers and evacuating. The tubes were sterilized with 1.2 Mrad gamma radiation from a Cobalt 60 source. Human blood samples were collected, after conventional clotting and centrifuging, in the tubes and, the tube surfaces were examined. No red cell or clot hangup was seen on the tube surfaces.

[0036] Serum from the blood samples collected in the tubes of the invention were used in a standard "chem screen 25" analyte study. No clinically significant differences in analyte assays were seen compared to serum controls collected in commercial evacuated blood collection tubes.

Example 2

[0037] In the same was as described in Example 1, blood sample tubes were prepared using a 4% aqueous solution of K120 PVP. These tubes, as those of Example 1, showed no red cell or clot hangup and no appearance of PVP in the water extract.

Example 3

[0038] In the same way as described in Example 1, blood sample tubes were prepared using a 10% aqueous solution of K90 PVP. These tubes, as those of Example 1, showed no red cell or clot hangup and no appearance of PVP in the water extract.

Example 4

[0039] If plasma is the desired product, Example 1 maybe repeated using an anticoagulant instead of the clot activator.

Comparative Example 5

[0040] Coated tubes were prepared as in Example 1 but not irradiated. When these tubes were subjected to the water extraction, PVP was found in the extracts.

Claims

1. A plastic tube (10, 50) having an open end (12), a closed end (14), a bottom wall (18), a side wall (20) and an inside wall surface (24, 60) being coated with a hydrogel coating (26, 62),
characterized in that the hydrogel coating (26, 62) is selected from crosslinked polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrrolidone, polyhydroxyalkyl acrylate, polystyrene sulfonate and copolymers or combinations thereof, wherein said hydrogel coating (26, 62) has been permanently bound to said inside wall surface (24, 60) by irradiation so as to be impervious to removal by blood.

2. The plastic tube (10) of claim 1 further comprising a stopper (16) in the open end (12).

3. The plastic tube (10) of claim 2, wherein the tube is evacuated.

4. The plastic tube (10) of claim 2, wherein the stopper (16) is puncturable.

5. The plastic tube (10) of any of claims 1 to 4 further comprising a thrombogenic agent, an antithrombogenic agent or a serum separating gel therein.

6. The plastic tube (10) of any of claims 1 to 5 wherein

said plastic is selected from the group consisting of a polyolefin, polyester, polystyrene, polyvinyl chloride, polyurethane, polyacrylic, polytetrafluoroethylene and copolymers and mixtures thereof.

7. The plastic tube (10) of any of claims 2 to 6 being a blood collection tube.

8. A method to prepare the plastic tube (10, 50) of claim 1 having a blood contacting surface comprising:

(a) coating the inside wall surface (24, 60) of a plastic tube (10, 50) having an open end (12), a closed end (14), a bottom wall (18), a side wall (20) and an inside wall surface (24, 60) with a hydrophilic polymer in water solution, said hydrophilic polymer selected from polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrrolidone, polyhydroxyalkyl acrylate, polystyrene sulfonate and copolymers or combinations thereof to obtain a coated surface; and
(b) irradiating said coated surface to crosslink said hydrophilic polymer to obtain said hydrogel coating (26, 62) and to bind it to said inside wall surface (24, 60).

Patentansprüche

1. Kunststoffröhrchen (10, 50) mit einem offenen Ende (12), einem geschlossenen Ende (14), einer Bodenwand (18), einer Seitenwand (20) und einer Innenwandfläche (24, 60), die mit einer Hydrogelbeschichtung (26, 62) beschichtet ist;
dadurch gekennzeichnet, dass die Hydrogelbeschichtung (26, 62) aus vernetztem Polyvinylalkohol, Polyvinylacetat, Polyvinylpyrrolidon, Polyhydroxyalkylacrylat, Polystyrolsulfonat und Copolymeren oder Kombinationen davon ausgewählt ist, wobei die Hydrogelbeschichtung (26, 62) durch Bestrahlung permanent an die Innenwandfläche (24, 60) gebunden ist, so dass sie unempfindlich gegen Entfernung durch Blut ist.

