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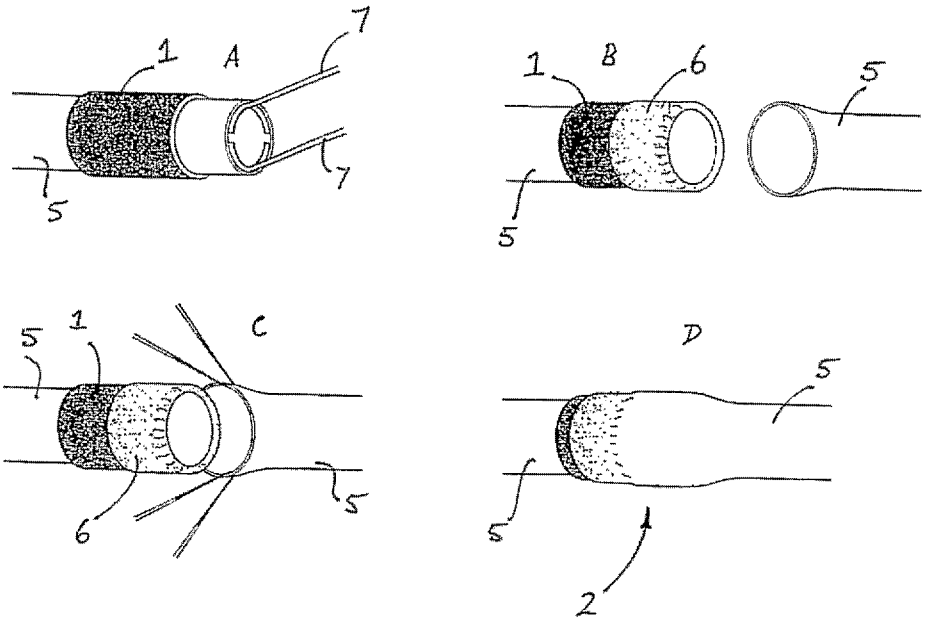

(57) Abstract: The present invention relates to a method for joining biological tissues, and in particular for making an anastomosis. In its preferred form, the method includes the steps of connecting tubular tissue to be anastomosed with a tube implant comprising a solid biomolecular solder. One or more medical glue, adhesive or sealants are then used to adhere the tube implant to the tubular tissue such that the anastomosis is sealed. The tube implant allows end-to-end or end-to-side vascular anastomoses.

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"Method of Tissue Repair III"

Technical Field

The present invention relates to improved methods for joining living tubular tissues; organs and their coverings; skin and appendages; as well as the various internal and peripheral nerves of the body, the spinal cord and its ramifications.

Background Art

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

In repairing living tissues, sutures, staples or clips are routinely used to close defects, join planes of tissues or to join bodily tubes together (anastomoses).

This involves the placing of materials in the body which cause some damage to the tissues involved, but hold those tissues in apposition while the body's own healing processes effect a more permanent join. The damage that various joining materials cause varies but even careful placement of microsutures in the smallest of bodily tubes during, for example, a vascular anastomosis, produces a fibrous tissue reaction around each of the suture materials left *in situ.*

Joins, however made, take time, and those joins made by placing individual sutures in tubular joins are the most time consuming. Sewing in a ring of sutures to effect such a join inside the body may demand a large incision to obtain the access required to effect

enough surgical freedom to manipulate the equipment and instruments required. Microsuturing requires considerable skill.

Protein solders have been described in vascular surgical research as a method to join tissue. One example of a protein solder is described in WO96/22054. An improved protein solder is described in WO99/65536. WO99/65536 describes *inter alia* a device for sutureless vascular anastomoses, comprising a tube made from at least partially denatured protein and, optionally, a light-absorbing dye. In brief, proteinaceous material is mixed into a paste. The paste can then be extruded or moulded into a tube or other shape as described. Tube devices prepared accordingly are then treated to cause at least partial denaturation of the protein, causing the tubes to become temporarily insoluble in body fluids. Using the energy absorbing properties of a dye, optionally added to the paste during its preparation, a fibre-coupled diode laser is used to transfer heat to the device, making it possible to weld vascular tissue during the anastomotic procedure more efficiently.

The device of WO99/65536 has the advantage that it is protein based and hence biologically "inert" and biodegradable, unlike conventional sutures or vascular staples. It also has the advantage that when it is hydrated it becomes flexible, allowing movement in the vessel. As the tube can be made with a human protein it is less likely to cause an adverse hypersensitivity reaction in patients, compared with conventional sutures or staples.

Surgical glues, medical adhesives and sealants are achieving increased acceptance in the clinical setting for the closure of surgical and traumatic wounds. First generation surgical glues lacked strength and flexibility.

State of the art surgical glues and medical adhesives, such as octyl cyanoacrylates and butyl cyanoacrylates, exhibit low cell toxicity and improved bond strength. Despite

these improvements, for many applications such as in vascular reconstruction, conventional suturing is still relied upon for the closure of tissue joins. This is because closures achieved with surgical glues and medical adhesives are too problematic for many applications to avoid the need for sutures. The advantages of surgical glues and medical adhesives include them being relatively inexpensive compared with using staples or laser based methods for tissue approximation; they deskill the operating procedure (compared to sutures); they require minimal additional surgical tools or instruments; they are rapid to apply; and their polymerisation is often a simple process.

Recently, surgical glues have been tested in combination with stay sutures in an effort to reduce the number of sutures required and the consequential inflammation and foreign body reaction. The need exists for alternative methods of securing tissue joins.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art or to provide a useful alternative.

Summary of the Invention

According to a first aspect the present invention provides a method of connecting a solid biomolecular solder to a biological tissue comprising adhering the solder to the tissue with one or more of a medical adhesive, glue or sealant.

According to a second aspect the present invention provides a method for joining biological tissues comprising the steps of:

applying a solid biomolecular solder to the biological tissues to be joined; and

adhering the solder to at least one of the tissues by means of one or more of a medical adhesive, glue or sealant.

The present inventors have surprisingly found that one or more surgical glues, medical adhesives or sealants used in conjunction with a substantially solid proteinaceous biomolecular solder allows for the circumvention of serious drawbacks associated with the use of sutures or mechanical devices to secure a tissue join. The present invention allows for rapid, effective sealing and securing of a tissue join through the combined use of a solid biomolecular solder as described in WO99/65536, the disclosure of which is incorporated entirely herein by reference, and one or more surgical glues, medical adhesives or sealants. In addition to providing effective sealing, the resulting tissue repair is physically supported by the solder during the healing process.

The solid biomolecular solder is according to the formulations, shapes and configurations provided by WO99/66536. The biomolecular solder technology of WO99/66536 includes a tubular device for performing vascular anastomosis. The tubular device is a tube implant allowing for end-to-end or end-to-side vascular anastomoses.

The biomolecular solder preferably comprises at least one partially denatured biomolecule. Preferably moistening the biomolecular solder alters its mechanical properties such that it exhibits similar mechanical properties to the biological tissues to be joined. In one embodiment the biomolecule(s) may be proteinaceous. Alternatively, the biomolecule(s) may be an analogue of a biological, biodegradable polypeptide in the form of a synthetic polypeptide or other molecule capable of forming the biomolecular solder. Preferably the biomolecular solder does not cause adverse reaction in the biological tissues to be joined.

In other embodiments, the biomolecule is a protein or a mixture of proteins which are biodegradable in the relevant host. Preferably the protein or proteins are selected from the

group consisting of albumins, collagen, fibrinogen and elastin. Desirably, the body can resorb the protein or proteins. If a mixture of proteins is used the proteins in the mixture have similar denaturation temperatures. Preferably the proteins in the mixture are albumin and collagen. In yet further embodiments, the protein is chosen from the group consisting of bovine, horse, human, rat, ovine and rabbit albumin, wherein the albumin is selected to reduce immunological reaction in the patient to the biomolecular solder. In preferred embodiments the albumin is human albumin chosen to match the patient's blood type, and histocompatibility markers.

Preferably the biomolecule(s) of the biomolecular solder are sufficiently denatured such that said biomolecular solder has sufficient longevity *in vivo* for the biological tissues to be joined.

Optionally, the biomolecular solder includes one or more adjuvants for promoting rapid and/or more complete tissue healing. Preferably the one or more adjuvants are selected from the group consisting of fibrinogen, growth factors, sodium hyluronate, hormones, and anticoagulants. In other optional embodiments, the biomolecular solder comprises one or more fibrous materials for improving the strength of the biomolecular solder. Preferably the one or more fibrous materials are selected from the group consisting of collagen, polytetrafluoroethylene fibre and ceramic fibres. For instance, the fibrous material comprises a biocompatible polymer.

Any medically approved glue, adhesive or sealant may be applicable to the present invention. Preferably, the one or more glue, medical adhesive or sealant is selected from the group of glue/adhesive/sealant family groups consisting of ethyl cyanoacrylates, butyl cyanoacrylates, octyl cyanoacrylates, polyethylene glycols, polyurethanes, glues or

adhesives combined with polymethylmethacrylate, glues or sealants combined with di-acrylate, proteins with a cross-linking agent, such as albumin and glutaraldehyde, hydrogels, alginates, fibrin and gelatin-resorcinol-formal (GRF). More preferably, the glue or adhesive is selected from the group consisting of ethyl cyanoacrylates, butyl cyanoacrylates, octyl cyanoacrylates and methyl methacrylates. Especially preferred is an octyl cyanoacrylate. Most preferably, the glue is 2 - octyl cyanoacrylate.

It will be appreciated by the person skilled in the art that the quantity of medical glue, adhesive or sealant required will be determined by the type and location of the tissue join. Adherence of the solder to the biological tissue may be achieved by applying the glue, medical adhesive or sealant continuously along the perimeter of the solder-tissue junction, or, at separate, advantageous locations in order to secure the junction. Where appropriate, the glue, medical adhesive or sealant may be allowed to polymerize for a predetermined period of time following application to the tissue, to prevent further, undesired, tissue adhesion.

The method of the present invention is applicable to various surgical procedures requiring the joining of biological tissues such as vascular anastomosis, sealing of tissue discontinuities, catheter puncture closure, sealing lacerations of the liver, spleen, lungs or other solid organs, colorectal anastomosis, improved approximation of large dermal breaches, neural and nepheral junctions or seals and other biological joins.

In a third aspect, the present invention provides a method for making an anastomosis comprising the steps of:

connecting tubular tissue to be anastomosed with a tube implant comprising a solid biomolecular solder; and

adhering the tube implant to both the tubular tissues by means of one or more of a medical adhesive, glue or sealant such that the anastomosis is sealed.

According to one embodiment of the invention, the anastomosis is a vascular anastomosis. The medical glue or adhesive is required to seal the vascular anastomosis and provide mechanical interlocks between the vascular tissue and the tube implant, while the protein-based tube implant provides structure and support to the anastomotic site.

As used in the context of the present invention, "tube implant" refers to the biomolecular solder formed into the shape of a tube, as described in WO99/66536. This device is also referred to herein as a "solder tube". The tube implant may include a flange at one or both ends, or may be flange-less. The tubular device may have a round or oval profile, or may be square or crenulated.

In one embodiment of the invention, the anastomosis is an end-to-end anastomosis.

According to another embodiment of the invention, the anastomosis is an end-to-side anastomosis.