2. Kunststoffröhrchen (10) gemäß Anspruch 1, das weiterhin einen Stopfen (16) im offenen Ende (12) umfasst.

3. Kunststoffröhrchen (10) gemäß Anspruch 2, wobei das Röhrchen evakuiert ist.

4. Kunststoffröhrchen (10) gemäß Anspruch 2, wobei der Stopfen (16) durchbohrbar ist.

5. Kunststoffröhrchen (10) gemäß einem der Ansprüche 1 bis 4, das weiterhin ein thrombogenes Mittel, ein antithrombogenes Mittel oder ein Serumtrenngel enthält.

6. Kunststoffröhrchen (10) gemäß einem der Ansprüche 1 bis 5, wobei der Kunststoff aus der Gruppe ausgewählt ist, die aus einem Polyolefin, Polyester, Polystyrol, Polyvinylchlorid, Polyurethan, Polyacryl, Polytetrafluorethylen und Copolymeren und Gemischen davon besteht.

7. Kunststoffröhrchen (10) gemäß einem der Ansprüche 2 bis 6, bei dem es sich um ein Blutsammelröhrchen handelt.

8. Verfahren zur Herstellung des Kunststoffröhrchens (10, 50) gemäß Anspruch 1, das eine Blutkontaktfläche aufweist, umfassend:

(a) Beschichten der Innenwandfläche (24, 60) eines Kunststoffröhrchens (10, 50), das ein offenes Ende (12), ein geschlossenes Ende (14), eine Bodenwand (18), eine Seitenwand (20) und eine Innenwandfläche (24, 60) aufweist, mit einem hydrophilen Polymer in wässriger Lösung, wobei das hydrophile Polymer aus Polyvinylalkohol, Polyvinylacetat, Polyvinylpyrrolidon, Polyhydroxyalkylacrylat, Polystyrolsulfonat und Copolymeren oder Kombinationen davon ausgewählt ist, wobei man eine beschichtete Oberfläche erhält; und
(b) Bestrahlen der beschichteten Oberfläche zur Vernetzung des hydrophilen Polymers, wobei man die Hydrogelbeschichtung (26, 62) erhält und diese an die Innenwandfläche (24, 60) gebunden wird.

Revendications

1. Tube en plastique (10, 50) ayant une extrémité ouverte (12), une extrémité fermée (14), une paroi de fond (18), une paroi latérale (20) et une surface de paroi intérieure (24, 60) étant revêtue d'un revêtement d'hydrogel (26, 62);
caractérisé en ce que le revêtement d'hydrogel (26, 62) est choisi parmi l'alcool de polyvinyle, l'acétate de polyvinyle, la polyvinylpyrrolidone, l'acrylate de polyhydroxyalkyle, le sulfonate de polystyrène et des copolymères ou combinaisons de ceux-ci, réticulés, dans lequel ledit revêtement d'hydrogel (26, 62) est lié de manière permanente à ladite surface de paroi intérieure (24, 60) par irradiation pour être impénétrable à l'élimination par du sang.

2. Tube en plastique (10) selon la revendication 1, comprenant en outre un bouchon (16) dans l'extrémité ouverte (12).

3. Tube en plastique (10) selon la revendication 2, dans lequel le tube est évacué.

4. Tube en plastique (10) selon la revendication 2, dans lequel le bouchon (16) est perçable.

5. Tube en plastique (10) selon l'une quelconque des revendications 1 à 4, comprenant en outre un agent thrombogène, un agent antithrombogène ou un gel séparant le sérum la dedans.

6. Tube en plastique (10) selon l'une quelconque des revendications 1 à 5, dans lequel ledit plastique est choisi dans le groupe consistant en polyoléfine, polyester, polystyrène, polychlorure de vinyle, polyuréthane, polyacryle, polytétrafluoroéthylène et des copolymères et mélanges de ceux-ci.