Preferably, the tube implant for end-to-side anastomosis comprises a tubular structure having a circumferential flange at either its proximal end or at both ends. Preferably, the flange may be positioned such that it forms either a right angle or an oblique angle with the axis of the tubular structure, as required by the anatomy of the target site at which the end-to-side anastomosis is to be formed. Preferably, an oblique angle of between 0 degrees and 180 degrees is formed between the flange and the axis of the tubular structure. More preferably, the angle is 40 degrees. Preferably, the interior surface of the flange is bevelled or rounded.

In one preferred embodiment, the end-to-side tubular device has an internal diameter that is consistent along its length such that the tubular structure is cylindrical. According to another preferred embodiment, the internal diameter of the tubular structure uniformly decreases along its length towards the proximal end such that the tubular structure is conical. According to a preferred embodiment, the tubular structure is cylindrical and the flange is positioned such that it forms a right angle with the axis of the cylinder. In this configuration, the internal diameter of the flange is equal to the internal diameter of the cylinder. According to further preferred embodiment, the tubular structure is cylindrical and the flange is positioned such that it forms an oblique angle with the axis of the cylinder. In this configuration, the flange is elliptical and having a major internal diameter that is longer than the internal diameter of the cylinder.

According to a further preferred embodiment, the tubular structure is conical and the flange is positioned such that it forms an oblique angle with the axis of the cone. Preferably, the area defined by the internal circumference of the flange is equal to the area defined by the internal circumference of the distal end of the conical tubular structure.

Although the combination of the solder and glue/adhesive/sealant may be sufficient to effect a good seal, staples and/or sutures can also be used with the present invention if desired.

According to a fourth aspect, the present invention provides a kit for joining biological tissues including:

a solid biomolecular solder; and

a tissue compatible adherent comprising one or more of a medical adhesive, glue or sealant.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Brief Description of the Drawings.

Preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1 shows a solid protein cylinder prepared according to the method described in WO99/65536 for preparing a solid biomolecular solder and to be utilized in an embodiment of the present invention.

Figure 2 shows a schema of an operative technique according to one embodiment of the present invention. A.: The tubular solder implant ("solder tube") is pushed over the proximal vessel end and the vessel wall is folded back. B.: Application of glue/adhesive to the edge of the vessel-solder tube junction formed by the foldback . C.: The distal end of the vessel to be joined is gently pulled over the foldback to connect with the solder tube at the desired location. D.: Application of glue/adhesive to the new vessel-solder tube junction formed at the proximal end of the solder tube.

Figure 3 is a schematic cross section of an anastomosis of a blood vessel formed using the sleeve technique.

Figure 4 shows a graft in side and cross sectional view formed using the sleeve technique, as illustrated in Figures 2 and 3, at both ends of the graft.

Figure 5 shows in schematic form, a join formed by placing a solder tube inside a body tube. Solder strips may be used externally to strengthen the anastomosis.

Figure 6 shows end-to-side anastomotic devices for use in an embodiment of the invention. Figure 6E shows an anastomotic device having a flange at both ends for use in an embodiment of the invention.

Figure 7 shows an end-to-side anastomosis utilizing a flanged solder tube. A.: An incision made in the side of a first body tube to be joined end-to-side with a second body tube to form an end-to-side anastomosis. B. and C.: End-to-side anastomoses formed using a solder tube having a flange at its proximal end.

Figure 8 shows butyl cyanoacrylate bonded solder tube implants at 1 week.

Figure 9 shows n-octyl-cyanoacrylate bonded solder tube implants at 1 week.

Detailed Description of the Invention.

The present invention allows for the rapid and effective sealing and securing of a tissue join through the combined use of a solid biomolecular solder 1 as described in WO99/65536, and one or more surgical glues, medical adhesives, or sealants. In addition to providing effective sealing, the resulting tissue repair is physically supported by the solder 1 during the healing process. These features together impart strength and support to repair site 2. The joining of tissues in this manner is also considered to be more efficient than the application of glue/adhesive/sealants to tissue alone, or the combined use of glues and sutures.

WO99/65536 describes *inter alia,* a solid biomolecular solder 1 that comprises an at least substantially solid composition of at least one biomolecule which has been mixed at high concentration with an aqueous solvent, which composition is treated to at least partially denature the biomolecular component(s) of the solder 1 and to at least partly dry the solder 1.

The solder 1 can be provided in a variety of shapes. In particular, the solder 1 is suitable for extruding into tubular forms, a form that cannot readily be achieved with prior art solders. It can also be extruded into a partial tube which has a curved cross section with an elongate open channel which can be wide or narrow. The solder 1 can be prepared with a smooth surface or with a surface that is at least slightly roughened. Roughening may be of assistance in enhancing contact between tissue and solder 1. The roughening may provide a profile which appears smooth at macroscopic level but rough at microscopic level. The tubular and partially tubular forms typically have a round or ovoid profile but other profiles are also contemplated including square, crenulated and other geometric forms. The tubular solder 1 can be tapered or of uniform cross section.

According to a preferred embodiment, the solder 1 is a tubular structure ("solder tube") having a circumferential flange 3 at both ends. According to another preferred embodiment, the solder tube 1 comprises a circumferential flange 3 at one end, its proximal end. These embodiments are well suited for achieving end-to-side anastomoses. Preferably, the flange 3, whether at both ends of the solder tube 1, or at one end, may be positioned such that it forms either a right angle or an oblique angle with the axis of the solder tube (Figure 6A and 6B, respectively), as required by the anatomy of the target site at which the end-to-side anastomosis is to be formed. Preferably, an oblique angle of between 0 degrees and 180 degrees is formed between the flange 3 and the axis of the solder tube 1. More preferably,

the angle is 40 degrees (Figure 6B). Preferably, the interior surface 4 of the flange 3 is bevelled or rounded (Figure 6C).

In one preferred embodiment, the end-to-side solder tube 1 has an internal diameter that is consistent along its length such that the tubular structure is cylindrical (Figure 6A, 6B and 6C). According to another preferred embodiment, the internal diameter of the solder tube 1 uniformly decreases along its length towards the proximal end such that the solder tube 1 is conical (Figure 6D). According to a preferred embodiment, the solder tube 1 is cylindrical and the flange 3 is positioned such that it forms a right angle with the axis of the cylinder (Figure 6A). In this configuration, the internal diameter of the flange 3 is substantially equal to the internal diameter of the cylinder. According to further preferred embodiment, the solder tube 1 is cylindrical and the flange 3 is positioned such that it forms an oblique angle with the axis of the cylinder (Figure 6B). In this configuration, the flange 3 is elliptical and having a major internal diameter that is longer than the internal diameter of the cylinder.

According to a further preferred embodiment, the solder tube 1 is conical and the flange 3 is positioned such that it forms an oblique angle with the axis of the cone (Figure 6D). Preferably, the area defined by the internal circumference of the flange 3 is substantially equal to the area defined by the internal circumference of the distal end of the conical solder tube 1.

The solder tube 1 is well suited to nerve repair applications and is particularly well suited to vascular applications in which the moisture content makes prior art solders unsuitable. The solder, as described in WO99/65536, can be prepared in other shapes as

required for particular applications including strips, patches, solid rods and hollow tubes with at least one flanged end.

Application of the biomolecular solder in the method of the invention.

Achieving anastomosis of biological tubular structures ("body tubes") can involve attaching at least one edge of the circumference of the solder tube 1 to the inside or outside of the cylindrical surface of a body tube 5. The join between a body tube 5 and the solder tube 1 can be achieved by placing both ends of the tube 5 within the solder tube 1 and applying surgical glue, medical adhesive or sealant along the circumference or perimeter of the solder tube 1 – body tube 5 junction (Figure 5), or, by placing both ends of the body tube 5 over the solder tube 1 and applying surgical glue/medical adhesive along the circumference or perimeter of the solder tube 1-body tube 5 junction, or, by placing one end of the body tube 5 within the solder tube 1 and one end over the solder tube 1 and applying surgical glue/medical adhesive along the circumference or perimeter of the solder tube 1-body tube 5 junction (Figure 4). Where the body tube 5 to be repaired includes a damaged section which requires replacement, a graft material with the solder tube 1 applied at least at the graft ends can be joined at either end to a free end of the severed tube (Figure 4).

Where the tissue repair 2 is with respect to nerve tissue or other tissue tubes where the tube contents need to be protected from damage, it is especially important that the surgical glue/medical adhesive should not be applied directly to the free edges of the nerve tissue being joined as this can damage extruded tissue. Rather, the surgical glue/medical adhesive should be placed transverse to the edge of the discontinuity. The biomolecular solder 1 can be used, in conjunction with suitable promoters of neuron growth, in tubular form, to provide guides for nerve regeneration. In this use the severed nerve ends are

inserted into the ends of the solder tube 1 and adhered into place with surgical glue/medical adhesive or sealant.

The biomolecular solder 1 can also be used in tubular form with a sealed end as a cap for the ends of severed nerves to assist patients who experience discomfort, which can be extreme, where severed nerves cannot be rejoined, for instance, in amputation stumps.

Where the tissue to be repaired is an essentially wide hollow body tube 5, the repair can comprise the insertion of a thin-walled hollow cylinder of biomolecular solder 1 inside the tube under repair so that the cylinder spans the severed portions of the body tube 5.

Repairs of body tubes 5 in accordance with the method of the invention can include end-to-side as well as end-to-end tubular repairs.

End-to-end repairs can also be performed by pulling one free end of the body tube 5 to be repaired through the solder tube 1 and folding back a cuff ("foldback") 6 of tissue over the solder tube 1. The solder tube 1 is secured to the body tube 5 by applying surgical glue/medical adhesive at the solder tube 1-body tube 5 junction. The other free end of the body tube 5 to be repaired (second body tube) is then gently sleeved over the foldback until it contacts with the solder tube 1 at the desired distance from the end of the foldback 6, and surgical glue/medical adhesive is applied to the new body tube 5-solder tube 1 junction to secure the repair (Figure 2). A single application of glue/medical adhesive may also serve to secure the end-to-end repair. The single application of surgical glue/medical adhesive is applied at the solder 1/foldback 6/second body tube 5 junction to adhere all three surfaces to one another at once, i.e. the surgical glue/medical adhesive is applied such that it adheres together the solder tube 1, the foldback 6 and the second body tube 5 with a single

application of surgical glue/medical adhesive at the site where the three elements of the repair meet.

End-to-side repairs can be performed by providing a tube 1 with a circumferential flange at one end or at both ends. The following non-limiting example describes an end-to-side repair using a solder tube 1 having a circumferential flange 3 at one end. An x-shaped, round, ovular or straight incision is made in the side of the first body tube 5 to be joined (Figure 7A). The free end of the second body tube 5 to be joined end-to-side is sleeved through the tubular end of the solder tube 1 and folded back over the flange (the "foldback") 6. Preferably, the foldback 6 extends over the flange 3 and along the shaft of the solder tube 1. The body tube 5 and the solder tube 1 are adhered to one another with surgical glue/medical adhesive applied at the circumference of the body tube- flange junction. The second tube 5 having the tubular implant is then placed inside the incision of the first tube and the edges of the incision gently pulled over the solder tube 1 either part way along the foldback 6 or beyond the foldback 6, depending on the tube geometry. The edge of the incision is secured at the new junction with surgical glue/medical adhesive applied at the circumference of the junction (Figure 7C). In another embodiment, the entire end-to-side repair is secured by a single application of surgical glue/medical adhesive applied at the solder-tube/foldback/incision junction to adhere all three surfaces to one another at once, i.e. the surgical glue/medical adhesive is applied such that it adheres together the solder tube 1, the foldback 6 and the edge of the incision in the first body tube 5 with a single application of surgical glue/medical adhesive where the three elements of the repair meet. The end-to-side join can be at a variety of angles and thus the flanged portion 3 of the tube 1 can be provided at the appropriate angle for the join to be formed.

It will be appreciated by the person skilled in the art that a solder tube 1 having a flange 3 at its proximal and distal ends (Figure 6E) may be similarly applied using the sleeve and foldback procedure described above. Preferably, the foldback 6 may extend over the proximal flange and along the shaft of the solder tube 1 but no further than the base of the distal flange, or, the foldback 6 may be extended to cover both flanges. In the latter arrangement, vascular elasticity may be relied upon to crimp the foldback between the two flanges.

The repair methods of the invention may be utilised for joining a diversity of living tubular tissues including arteries, veins, lymphatics, microvessels, any of the body's tubes such as its ducts – pancreatic, liver, cystic, tear, prostatic, and the ureters, urethra, epididymis, vas, fallopian tubes, bowel, bronchi and other gastroenterological and respiratory and body and brain ducts and tubes.

The repair method of the invention can also be applied to the repair of organs and their coverings such as liver, spleen, kidney, uterus, testicles, bladder, cystic, correal, brain and other capsules, coverings and skin and appendages, as well as the various internal and peripheral nerves of the body, the spinal cord and its ramifications by use of at least one appropriately shaped solder of the invention for the repair being made.

Example 1: Preparation of the Solder.

The following is one example of the preparation of biomolecular solder 1 as described in WO99/65536.

Starting Composition:

protein	55-75% (w/w)
water	45-25% (w/w)

optional dye 0.25% (w/w)

The protein is bovine, rabbit, human, porcine, ovine or rat albumin. Suitable concentrations for bovine serum albumin include about 55% and include about 57% for human and rabbit albumin. Indocyanine green is a suitable dye. Albumins, for instance, can be obtained from ZLB-Behring Inc, CSL Ltd or Sigma-Aldrich Corporation. Suitable albumin preparations include, but are not limited to, for example:

Bovine albumin - A 2153 Fraction V powder (minimum 96%);

Human albumin
- A 1653 Fraction V powder (96-99% albumin)
- CSL's Albumex® 20 human serum albumin
- ZLB-Behrings' 25% solution human serum albumin

Sheep albumin - A 3264 Fraction V powder;

Porcine albumin

These albumin examples may also be utilized in the form of albumin solutions.

Indocyanine green dye can be obtained from Becton Dickinson Microbiology Systems, Maryland 21030 USA.

A particular formulation for human and rabbit albumin is as follows:

Starting Composition:

albumin	57.3% (w/w)
water	42.45% (w/w)
ICG dye (optional)	0.25% (w/w)

Construction:

1. The components are mixed into a paste form to obtain optimum consistency for extrusion or pressing. For example, the water and optional dye are first mixed by vortexing to form a consistent dye solution which is then added to the protein followed by mixing to form the paste. Mixing can be performed physically or mechanically and for small batches (<2g total mass) was performed using a vortex mixer to provide consistency. The solder was not allowed to dry at this stage as this would cause the solder to become brittle and thus unsuitable for extrusion or pressing.

2. The paste can be extruded at this stage but as noted below a superior product can be achieved by deferring final shaping.

3. The extruded paste was then allowed to dehydrate thus increasing the protein concentration and allowing the solder to take a more rigid form.

4. The rigid solder was immersed in hot water at 80-100°C (for example 85°C for bovine albumin) for approximately 1 minute to denature the protein. Where the solder is prepared from human albumin the relevant treatment is with steam at about 120°C for 10 minutes (it is envisaged that the temperature could be as low as 100°C or up to 150°C). This denaturation treatment causes the solder to bond within itself and the solder becomes less soluble in water or body fluid.

5. The solder at this stage is elastic and may be further cut into desired shapes easily without inducing stress or fracture. Desired shapes include sheets, tubes, partial tubes and rods. If cut to shape before step 4,the solder may fracture through the presence of crystalline structure if it is too dry or else it may deform if it is too moist.

6. The solder is preferably dehydrated at this stage and gamma irradiated or autoclaved for sterilisation and stored in a dry, sterile and light-proof container.

A particular protocol that has been used successfully with the human or rabbit serum albumin formulation mentioned above is:

1. mix the protein preparation
2. extrude the preparation
3. allow the preparation to dry

The preparation is then autoclaved at 120°C for 10 minutes.

As an alternative to extrusion, the solder may be shaped by forcing the protein paste into a mould under pressure. The entire mould is heated by manner of autoclave or by integrated heating elements, prior to extricating the shaped solder. The solder can be autoclaved at various temperatures and pressures prior to its removal from the mould. Once autoclaved, the mould is 'broken' and the shaped solder removed. It may then be sterilized by any suitable means, such as by gamma ray irradiation, for instance at 2000 rad/min for 50 minutes, autoclaving, steam treatment, heat treatment, gas sterilization such as ethylene oxide and peroxide based sterilization.

Example 2. End-to-end microvascular anastomosis.

Studies were conducted to create an end-to-end anastomosis using a solder tube according to WO99/65536 and surgical glues. The anastomoses were performed in rats and data was collected at 1 week and 6 weeks post anastomosis. 100% patency of the anastomoses was observed at 1 week (n=12). Histological examination indicated there was no damage by the surgical glue to the lumen of the anastomosed blood vessel.

Materials and Methods.

Solder tubes 1 were prepared according to the method of WO99/65536, and shaped by moulding as described above. The anastomoses were performed according to the sleeve technique also set out in WO99/65536.

As illustrated in Figure 2, the sleeve technique involves the following steps. The severed end of the proximal artery or proximal body tube 5 is pulled through a solder tube 1 and turned back over the solder tube 1 a short distance (the "foldback") 6 using purpose built forceps 7 that have ends adapted to provide a surface which functions to maintain the tube end 5 in open form (Figure 2(A)). Surgical glue is applied to the edge of the artery-solder tube 1 junction formed by the foldback (Figure 2(B)). The end of the vessel 5 to be joined is gently pulled over and beyond the foldback 6 until it contacts the solder tube 1. (Figure 2(C)), and surgical glue is applied to the new artery-solder tube junction formed at the proximal end of the solder tube 1 (Figure 2(D)).

Anastomoses were performed on the abdominal aorta of female Wistar rats, equal to or greater than 250g. Approximately 1μL of the designated cyanoacrylate glue but not more than 5μL was applied to the vessel-solder tube junction at steps B and D. Once applied to the foldback, the surgical glue was allowed to polymerise for 2 minutes prior to commencing pullover of the vessel to be joined. Application of the surgical glue to the pullover was followed by a 2 minute rest period prior to releasing the vascular clams and closing the wound site.

Two different protein solder 1 formulations were tested, as set out in WO99/65536. Specifically, green solder tubes included indocyanine green and albumin in their formulation. Un-dyed tubes made of albumin alone were also tested.

Results

Follow-up at week 1 yielded excellent results (Table 1), with substantially no visual indication of mediated tissue reactions towards the implanted solder tube 1 device. As shown in Table 1, one hundred percent patency of the anastomoses (12/12) was achieved by week 1 using the surgical glue n-octyl-cyanoacrylate. The surgical glue butyl cyanoacrylates achieved patency in 9 of 9 anastomoses at week 1.

As shown in the follow-up photographs of Figures 6 and 7, both butyl-2-cyanoacrylate- and n-octyl-cyanoacrylate- bonded implants are free of macroscopic inflammation at 1 week. These images are typical of excised solder tube devices from the two groups.

Burst pressure results for each of the cyanoacrylate glues trialled averaged over 820mmHg. Physiological blood pressure rarely exceeds 300mmHg in even extreme cases (see Table 1).

Table 1: Patency and burst pressure results.

Bonding method	**Cohort size**	**Patency %**	**Burst pressure (mmHg)(sample #)**
n-octyl-cyanoacrylate	12	100	721 (6)
butyl-2-cyanoacrylate	8	100	828 (5)
Physiological	-	-	Max 300

Necrosis (conversely cell survival) of the smooth muscle cells (media layer) of the artery at the site of the anastomosis was scored. Necrosis of the media layer is a result of damage due to the procedure or cytotoxicity due to the surgical glue used. The results are used to assess the damage to the luminal domains within the anastomosis and are used as a

predictive measure of anastomosis success. An average of 40% of smooth muscle cells were necrotic at 1 week in the key luminal domain of the anastomosis.

Discussion

Of the cyanoacrylate glues tested, the preferred cyanoacrylate is n-octyl-cyanoacrylate. N-octyl cyanoacrylate is easier to manipulate and apply, leaving a smooth exterior finish that provides for a simple pullover during the second phase of the anastomotic procedure (sleeve technique). Butyl-2-cyanoacrylate polymerizes more rapidly, adheres instruments to tissue and instruments to instruments, whilst leaving a crusty/crystalline exterior on vascular tissue after it has set. This surface finish then makes it difficult to manipulate the pullover during the second phase of the sleeve technique.

These results show that patency of anastomoses may be achieved through the combined use of surgical glue and the solder tube 1 described in WO99/65536 in the absence of histologically evident inflammation or foreign body reaction. Whereas suture-only anastomoses or glue/adhesive-assisted sutured anastomoses necessarily result in perivascular inflammation due to the reliance on sutures or microsutures to secure the join, the method of the present invention provides a true suture-less approach which is effective in achieving patency, may result in minimal inflammation and tissue trauma, and provides the long term added benefit that the protein solder implant biodegrades with time, resulting in improved vascular integrity.

Example 3: Glue strength is enhanced with some glues when used in conjunction with the biomolecular protein solder.

Tensile strength tests were carried out to determine the comparative strengths of tissue-tissue junctions, tissue-solder junctions, and tissue- SLA resin junctions adhered by

either a butyl cyanoacrylate, an octyl cyanoacrylate, or bovine serum albumin cross-linked with glutaraldehyde. An overlapping junction of 6mm^2 was adhered.

For two of the three glues tested, the tissue-solder junction possessed greater tensile strength than the respective tissue-tissue junction. This indicates that for certain glues there exists an added advantage in creating the tissue join using a proteinaceous solder and a medical glue. This advantage is in addition to those provided by the combination of a proteinaceous solder and one or more glues, adhesives or sealants according to the invention.

Table 2

Glue	Junction	Area (mm^2)	Tensile Strength (mN)	Average gF
butyl-2-cyanoacrylate	tissue-tissue	6	2531	
			2475	
			2303	
			2538	
			2462	
			Mean = 2462	251
	tissue-solder	6	4395	
			2876	
			4346	
			3321	
			3636	
			Mean = 3725	379
	tissue- SLA resin	6	2929	
			2049	
			2927	
			1753	
			2194	
			Mean = 2370	242
octyl-2-cyanoacrylate	tissue-tissue	6	4261	
			2658	

			4621	
			4275	
			3930	
			Mean = 3949	403
	tissue-solder	6	2265	
			3086	
			3919	
			5538	
			3364	
			Mean= 3634	371
BSA + glutaraldehyde	tissue-tissue	6	1548	
			516	
			1509	
			241	
			803	
			Mean= 923	94
	tissue-solder	6	3185	
			885	
			4647	
			3415	
			1446	
			Mean = 2716	277

Example 4: Assessment of cytotoxicity of surgical glues/medical adhesives utilized in the method of the invention.