7. Tube en plastique (10) selon l'une quelconque des revendications 2 à 6, qui est un tube de prélèvement sanguin.

8. Procédé pour préparer le tube en plastique (10, 50) selon la revendication 1 ayant une surface de contact sanguin, comprenant les étapes consistant à:

(a) revêtir la surface de paroi intérieure (24, 60) d'un tube en plastique (10, 50) ayant une extrémité ouverte (12), une extrémité fermée (14), une paroi de fond (18), une paroi latérale (20) et une surface de paroi intérieure (24, 60) avec un polymère hydrophile en solution aqueuse, ledit polymère hydrophile étant choisi parmi l'alcool polyvinylique, l'acétate de polyvinyle, la polyvinylpyrrolidone, l'acrylate de polyhydroxyalkyle, le sulfonate de polystyrène et des copolymères et combinaisons de ceux-ci pour obtenir une surface revêtue; et
(b) irradier ladite surface revêtue pour réticuler ledit polymère hydrophile pour obtenir ledit revêtement d'hydrogel (26, 62) et pour le lier à ladite surface de paroi intérieure (24, 60).

FIG. 1

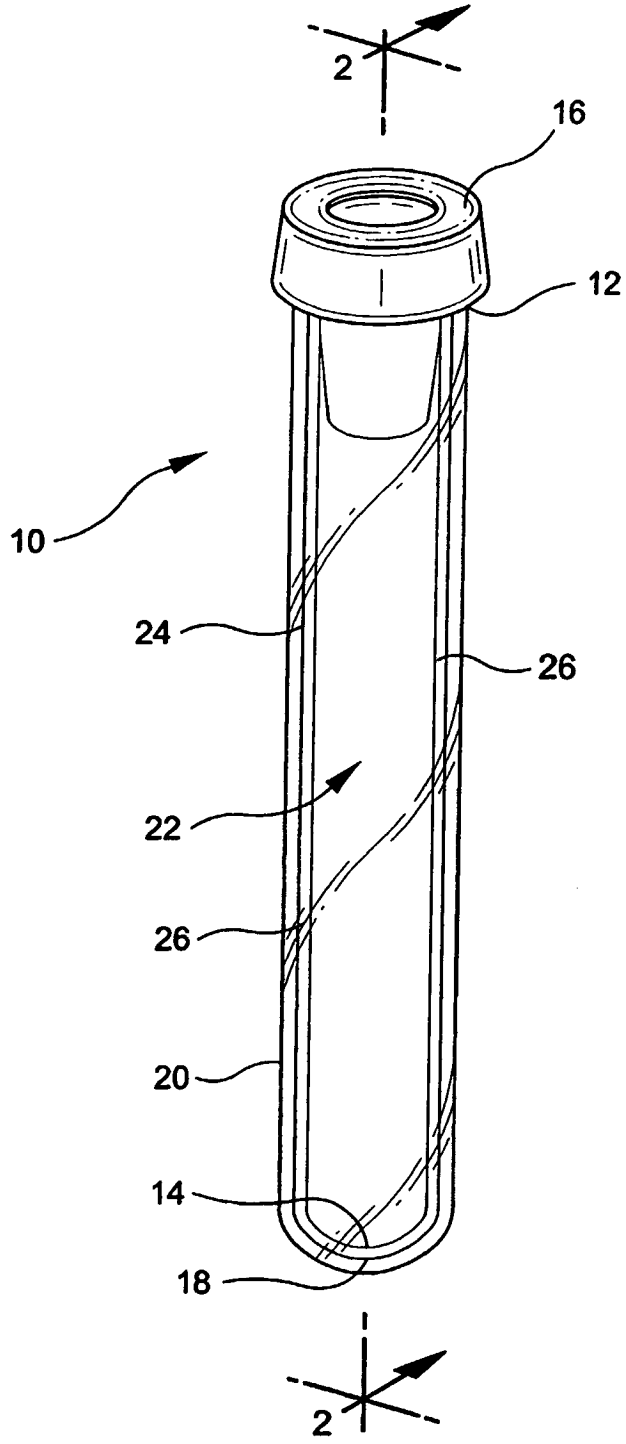
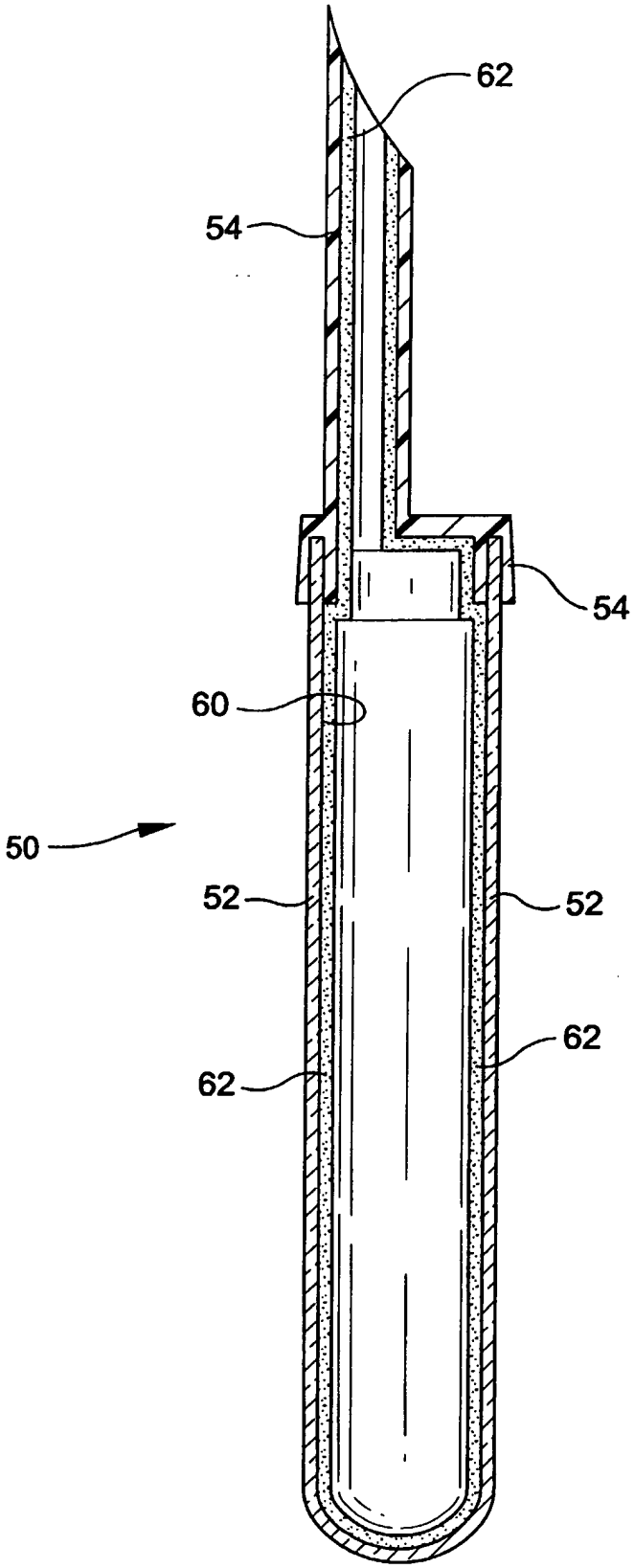


FIG. 2



REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	具有血液接触表面的医疗物品		
公开(公告)号	EP1199104B1	公开(公告)日	2010-01-27
申请号	EP2001123563	申请日	2001-10-01
[标]申请(专利权)人(译)	贝克顿·迪金森公司		
申请(专利权)人(译)	碧迪公司		
当前申请(专利权)人(译)	流式细胞Dickinson公司		
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发明人	COHEN, RICHMOND R. KEUSCH, PRESTON		
IPC分类号	B01L3/14 A61B5/00 A61L33/00 A61L33/06 A61B5/145 A61B5/154 A61B5/15 A61B17/00 A61B17/12 A61J1/05 A61M25/00		
CPC分类号	B01L3/5082 A61B5/15003 A61B5/150351 A61B5/150389 A61B5/150503 A61B5/150755 A61L33/0064 A61L33/064		
优先权	09/691423 2000-10-18 US		
其他公开文献	EP1199104A2 EP1199104A3		
外部链接	Espacenet		

摘要(译)

塑料医疗制品，例如导管或血液收集管，涂覆有永久地结合到管内壁的交联水凝胶。由水凝胶提供的亲水表面防止血液成分粘附到表面，并且水凝胶的永久粘附防止其被血液去除。

FIG. 1