Cytotoxicity of surgical glues/medical adhesives when utilized in the method of the invention may be assessed by applying directly to vascular tissue prepared as it would be prior to transection for the anastomosis and distal to the site of anastomosis. Marker sutures are placed through the adventitia of the vessel, and 1µl of the chosen glue/adhesive applied to the tissue. Cytotoxicity of the surgical glue/medical adhesive may then be assessed histologically following excision of the small vascular patch distal to the anastomosis. The level of cytotoxicity exhibited in the distal patch should reflect cytotoxicity at the site of the anastomosis.

Example 5: Performance of solder tubes having transluminal pores in the method of the invention.

Solder tubes with small transluminal pores, made by piercing the solder tube with a fine micro needle may be utilized in the method of the invention. Whilst increasing the solder tube surface area, perforated tubes may allow for greater mechanical interlocks with the cyanoacrylate glues and improve both cellular migration and signaling at the anastomotic site, therefore improving the wound healing outcome.

As will be apparent to those skilled in the art from the teaching hereof, the invention may be performed in other ways and using different formulations without departing from the inventive concept herein disclosed.

CLAIMS:-

1. A method of connecting a solid biomolecular solder to a biological tissue comprising adhering said solder to said tissue with one or more of a medical adhesive, glue or sealant.

2. A method for joining biological tissues comprising the steps of:

applying a solid biomolecular solder to said biological tissues to be joined; and

adhering said solder to at least one of said tissues by means of one or more of a medical adhesive, glue or sealant.

3. A method according to claim 2 wherein said joining of said biological tissues is part of a procedure selected from the group consisting of vascular anastomosis, sealing of tissue discontinuities, catheter puncture closure, sealing lacerations of the liver, spleen, lungs or other solid organs, colorectal anastomosis, improved approximation of large dermal breaches, neural and nepheral junctions or seals and other biological joins.

4. A method for making an anastomosis comprising the steps of:

connecting tubular tissue to be anastomosed with a tube implant comprising a solid biomolecular solder; and

adhering said tube implant to both said tubular tissue by means of one or more of a medical adhesive, glue or sealant such that said anastomosis is sealed.

5. A method according to any one of the preceding claims wherein said adhesive, glue or sealant is selected from the group consisting of ethyl cyanoacrylates, butyl cyanoacrylates, octyl cyanoacrylates, polyethylene glycols, polyurethanes, glues or

adhesives combined with polymethylmethacrylate, glues or sealants combined with di-acrylate, or proteins with a cross-linking agent.

6. A method according to claim 5 wherein said cross-linking agent is chosen from the group consisting of albumin and glutaraldehyde, hydrogels, alginates, fibrin and gelatin-resorcinol-formal (GRF).

7. A method according to claim 5 or claim 6 wherein said glue or adhesive is selected from the group consisting of ethyl cyanoacrylates, butyl cyanoacrylates, octyl cyanoacrylates and methyl methacrylates.

8. A method according to any one of claims 5 to 7 wherein said adhesive, glue or sealant is an octyl cyanoacrylate.

9. A method according to any one of claims 5 to 8 wherein said adhesive, glue or sealant is 2-octyl cyanoacrylate.

10. A method according to any one of the preceding claims wherein said solder is adhered to said biological tissue by applying said adhesive, glue or sealant continuously along a perimeter of said solder-tissue junction to secure said junction.

11. A method according to any one of the preceding claims wherein said solder is adhered to said biological tissue by applying said adhesive, glue or sealant at separate, advantageous locations in order to secure said junction.

12. A method according to any one of the preceding claims wherein said adhesive, glue or sealant is allowed to polymerize for a predetermined period of time following application to said tissue, to prevent further, undesired, tissue adhesion.

13. A kit for joining biological tissue including:

a solid biomolecular solder; and

a tissue-compatible adherent comprising one or more of a medical adhesive, glue or sealant.

14. A kit according to claim 13 or a method according to any one of claims 1 to 12 wherein said biomolecular solder is substantially solid.

15. A kit according to claim 13 or claim 14 or a method according to any one of claims 1 to 12 wherein said biomolecular solder comprises at least one partially denatured biomolecule.

16. A kit according to claim 15 or a method according to claim 15 wherein said biomolecule(s) is proteinaceous or an analogue of a biological, biodegradable polypeptide.

17. A kit according to claim 16 or a method according to claim 16 wherein said analogue of a biological, biodegradable polypeptide is a synthetic polypeptide or other molecule capable of forming said biomolecular solder, wherein said biomolecular solder does not cause adverse reaction in said biological tissues to be joined.

18. A kit according to claim 16 or claim 17 or a method according to claim 16 or claim 17 wherein said biomolecule is a biodegradable protein or a mixture of biodegradable proteins.

19. A kit according to claim 18 or a method according to claim 18 wherein said biodegradable protein or biodegradable proteins are selected from the group consisting of albumins, collagen, fibrinogen and elastin.

20. A kit according to claim 18 or claim 19 or a method according to claim 18 or claim 19 wherein said biodegradable protein or biodegradable proteins can be resorbed by the body.

21. A kit according to any one of claims 15 to 20 or a method according to any one of claims 15 to 20 wherein said biomolecule(s) of said biomolecular solder are sufficiently denatured such that said biomolecular solder has sufficient longevity *in vivo* for said biological tissues to be joined.

22. A kit according to any one of claims 13 to 21 or a method according to any one of claims 1 to 12 or 14 to 21 wherein said biomolecular solder includes one or more adjuvants for promoting rapid and/or more complete tissue healing.

23. A kit according to claim 22 or a method according to claim 22 wherein said one or more adjuvants is selected from the group consisting of fibrinogen, growth factors, sodium hyluronate, hormones, and anticoagulants.

24. A kit according to any one of claims 13 to 23 or a method according to any one of claims 1 to 12 or 14 to 23 wherein said biomolecular solder comprises one or more fibrous materials for improving the strength of said biomolecular solder.

25. A kit according to claim 24 or a method according to claim 24 wherein said one or more fibrous materials is selected from the group consisting of collagen, polytetrafluoroethylene fibre and ceramic fibres.

26. A kit according to claim 24 or claim 25 or a method according to claim 24 or claim 25 wherein said fibrous material comprises a biocompatible polymer.

27. A kit according to any one of claims 13 to 26 or a method according to any one of claims 1 to 12 or 14 to 26 wherein said biomolecular solder is a tube implant for performing vascular anastomosis.

28. A kit according to claim 27 or a method according to claim 27 wherein said tube implant has a round or oval profile.

29. A kit according to claim 27 or a method according to claim 27 wherein said tube implant has a square or crenulated profile.

30. A kit according to any one of claims 27 to 29 or a method according to any one of claims 27 to 29 wherein said tube implant has an internal diameter consistent along its length such that said tube implant is cylindrical.

31. A kit according to any one of claims 27 to 29 or a method according to any one of claims 27 to 29 wherein the internal diameter of said tube implant uniformly decreases along its length from a distal end to a proximal end such that said tube implant is conical.

32. A kit according to any one of claims 27 to 31 or a method according to any one of claims 27 to 31 wherein said tube implant allows end-to-end vascular anastomoses.

33. A kit according to any one of claims 27 to 31 or a method according to any one of claims 27 to 31 wherein said tube implant allows end-to-side vascular anastomoses.

34. A kit according to claim 33 or a method according to claim 33 wherein said tube implant includes a circumferential flange at one or both ends.

35. A kit according to claim 34 or a method according to claim 34 wherein the interior surface of said flange is beveled or rounded.

36. A kit according to claim 33 or claim 34 or a method according to claim 33 or claim 34 wherein said circumferential flange is positioned such that it forms an angle with the axis of said tube implant, as required by the anatomy of the target site at which the end-to-side anastomosis is to be formed.

37. A kit according to claim 36 or a method according to claim 36 wherein said angle is between 0 to 180 degrees.

38. A kit according to claim 36 or claim 37 or a method according to claim 36 or claim 37 wherein said angle is 90 degrees.

39. A kit according to any one of claims 36 to 38 or a method according to any one of claims 36 to 38 wherein said angle is 40 degrees.

40. A kit according to any one of claims 34 to 39 or a method according to any one of claims 34 to 39 wherein the internal diameter of said flange is equal to the internal diameter of said tube implant.

41. A kit according to any one of claims 34 to 39 or a method according to any one of claims 34 to 39 wherein said flange is elliptical having a major internal diameter longer than the internal diameter of said tube implant.

42. A kit according to any one of claims 34 to 39 or a method according to any one of claims 34 to 39 wherein the area defined by the internal circumference of said flange is equal to the area defined by the internal circumference of distal end of said conical tube structure.

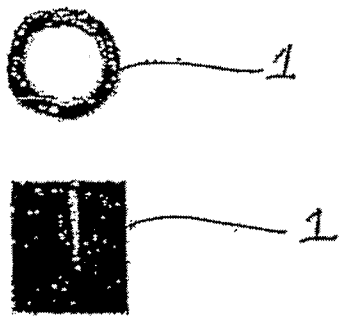

FIGURE 1

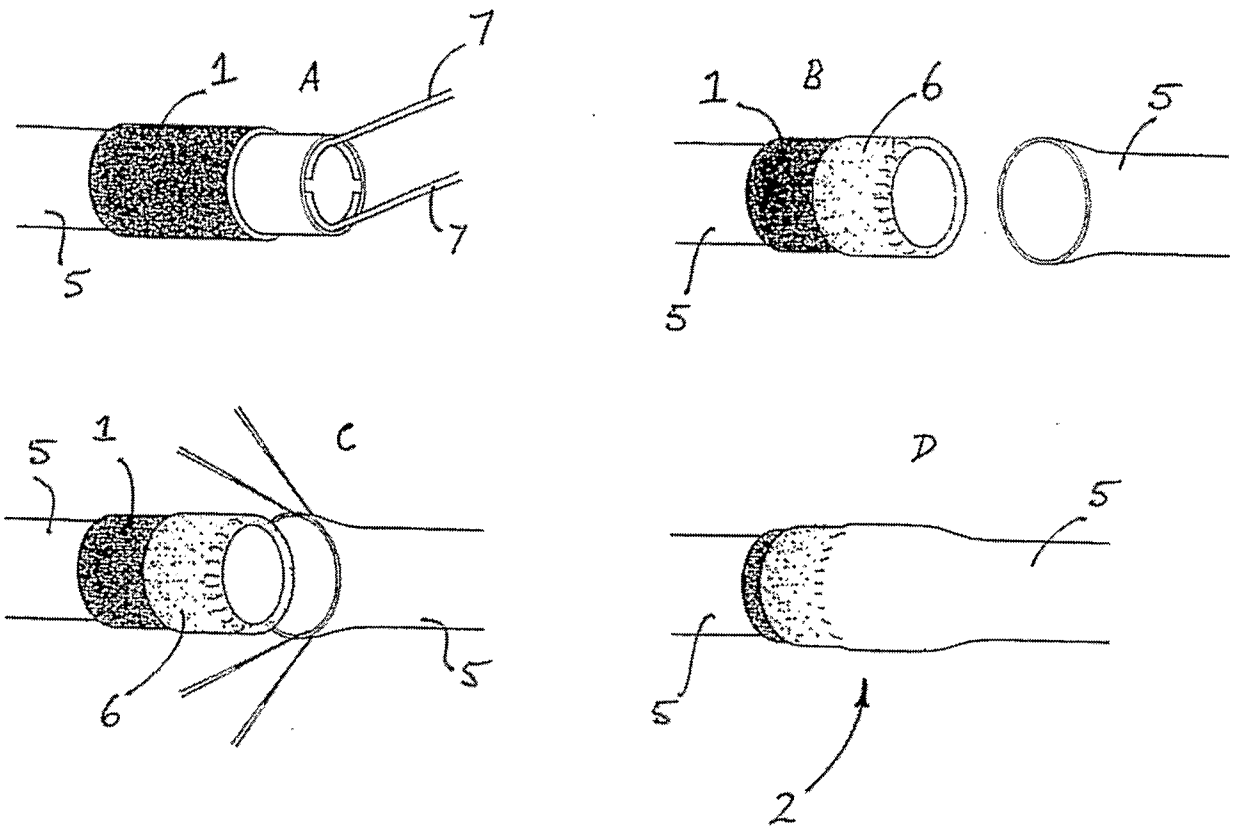

FIG. 2

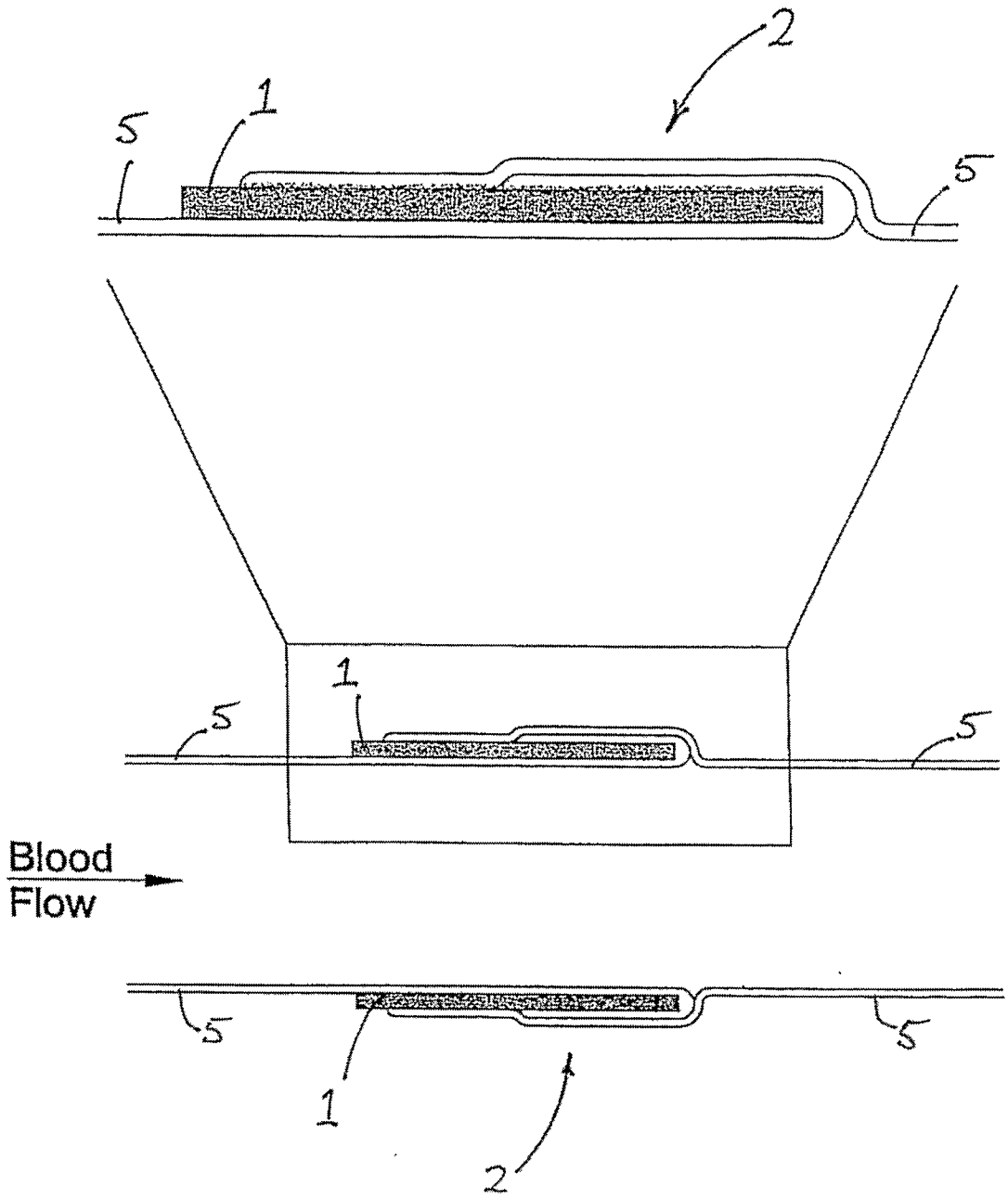

Fig. 3

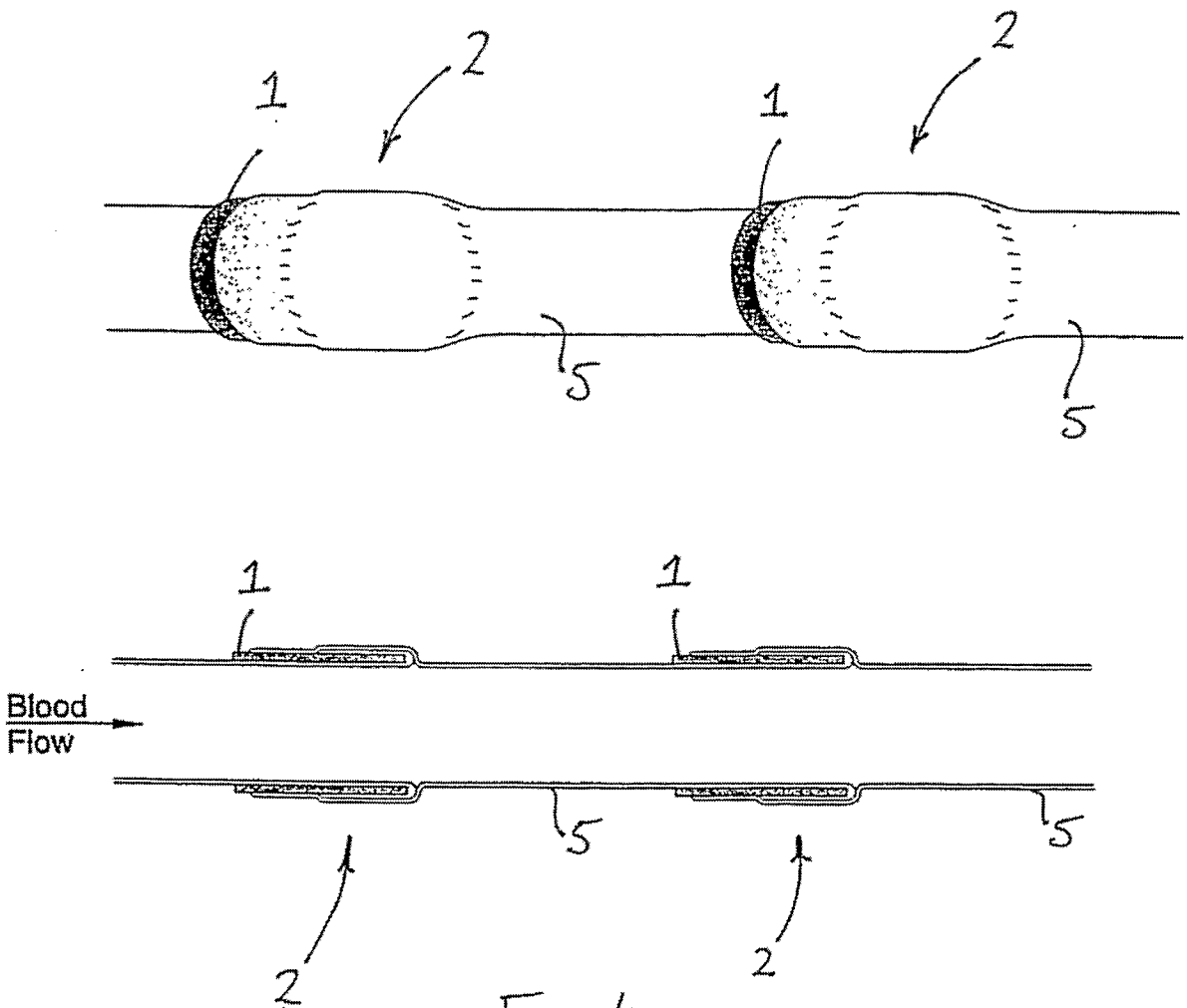

FIG. 4

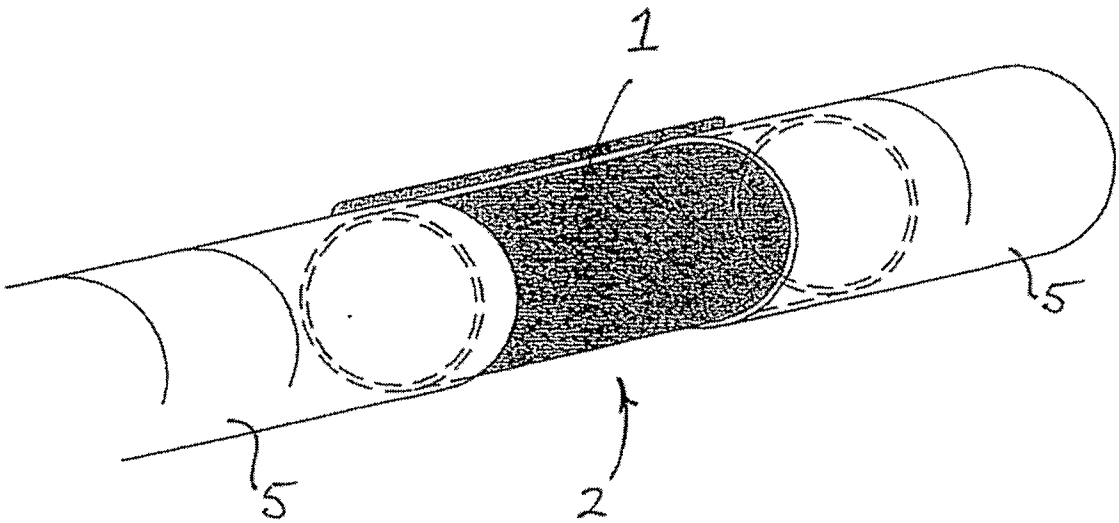

FIG. 5

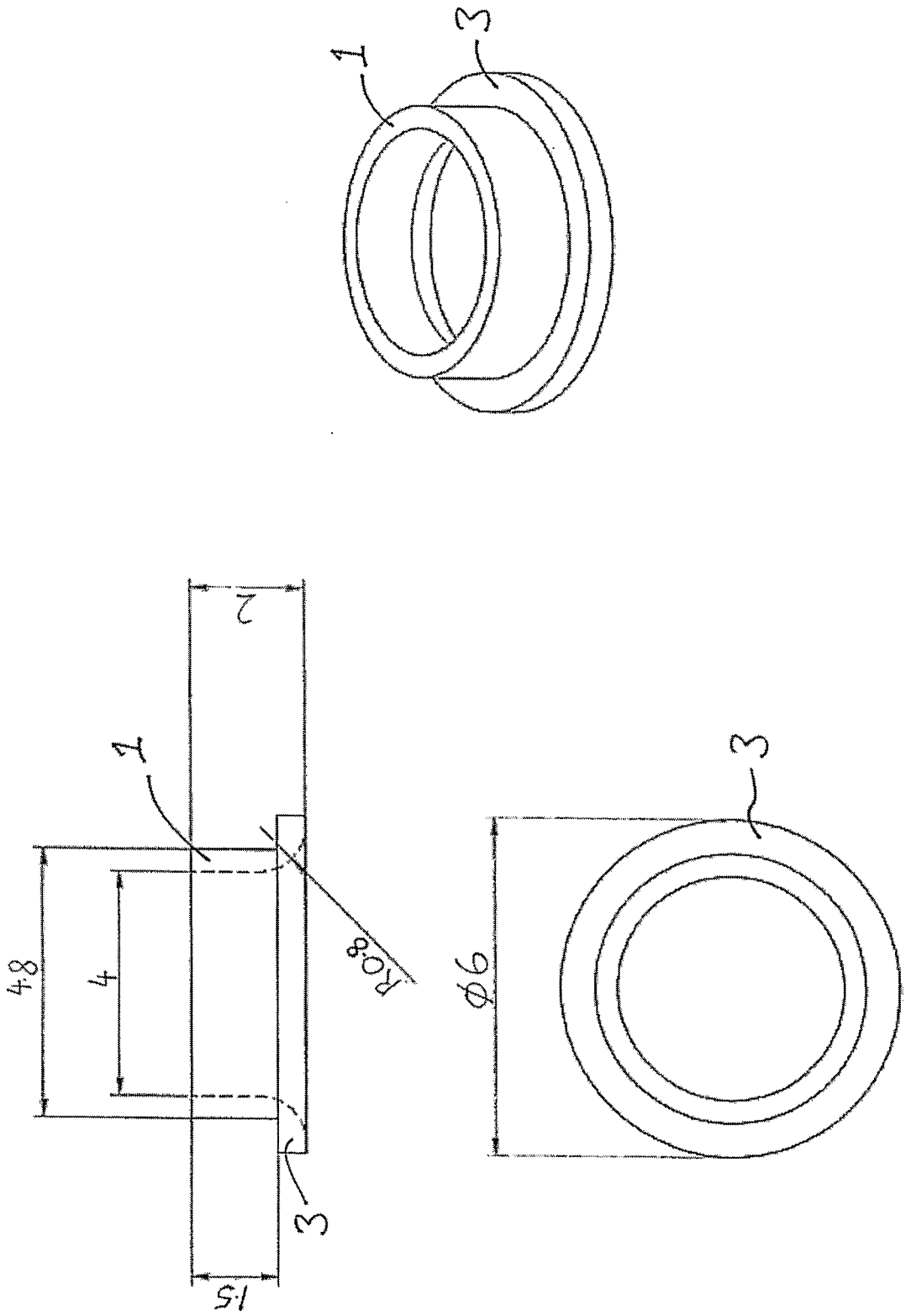

Fig. 6A

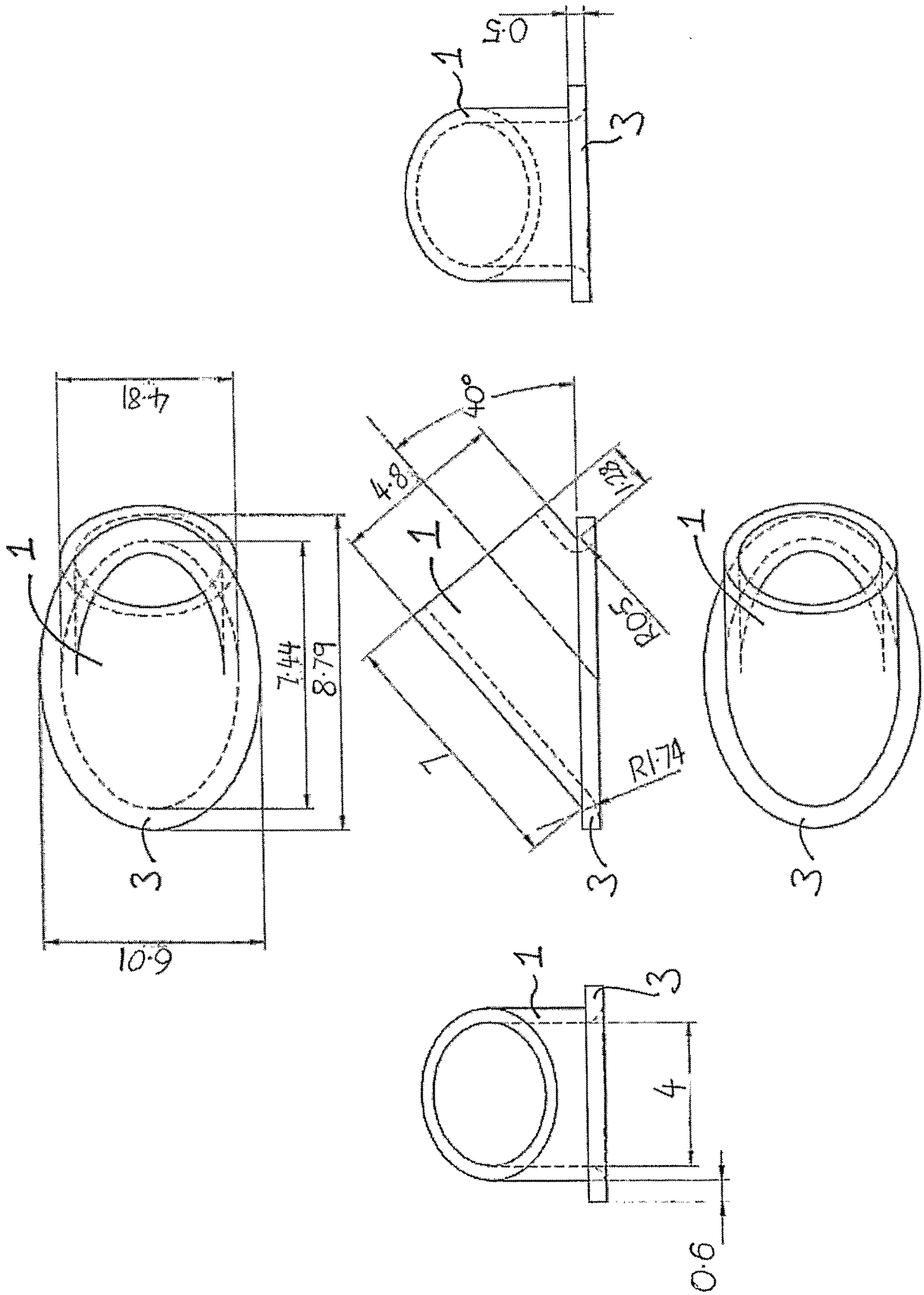

Fig. 6B

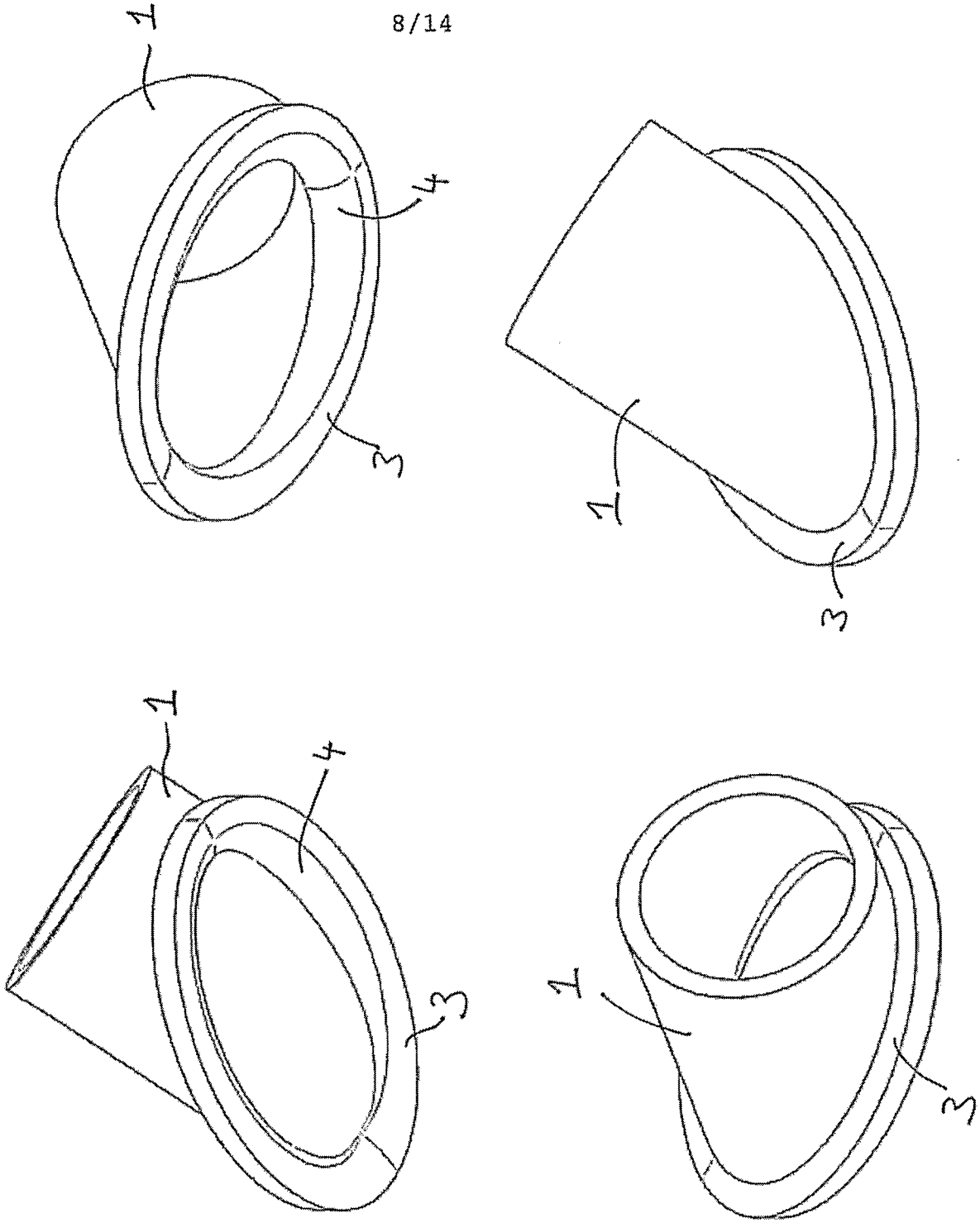

Fig. 6C

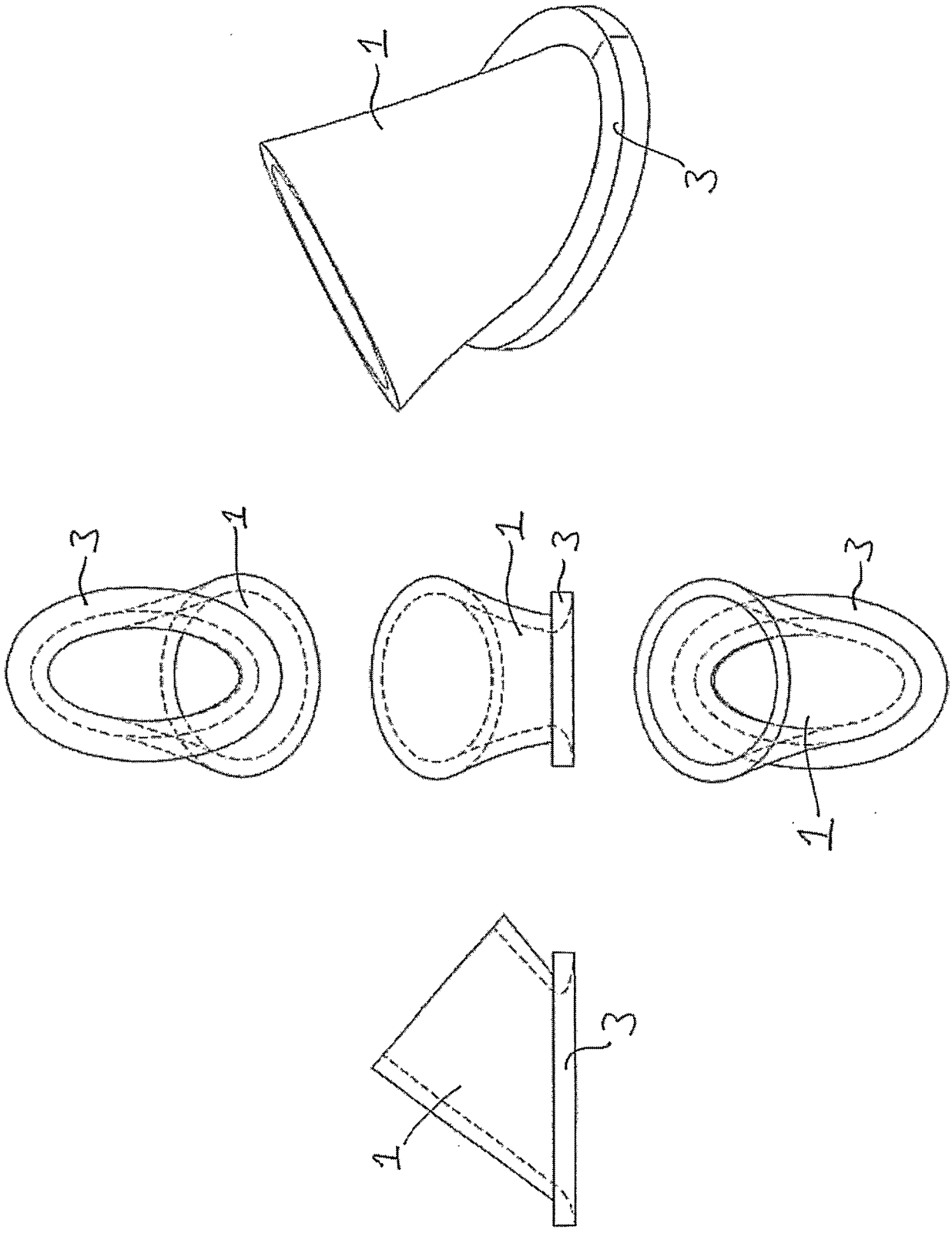

Fig. 6D

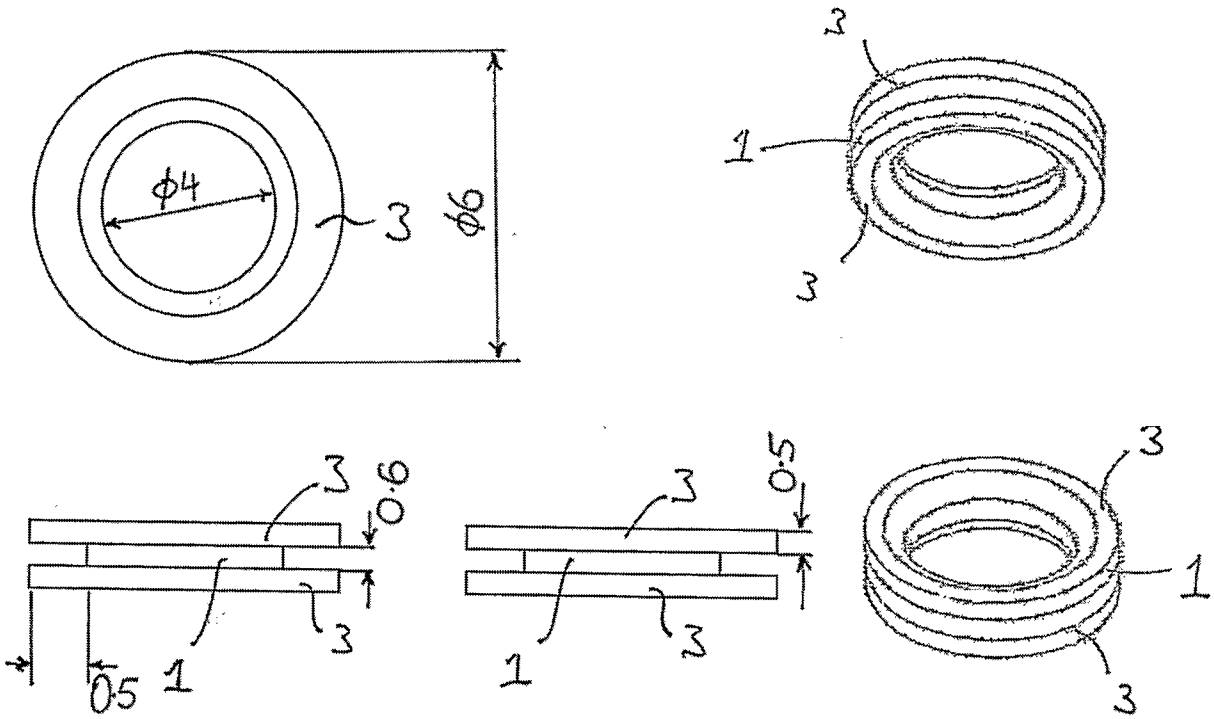

Fig. 6E

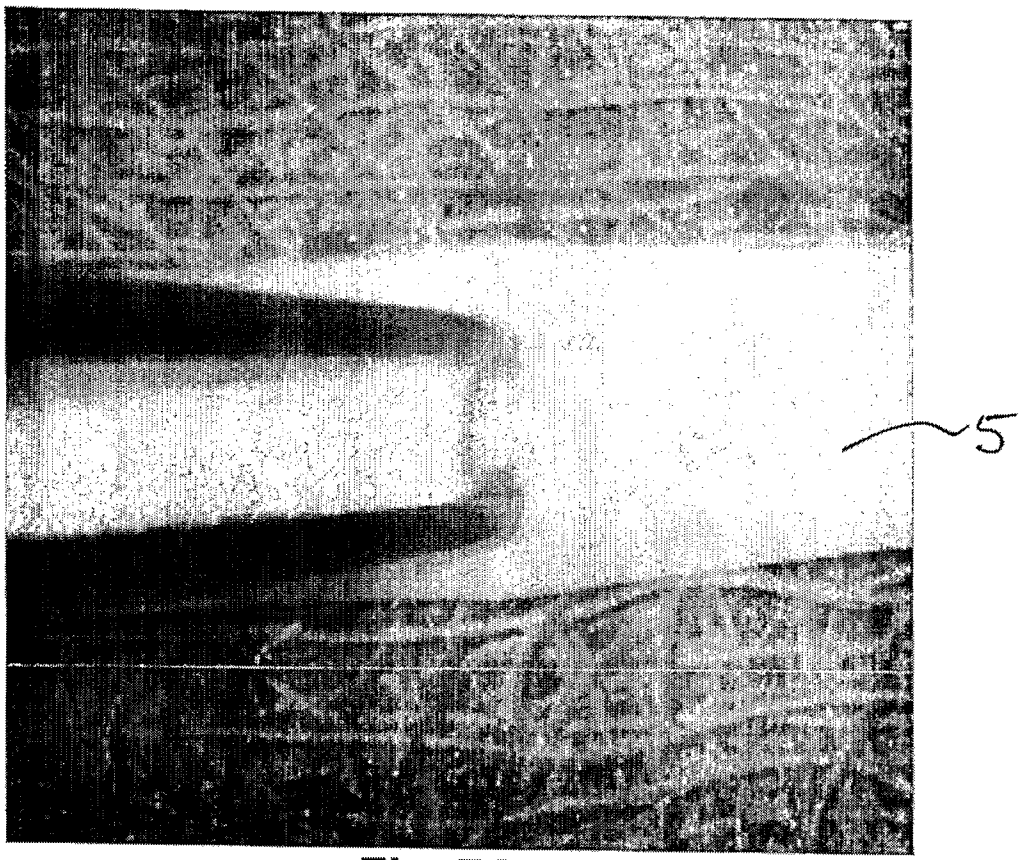

Fig. 7A

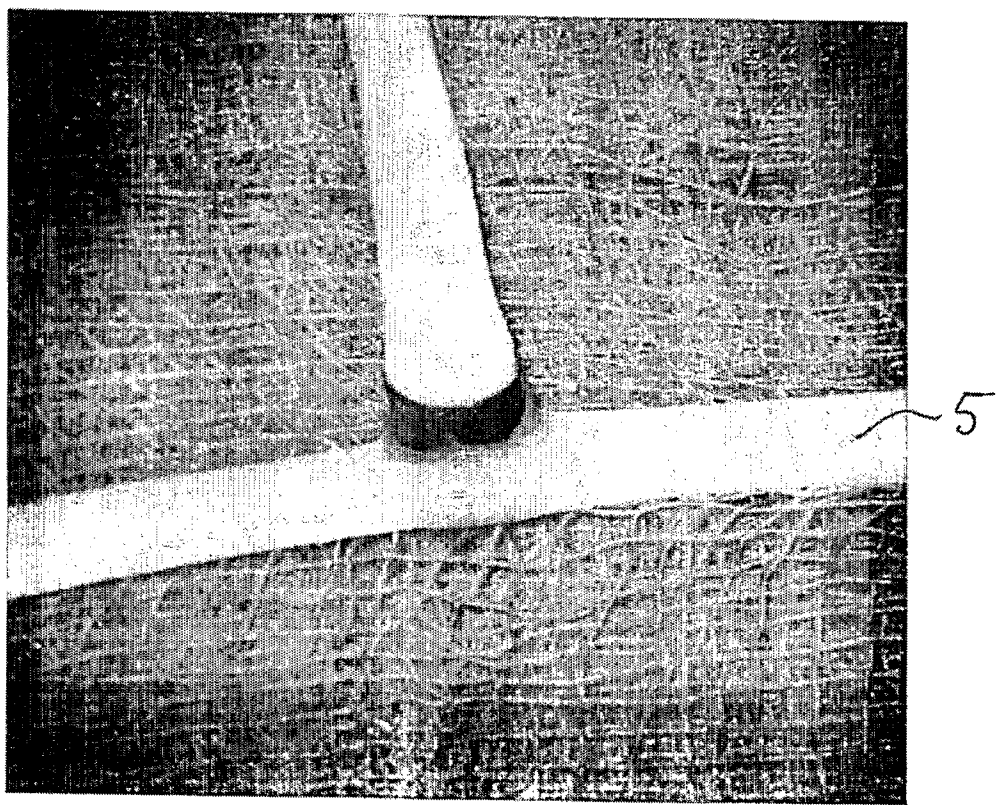

Fig. 7B

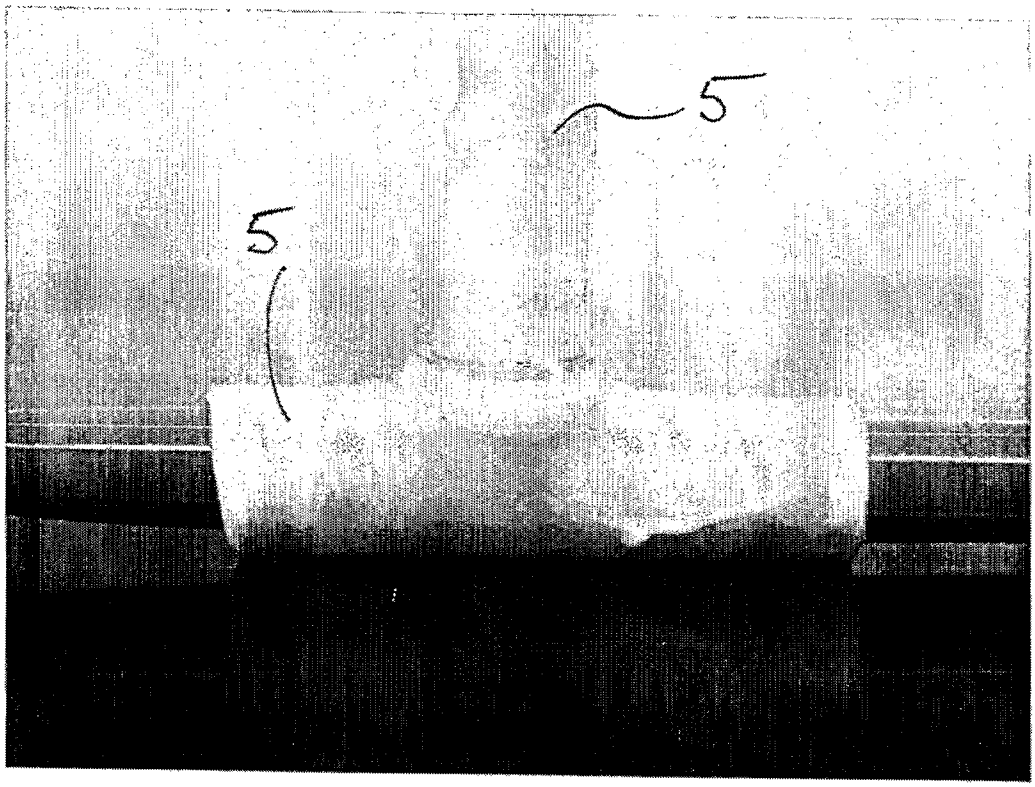

FIG. 7C

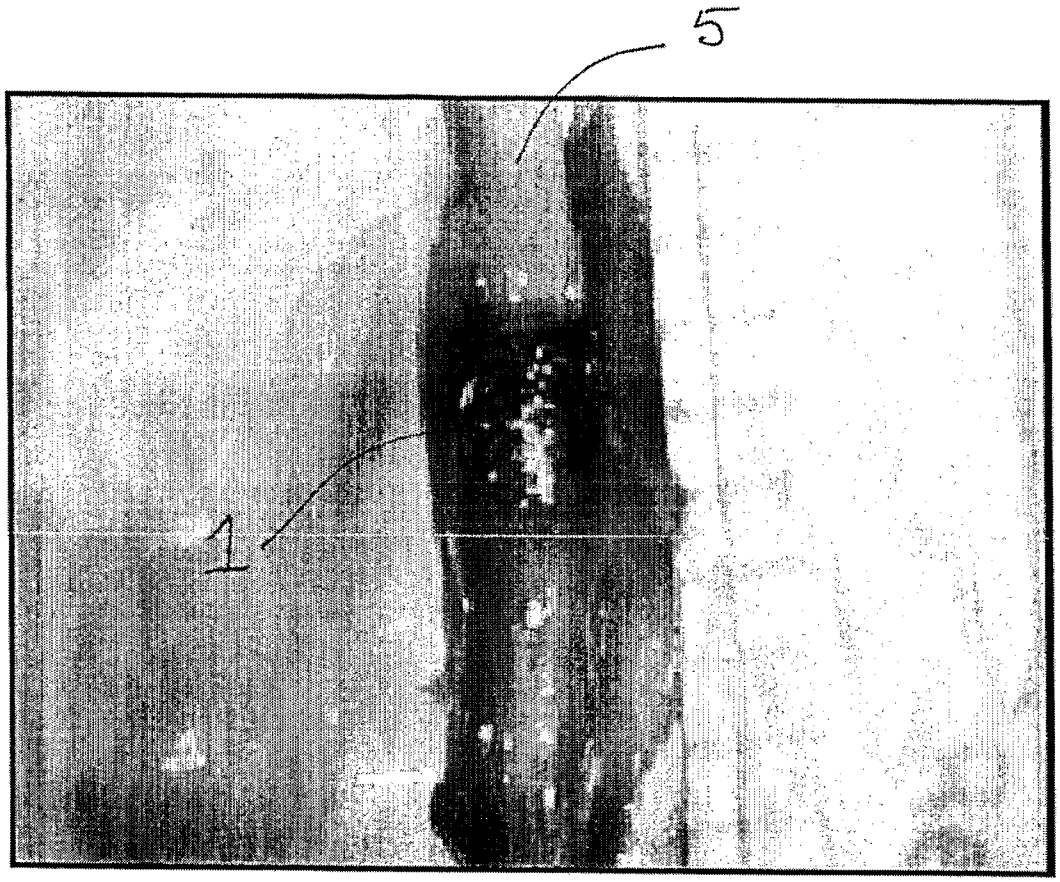

FIG. 8

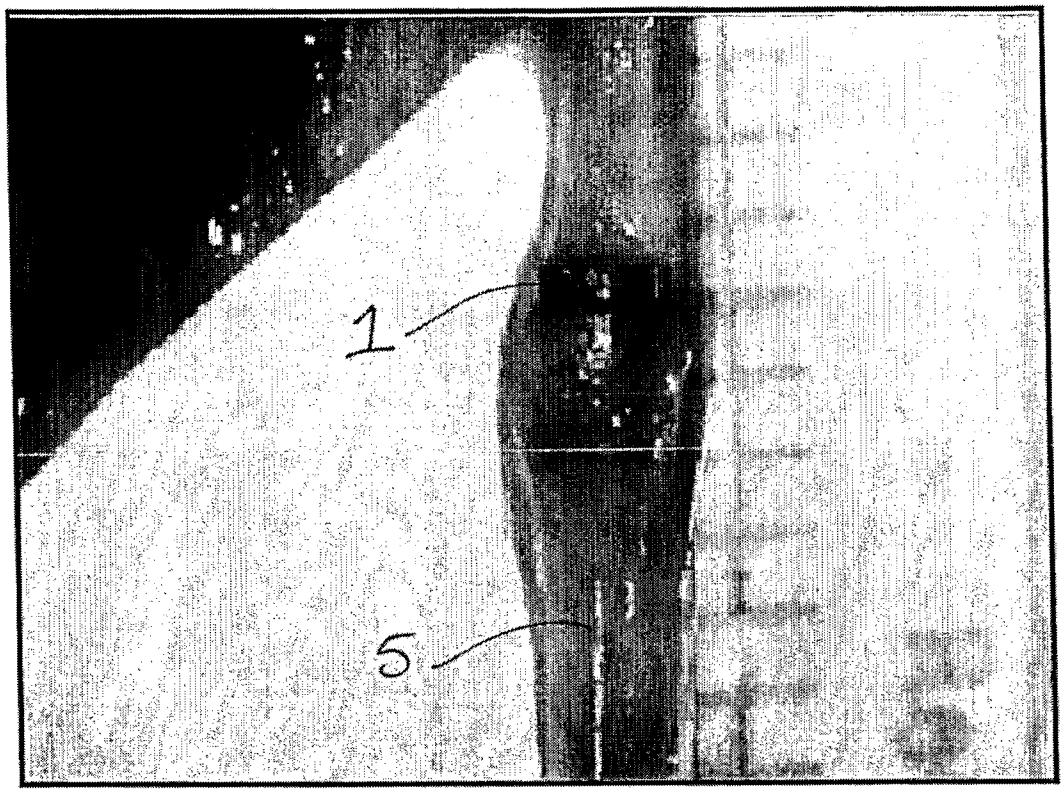

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/001361

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61B 17/11 (2006.01) *A61F 2/06* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI. IPC: A61B, A61F, A61L and keywords: anastomosis, join, connect, biomaterial, protein, glue, adhesive and similar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 1998/016165 A1 (FUSION MEDICAL TECHNOLOGIES) 23 April 1998	
X	See whole document	1–4, 13
	WO 1996/022054 A1 (THE MICRO RESEARCH FOUNDATION OF AUSTRALIA et al) 25 July 1996	
X	Whole document: Especially figure 5.	13
Y		1–4, 13
	US 5921995 A (KLESHINSKI) 13 July 1999	
Y	Whole document: especially figures 2–3	1–4, 13
Y	Column 3 lines 20–40.	5–12
	WO 1999/048427 A (ROY et al) 30 September 1999	
Y	Whole document	1–4, 13
Y	Page 7 lines 11–15	5–12

[X] Further documents are listed in the continuation of Box C [X] See patent family annex .

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2006	04 DEC 2006
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **Matthew FORWARD** Telephone No : (02) 6283 2606

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Patent Abstract of JP 04-028360 (NIPPON ZEON Co LTD) 30 January 1992	
Y	See abstract	1–4, 13
Y		5–12
	US 2006/0135992 A (BETTUCHI et al) 22 June 2006	
P, Y	Whole document	1–4, 13
P, Y	[0012]-[0013], [0027], [0086]	5–12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2006/001361

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **14–42**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 14–42 are all unclear according to Art 17(2)(ii) of the PCT. All of the claims are appended to BOTH a kit or a method, rendering these claims of indeterminate scope.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2006/001361

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9816165	AU	14442/92	AU	35064/95	AU	35069/95
		AU	48198/97	CA	2103727	EP	0572526
		EP	0786960	EP	0901345	EP	0959795
		US	5156613	US	5669934	US	5690675
		US	5749895	US	5791352	US	5824015
		US	5931165	WO	9214513	WO	9607355
		WO	9607356				
WO	9622054	AU	44277/96	CA	2210894	EP	0804123
		HK	1003613	NZ	298721	US	6211335
		US	6583117	US	2002045732	US	2005079997
US	5921995	AU	47457/97	CA	2269064	EP	1011522
		US	5755778	WO	9816174		
WO	9948427	AU	36310/99	CA	2324105	EP	1063923
		NO	20004689	US	6743243		
JP	4028360						
US	2006135992	AU	2005222502	CA	2523333	EP	1647231
		JP	2006110356	US	2006085034	WO	2006044490

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX