

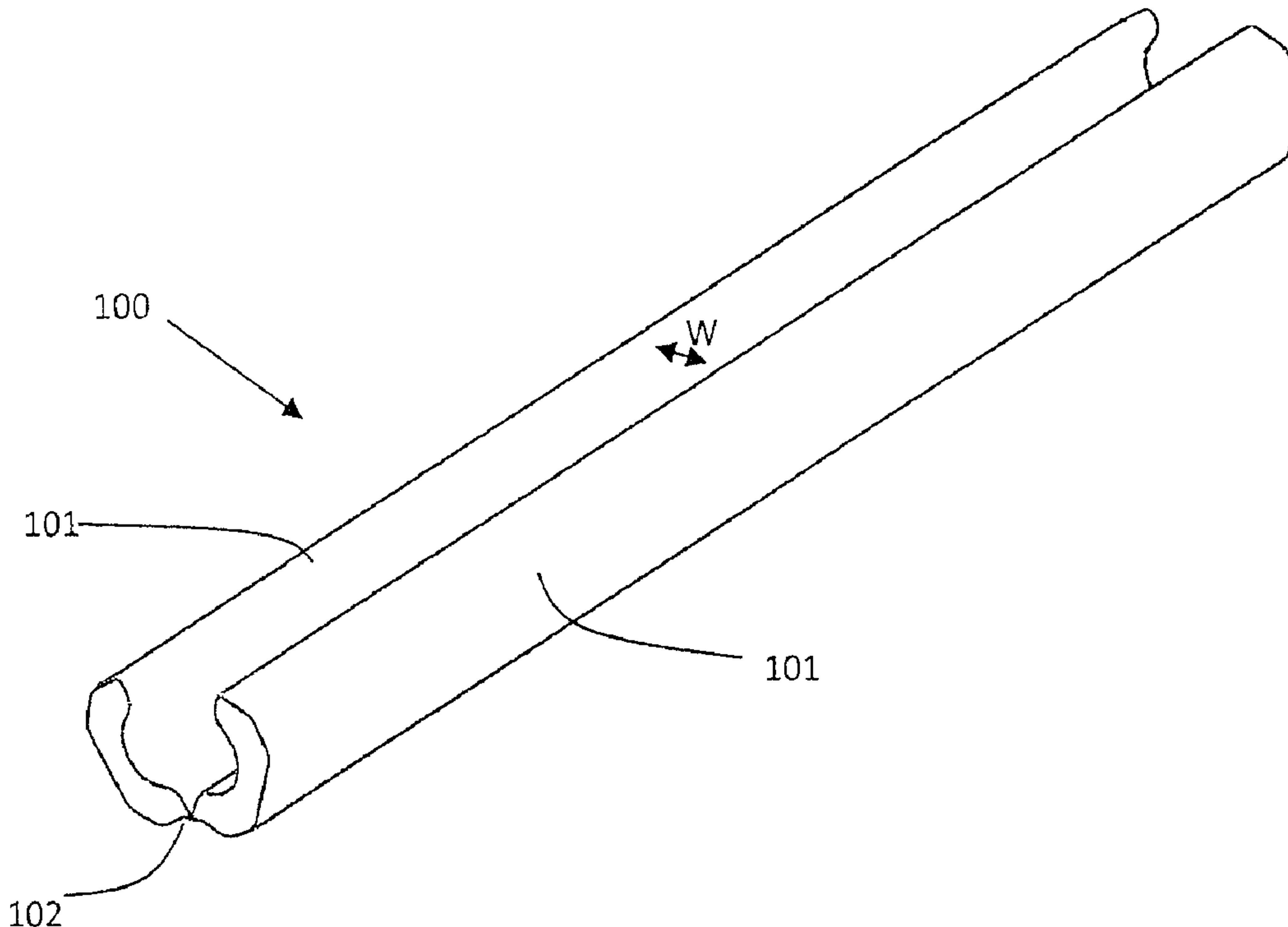


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(72) Inventeurs/Inventors:
LEVIN, OFEK, IL;
LEVY, ARIE, IL
(73) Propriétaire/Owner:
TYCO HEALTHCARE GROUP LP, US
(74) Agent: OSLER, HOSKIN & HARCOURT LLP

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(57) Abrégé/Abstract:

This invention generally relates to minimal invasive surgery. More specifically the current invention relates to an apparatus especially adapted to fold prosthetic patches and to insert said patches into a body cavity through a cannula or an incision.

ABSTRACT

This invention generally relates to minimal invasive surgery. More specifically the current invention relates to an apparatus especially adapted to fold prosthetic patches and to insert said patches into a body cavity through a cannula or an incision.

DEVICE AND METHOD FOR ROLLING AND INSERTING A PROSTHETIC PATCH INTO A BODY CAVITY

FIELD OF THE INVENTION

This invention generally relates to minimal invasive surgery. More specifically the current

5 invention relates to an apparatus especially adapted to fold prosthetic patches and to insert said patches into a body cavity through a cannula or an incision.

BACKGROUND OF THE INVENTION

An aspect of the present invention is to provide apparatus and a method for performing corrective surgery on internal wounds such as hernia where invasion of the patient's body

10 tissues is minimized and resultant trauma is reduced.

A hernia is a protrusion of a tissue, structure, or part of an organ through the muscular tissue or the membrane by which it is normally contained. In other words a hernia is a defect in the abdominal wall through which a portion of the intra-abdominal contents can protrude. This often causes discomfort and an unsightly, visible bulge in the abdomen. When such a hernia defect

15 occurs in the abdominal region, conventional corrective surgery has required opening the abdominal cavity by surgical incision through the major abdominal muscles. While this technique provides for effective corrective surgery of the hernia defect, it has the disadvantage of requiring a hospital stay of as much as a week, during which pain is frequently intense, and it requires an extended period of recuperation. After the conventional surgery patients frequently

20 cannot return to a full range of activity and work schedule for a month or more. Accordingly, medical science has sought alternative techniques that are less traumatic to the patient and provide for more rapid recovery.

Laparoscopy is the science of introducing a viewing instrument through a port into a patient's body, typically the abdominal cavity, to view its contents. This technique has been used for

25 diagnostic purposes for more than 75 years. Operative laparoscopy is performed through tiny openings in the abdominal wall called ports. In most surgical techniques several ports, frequently three to six, are used. Through one port is inserted the viewing device, which conventionally comprises a fiber optic rod or bundle having a video camera affixed to the outer end to receive and display images from inside the body. The various surgical instruments are

30 inserted through other ports to do the surgery that normally would be performed through an

open incision through the abdominal wall. Because the laparoscopic surgical techniques require only very small holes through the abdominal wall or other portions of the body, a patient undergoing such surgery may frequently leave the hospital within one day after the surgery and resume a full range of normal activities within a few days 5 thereafter.

In repairing hernia the physician needs to first roll the patch in order to insert the same into the abdominal cavity.

Such rolling of the patch can be a time consuming process and sometimes even a highly difficult procedure. In addition, insufficient rolling of said patch may damage the 10 patch during its insertion and may require operation of large forces during said insertion; such forces may lead to patient injuries and/or damage to the insertion tool.

Thus, there is still a long felt need for a device that will enable an easy rolling of the patch prior to the insertion of the same to the abdominal cavity.

SUMMARY OF THE INVENTION

15 It is one aspect of the present invention to provide a patch rolling apparatus (PRA) adapted to enable a tight and easy rolling of a prosthetic patch onto a surgical tool such that a minimum effective cross-section of said rolled prosthetic patch perpendicular to the direction of insertion, prior to, and during, said insertion into either a cannula or an opening is obtained. Exemplary surgical tools include patch 20 deployment devices as described in U.S. Patent Publication No. 2010/0312357.

One embodiment of the present invention provides a device for facilitating rolling of a surgical mesh onto a surgical instrument. The device comprises a sleeve having two parts joined together and movable from an open configuration for operably coupling with an unrolled mesh on a surgical instrument, to a closed configuration for facilitating 25 rolling of the mesh onto the instrument, and a plurality of fins connected to a distal end of the sleeve, wherein the fins open a valve of a port.

A further embodiment provides a device for facilitating rolling of a mesh onto a surgical instrument which comprises a sleeve having two parts joined together and defining a slit along a length of the sleeve, wherein the two parts of the sleeve are

movable from an open configuration for operably coupling with an unrolled mesh on a surgical instrument, to a closed configuration for facilitating rolling of the mesh onto the instrument; and a plurality of rigid fins connected to a distal end of the sleeve, wherein the fins open a valve of a port.

5 It is another aspect of the present invention to provide the PRA as defined above, wherein said PRA comprises at least two sections hinge-like coupled together; said PRA is characterized by at least two configurations: (i) an open configuration (OC) in which said two sections are apart to create a gap into which said prosthetic patch can be inserted; and, (ii) a closed configuration (CC) in which said gap is minimized or
10 eliminated such that said PRA substantially envelops said prosthetic patch and enables said rolling of said prosthetic patch.

It is another aspect of the present invention to provide the PRA as defined above, additionally comprising a locking section (LS) adapted to maintain said PRA in its said closed configuration.

15 It is another aspect of the present invention to provide the PRA as defined above, wherein said LS comprises a locking hook, attached to at least one section of said PRA and a locking groove located on the second section of said PRA.

It is another aspect of the present invention to provide the PRA as defined above, wherein said LS comprises a release tab adapted to allow said release of said locking;
20 such that once said release tab is pressed said PRA is transformed into said open configuration.

It is another aspect of the present invention to provide the PRA as defined above, wherein said LS additionally comprises an automatic release section (ARS) which automatically releases the two sections of said PRA once said patch is at least partially
25 inserted into said body cavity; said ARS comprising a tilted tab and pin.

It is another aspect of the present invention to provide the PRA as defined above, wherein said PRA additionally comprises an anti-buckling section ABS adapted to prevent buckling of said distal portion of said PIS during said insertion of said patch.

It is another aspect of the present invention to provide the PRA as defined above, wherein said PRA additionally comprises an insertion tip adapted to enable better insertion of said PRA.

One embodiment of the present invention provides a method for facilitating rolling of a mesh onto a surgical instrument. The method comprises: operably coupling a device that facilitates rolling of a mesh onto a surgical instrument to an unrolled mesh; and using the device to thereby roll the mesh onto the instrument; wherein the device comprises a sleeve comprised of two parts joined together and a plurality of rigid fins connected to a distal end of the sleeve; wherein the two parts of the sleeve are movable to effect an open configuration for operably coupling with the unrolled mesh on the surgical instrument, and a closed configuration for facilitating rolling of the mesh onto the instrument and said plurality of fins open a valve of a port.

It is another aspect of the present invention to provide a method for rolling a prosthetic patch onto a surgical tool. The method comprising steps selected inter alia from:

- 15 a. obtaining said prosthetic patch to be rolled on said surgical tool;
- b. obtaining a patch rolling apparatus (PRA) comprising at least two sections hinge-like coupled together; said PRA is characterized by at least two configurations; (i) an open configuration (OC) in which said two sections are apart to create a gap into which said prosthetic patch can be inserted; and, (ii) a closed configuration (CC) in which
20 said gap is minimized or eliminated such that said PRA substantially envelops said prosthetic patch and enables said rolling of said prosthetic patch;
- c. configuring said PRA to be in said OC;
- d. at least partially coupling said patch to said surgical tool;
- e. inserting said surgical tool coupled to said patch into said PRA through said gap;
- 25 and
- f. rolling said patch inside said PRA while continually transforming said PRA from its said open configuration into its said closed configuration.

It is another aspect of the present invention to provide the method as defined above, additionally comprising the step of continuing rotating said patch inside said PRA until the entire patch is rolled inside PRA.

It is another aspect of the present invention to provide the PRA as defined above,

5 additionally comprising the step of inserting said rolled patch into a body cavity through a laparoscopic cannula or through an incision.

It is another aspect of the present invention to provide the PRA as defined above, additionally comprising the step of transforming said PRA into its said open configuration and decoupling it from said surgical tool.

10 It is another aspect of the present invention to provide the PRA as defined above, additionally comprising the step of providing said PRA with a locking section (LS) adapted to maintain said PRA in its said closed configuration.

It is another aspect of the present invention to provide the PRA as defined above, additionally comprising the step of providing said PRA with a release tab adapted to

15 allow said release of said locking; such that once said release tab is pressed said PRA is transformed into said OC.

It is another aspect of the present invention to provide the PRA as defined above, additionally comprising the step of providing said PRA with an automatic release section (ARS) which automatically releases the two sections of said PRA; said ARS

20 comprising a tilted tab and pin.

It is still an aspect of the present invention to provide the PRA as defined above, additionally comprising the step of providing said PRA with an anti-buckling section ABS.

It is lastly an aspect of the present invention to provide the PRA as defined above, additionally comprising the step of providing said PRA with an insertion tip.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying 5 drawings, wherein:

Figs. 1A-1B illustrate a preferred embodiment of the present invention.

Figs. 2A-2G illustrate a method in which said PRA 100 is being utilized together with a patch introducing system 202 (PIS).

10 Figs. 3A-3B illustrate another embodiment of the present invention in which a locking section (LS) is used.

Figs. 3C-3F illustrate another embodiment of the present invention in which an automatic release section (ARS) is used.

Figs. 4A-4C illustrate another embodiment of the present invention in which an anti-buckling section ABS 112 and an insertion tip 113 is used.

15 Figs. 5A-E illustrate another embodiment of the present invention in which a furling clip is used.

DETAIL DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The following description is provided, alongside all chapters of the present invention, so as to enable any person skilled in the art to make use of the invention and sets forth the best modes contemplated by the inventor of carrying out this invention. Various modifications, however, is 20 adapted to remain apparent to those skilled in the art, since the generic principles of the present invention have been defined specifically to provides a device and method for rolling and inserting a prosthetic patch into a body cavity.

The present invention provides a patch rolling apparatus (PRA) wherein said PRA is adapted to assist in rolling a prosthetic patch (e.g. hernia patch) onto a surgical tool (e.g. grasper, patch 25 deployment system) such that said patch can be inserted into a body cavity (e.g. abdominal cavity) during a minimal invasive surgery.

It should be emphasized that some of the major advantages of the present invention, with respect to the prior art, is the ability to roll prosthetic patches, especially large patches, faster and easier relatively to the current manual rolling manner.

Furthermore, the present invention enables an easier insertion of said patch into said body
5 cavity relatively to the current manner.

The term "**Hernia**" refers hereinafter to umbilical hernia, hiatal hernia, ventral hernia, postoperative hernia, epigastric hernia, spiegelian hernia, inguinal hernia and femoral hernia, generally any abdominal wall related hernia.

10 The term "**mesh deployment system**" refers hereinafter to any device adapted to deploy a mesh/patch during a hernia surgery.

The term "**hinge**" or "**hinge-like connection**" refers hereinafter as to a type of bearing that connects two solid objects typically allowing only a limited angle of rotation between them. Two objects connected by an ideal hinge rotate relative to each other about a fixed axis of rotation (the geometrical axis of the hinge). Hinges may be made of flexible material or of
15 moving components. The term "**hinge like connection**" can refer to a standard hinge or to a living hinge (i.e., a thin flexible hinge (flexure bearing) made from plastic that joins two rigid parts together while allowing them to bend along the line of the hinge).

20 The term "**minimally invasive surgery**" refers hereinafter to procedures that avoid open invasive surgery in favor of closed or local surgery with fewer traumas. Furthermore, the term refers to a procedure that is carried out by entering the body through the skin or through a body cavity or anatomical opening, but with the smallest damage possible.

The term "**pressurized body cavity**" refers hereinafter to a body cavity (e.g. intraperitoneal cavity) which is insufflated by gas (e.g. CO₂) during a minimal invasive surgery.

25 The term "**closed configuration**" refers hereinafter to the configuration of the PRA 100 shown in figure 1B.

The term "**open configuration**" refers hereinafter to the configuration of the PRA 100 shown in figure 1A.

Before explaining the figures, it should be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention can be carried out in various ways.

5 Reference is now made to Fig 1A-1B illustrating a preferred embodiment of the present invention. According to this embodiment a patch rolling apparatus (PRA) 100 is provided. Said PRA 100 comprises two sections 101 connected to each another via a hinge 102 such that a movement of each of said sections relatively to each other is enabled along and around said hinge 102. Hinge 102 can be either a living hinge on a conventional hinge. Said PRA 100 is
 10 characterized by two separate configurations: an open configuration (OC), as can be seen in Fig 1A and a closed configuration (CC), as can be seen in Fig 1B.

In the open configuration said two sections 101 are positioned apart from each other such that a gap (W) is created between them, through which a pre-rolled patch can be at least partially inserted and encapsulated within said two sections 101.

15 In the closed configuration said two portions 101 are substantially adjacent to one another, creating an internal cavity 103. In a preferred embodiment said cavity 103 contains no sharp edges so as to prevent any damage that may be caused to the patch during said rolling operation.

Reference is now being made to Figs. 2A-2G illustrating a method in which said PRA 100 is
 20 utilized together with a patch introducing system 202 (PIS) in order to roll and insert a patch 201 into a body cavity of a patient during a surgery (e.g. laparoscopic hernia repair surgery).

PIS 202 is defined as a surgical tool intended to insert a patch into the abdominal cavity, e.g. a patch deployment system (as illustrated in Figs 2A-2G), a patch introducer, a laparoscopic grasper or any combination thereof.

25 PIS 202 comprises a distal portion 203 (on which said patch 201 is rolled), proximal portion 204 (which is held by the surgeon) and a shaft 205 connecting said proximal portion 204 and distal portion 203 together.

The method comprises steps selected inter alia from:

1. Obtaining a patch 201 and a PIS 202.
2. Attaching said patch 201 to said distal portion of said PIS 202 (Fig 2A).
3. Obtaining PRA 100 in its said open configuration.
4. Inserting said distal portion 203 of said PIS 202 and at least a portion of said patch 201 into said PRA 100 through said gap W (Fig 2B).
5. Rotating (rolling) said distal portion 203 and said patch 201 inside said PRA 100 while continually transforming said PRA from its said open configuration into its said closed configuration (Fig 2C).
6. Continue rotating said distal portion 203 and said patch 201 inside said PRA 100 until the entire patch 201 is rolled inside PRA 100 (Fig 2D).
7. Inserting said rolled patch 201 into a body cavity (e.g. abdominal cavity) through a laparoscopic cannula 206 or through an incision (Fig 2E-2F).
8. Transforming said PRA 100 into its said open configuration and de-coupling it from said PIS 202 (Fig 2G).

15 It should be mentioned that during said insertion of said patch into said body cavity, the distal portion can be subjected to large forces and therefore may be buckled or deformed. In order to prevent such deformation, said PRA 100 additionally provides external support in order to prevent said buckling or deformation.

20 It also should be mentioned that said PRA 100 holds said patch 201 tightly rolled during said insertion to said body cavity. As a result said insertion is made with less resistance and therefore is faster and safer compare to manual insertion.

Reference is now being made to Figs. 3A-3B which describe another embodiment of the present invention. According to this embodiment, said PRA 100 additionally comprises locking section (LS) 104 which is adapted to hold said PRA 100 in its said closed configuration. 25 Additionally said LS 104 allows the surgeon to release said locking when desired. According to this embodiment, said LS 104 comprises a locking hook 200, attached to one section 101 of said PRA 100 and a locking groove 105 located on the outer surface of the second section 101 of said PRA 100.

Said locking hook 200 comprises a locking tab 106, adapted to be hinged inside said groove 30 105 and a release tab 107, adapted to allow said release of said locking.

Fig 3A describes said PRA 100 in its said open configuration; as can be seen from this figure, in the open configuration said locking tab 106 is not hinged inside said groove 105, therefore a free motion of said two sections 101 is enabled.

Once the said PRA 100 is transformed into its said close configuration, said locking tab 106 is 5 inserted into said groove 105; and, therefore holding the two sections 101 together (see Fig. 3B). In order to reopen said PRA 100, the surgeon presses the release tab 107 of said LS 104 therefore elevating said hook tab out of said groove 105 and releasing the two sections 101 from one another.

Reference is now being made to Figs. 3C-3F which illustrate another embodiment of the present 10 invention. According to this embodiment, said LS 104 additionally comprises an automatic release section (ARS) which automatically releases the two sections 101 of said PRA 100 once said patch 201 is at least partially inserted into said body cavity.

Said ARS comprises a tab 109 and a pin 110. Said tab 109 has a tilted end and is initially located at the proximal end (relative to the surgeon) of said groove 105. Said pin 110 is located 15 inside a hole 111 at section 101.

Once said PRA 100 is transformed into its said closed configuration said locking hook 110 is inserted into said groove 105 (see Fig. 3D).

Once said rolled patch is at least partially inserted into said body cavity, the proximal portion 204 of said PIS 202 pushes said pin 110 and said tab 109 toward the distal end of said groove 105.

As a result tab 109 is pushing said locking tab 106 out of said groove and therefore releasing the two sections 101 (see Figs. 3E and 3F).

Reference is now being made to Figs. 4A-4B which illustrate another embodiment of the present invention. According to this embodiment, said PRA 100 additionally comprises an anti-buckling 25 section ABS 112 and an insertion tip 113.

Said ABS 112 is characterized by having a smaller inner diameter than the rest of said PRA 100. Said ABS 112 is adapted to tightly envelop the shaft of said PIS 202 such that lateral

movement between said distal portion 203 of said PIS 202 and said shaft of said PIS is limited and therefore the risk that the distal portion of said PIS will buckle is reduced.

Said insertion tip 113 is characterized by having a conical shape and is adapted to assist inserting said rolled patch 201 into said body cavity through an incision. Once said patch is 5 completely rolled inside said PRA the surgeon can at least partially insert said insertion tip 113 into said incision, therefore said rolled patch is substantially centered in relation to said incision during the initial stage of said insertion; in addition, said insertion tip 113 opens said incision and allowing an easier insertion of said patch into said body cavity through said incision.

Reference is now made to Figure 4C which illustrate another embodiment of the present 10 invention. According to this embodiment, said PRA 100 additionally comprises insertion fins 401 and 402. These fins are adapted to allow a better insertion of a mesh through a port or an incision by opening the valve (in the case of a port) or the subcutaneous layer (in a case on an incision). This spreading is important since sometimes the port's valve or the tissue may drag the furled mesh backward along the shaft of the instrument during the insertion process, thus 15 increasing its overall cross section and interfering with the insertion process. Spreading of the valve or the tissue reduces the overall friction, therefore allowing better insertion. The fins may be covered by a cap 403.

Figure 5A-5E illustrate an embodiment of a furling clip (FC) 500. Said FC 500 is adapted to assist in rolling a prosthetic mesh around a surgical instrument (e.g. Grasper, mesh deployment 20 device) by securing said patch to the shaft of said surgical instrument during said rolling. Said FC 500 is removed once such rolling is at least partially obtained.

In a preferred embodiment, described in Figure 5A-5B, said FC 500 comprises two sections 501 and 502 which are connected via a hinge 504. A spring 503 is placed between sections 501 and 502 in order to provide clamping force. A clamping edge 505 is located at the distal end of each 25 section 501 and 502, said clamping edge 505 is adapted to hold said mesh and said shaft of said instrument, while allowing the mesh to be rolled only around them and not around the sections 501 & 502; therefore allowing better rolling of the mesh around the shaft and enabling the removal of said FC 500 from said shaft once said rolling is accomplished. Once the proximal end of each section 501 and 502 is squeezed, the two clamping edges are distanced from one 30 another, hence, allowing to locate said FC 500 on said shaft (Fig 5B). Once the pressure is removed spring 503 clamps said FC 500 on said mesh and shaft.

Figs 5C-5E describes a method of using FC 500 during rolling of a mesh 201 on a surgical instrument 509. In this case the instrument is a standard grasper which comprises a handle 508, a shaft 509 and a forceps 507 (Fig 5C). During the operation, the surgeon places a mesh 201 on top of the shaft 509 and secures it by forceps 507 (Fig 5D). In order to prevent slipping of the rear portion of the mesh, and in order to facilitate tight and even rolling of the mesh 201 around the shaft 509, the surgeon places a FC 500 at the proximal edge of the mesh 201 (Fig 5E). Said clamping edges 505 of said edge protrude beyond the edge of each section 501 and 502, enabling the surgeon to roll the mesh around them. The rolling can be made either manually or by a patch rolling apparatus. Once said patch 201 is substantially rolled, said FC 500 is removed from the shaft 509 by squishing sections 501 & 502 and pulling FC 500 back, then the mesh 201 is inserted to the abdominal cavity.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

The embodiments of the present invention for which an exclusive property or privilege is claimed are defined as follows:

1. A device for facilitating rolling of a surgical mesh onto a surgical instrument, the device comprising a sleeve having two parts joined together and movable from an open configuration for operably coupling with an unrolled mesh on a surgical instrument, to a closed configuration for facilitating rolling of the mesh onto the instrument, and a plurality of fins connected to a distal end of the sleeve, wherein the fins open a valve of a port.
2. The device according to claim 1, wherein the two parts of the sleeve are hingedly connected.
3. The device according to claim 1 or 2, further comprising a locking mechanism for locking the sleeve when it is in the closed configuration.
4. The device according to claim 3, wherein the locking mechanism further comprises a member that provides for automatic release of the locked sleeve once the mesh is at least partially inserted into a body cavity.
5. The device according to any one of claims 1 to 4, further comprising an insertion tip.
6. The device according to claim 1, wherein the fins cause spreading of a subcutaneous layer of tissue.
7. The device according to any one of claims 1 to 6, wherein the mesh is a patch.
8. The device according to any one of claims 1 to 7, wherein the instrument is a patch deployment apparatus or a laparoscopic grasper.
9. The device according to any one of claims 1 to 7, further comprising a member at a distal portion of the sleeve that prevents buckling of a shaft of a patch deployment apparatus or a laparoscopic grasper.
10. A device for facilitating rolling of a mesh onto a surgical instrument, the device comprising:

a sleeve having two parts joined together and defining a slit along a length of the sleeve, wherein the two parts of the sleeve are movable from an open configuration for operably coupling with an unrolled mesh on a surgical instrument, to a closed configuration for facilitating rolling of the mesh onto the instrument; and

a plurality of rigid fins connected to a distal end of the sleeve, wherein the fins open a valve of a port.

11. The device according to claim 10, wherein the fins cause spreading of a subcutaneous layer.
12. The device according to claim 10 or 11, wherein the two parts of the sleeve are hingedly connected.
13. The device according to any one of claims 10 to 12, further comprising a locking mechanism for locking the sleeve when it is in the closed configuration.
14. The device according to claim 13, wherein the locking mechanism further comprises a member that provides for automatic release of the locked sleeve once the mesh is at least partially inserted into a body cavity.
15. The device according to any one of claims 10 to 14, wherein the mesh is a patch.
16. The device according to any one of claims 10 to 15, wherein the instrument is a patch deployment apparatus.
17. The device according to any one of claims 10 to 15, further comprising a member at a distal portion of the sleeve that prevents buckling of a shaft of a patch deployment apparatus or a laparoscopic grasper.
18. A method for facilitating rolling of a mesh onto a surgical instrument, the method comprising:

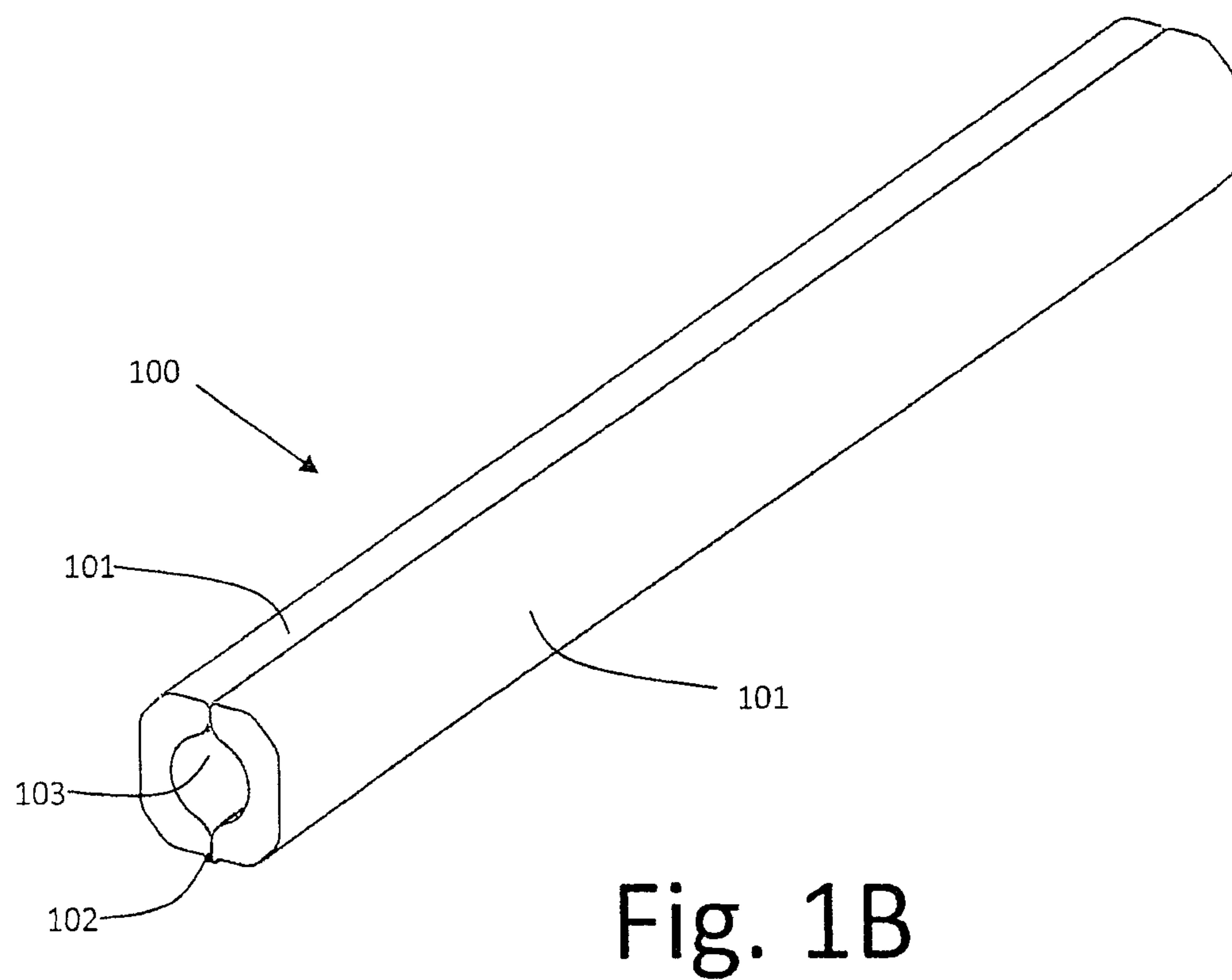
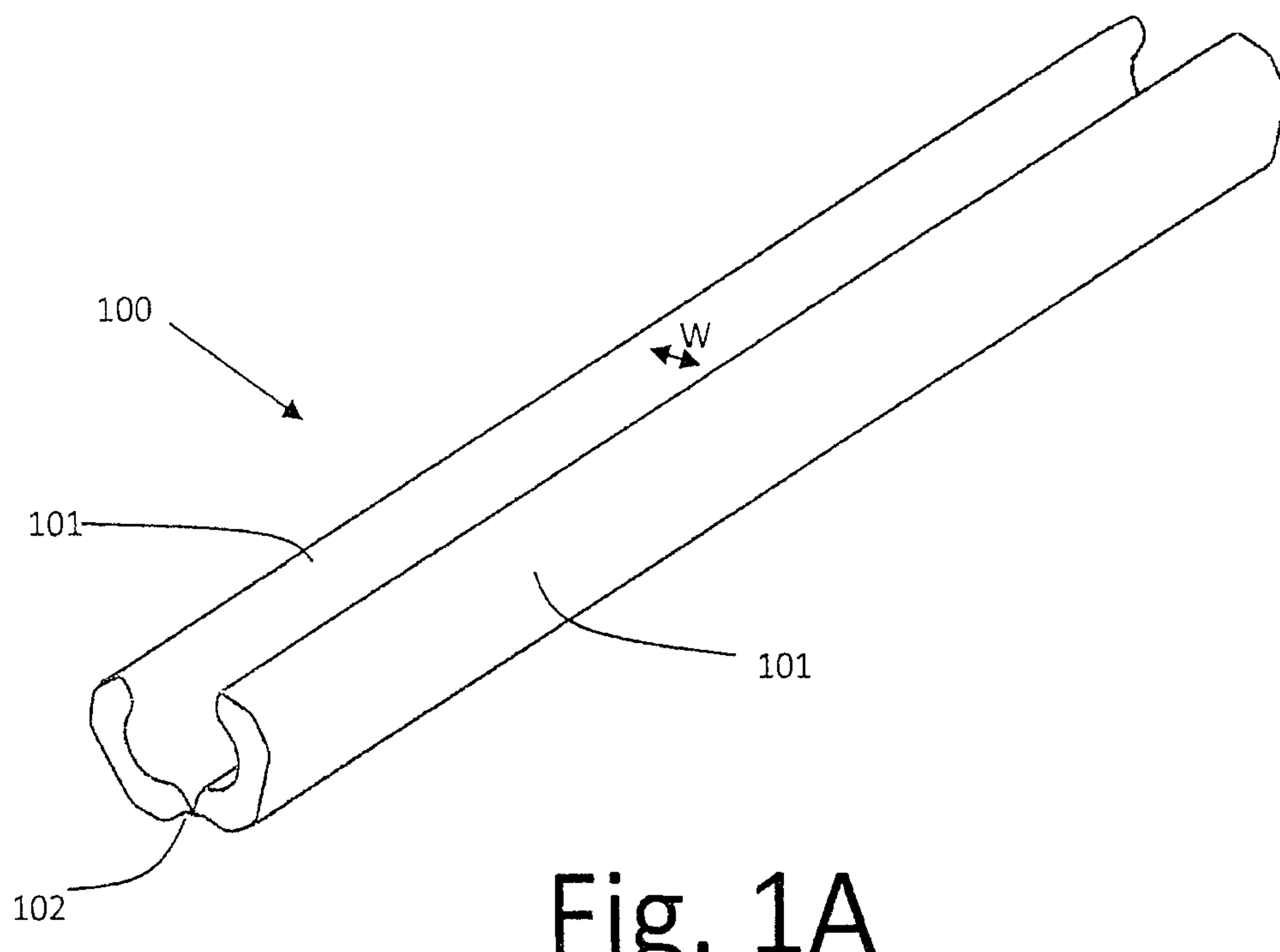
operably coupling a device that facilitates rolling of a mesh onto a surgical instrument to an unrolled mesh; and

using the device to thereby roll the mesh onto the instrument;

wherein the device comprises a sleeve comprised of two parts joined together and a plurality of rigid fins connected to a distal end of the sleeve;

wherein the two parts of the sleeve are movable to effect an open configuration for operably coupling with the unrolled mesh on the surgical instrument, and a closed configuration for facilitating rolling of the mesh onto the instrument and said plurality of fins open a valve of a port.

19. The method according to claim 18, further comprising prior to the coupling step, placing the unrolled mesh onto the surgical instrument.
20. The method according to claim 18 or 19, further comprising prior to the coupling step, attaching the unrolled mesh to the instrument via a clip.
21. The method according to claim 18, 19 or 20, wherein the mesh is a patch.
22. The method according to any one of claims 16 to 19, wherein the instrument is a patch deployment apparatus.



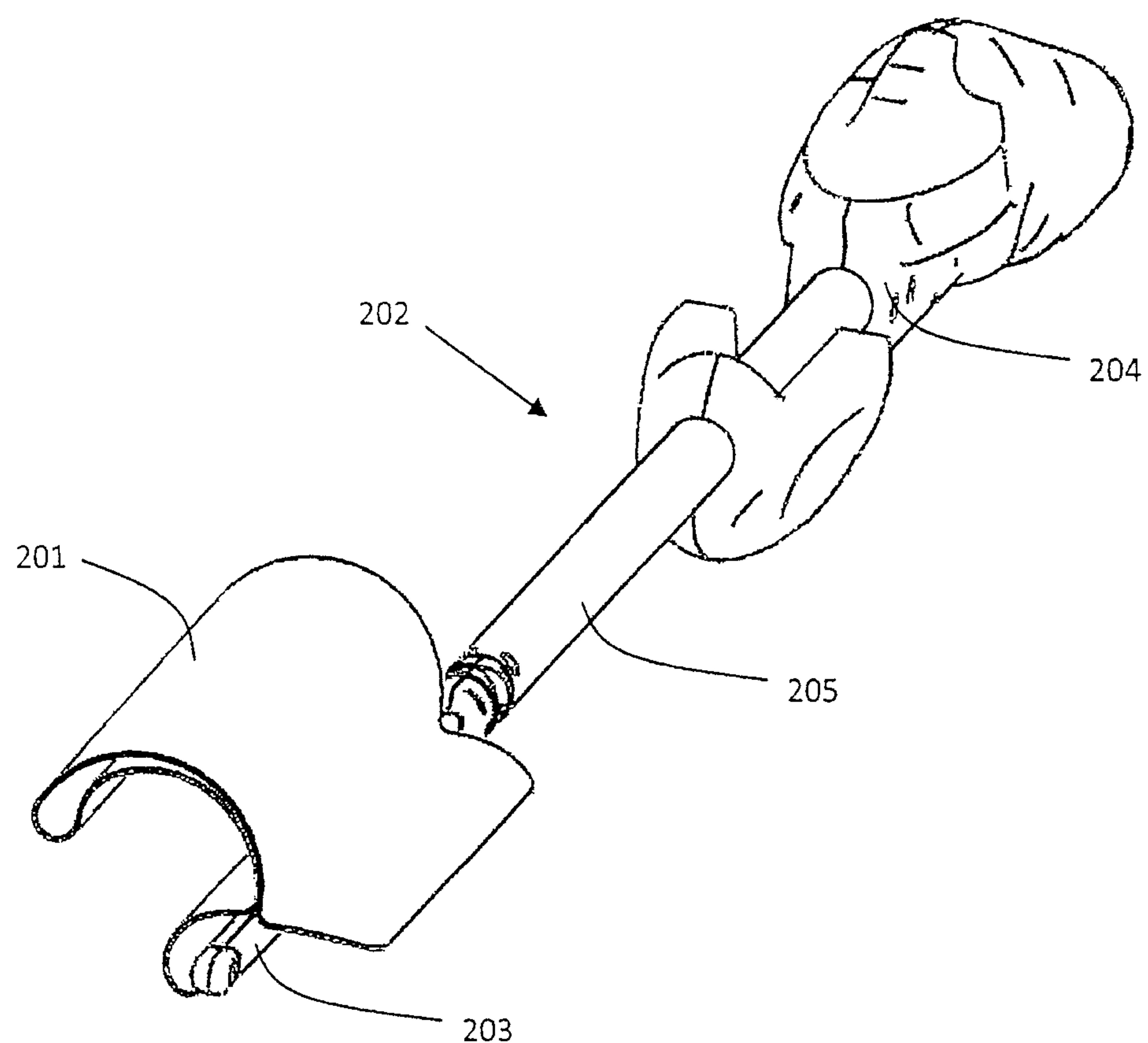


Fig. 2A

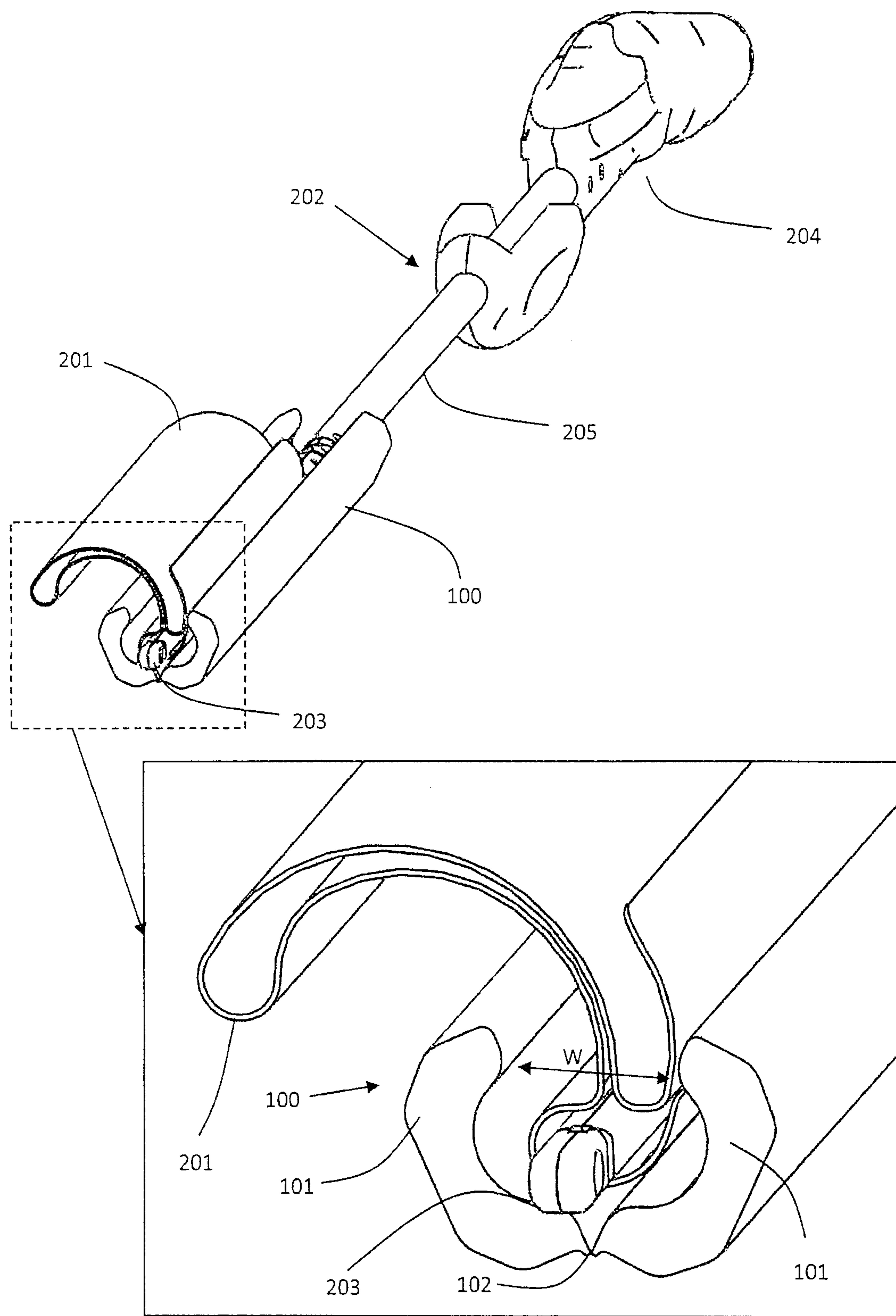


Fig. 2B

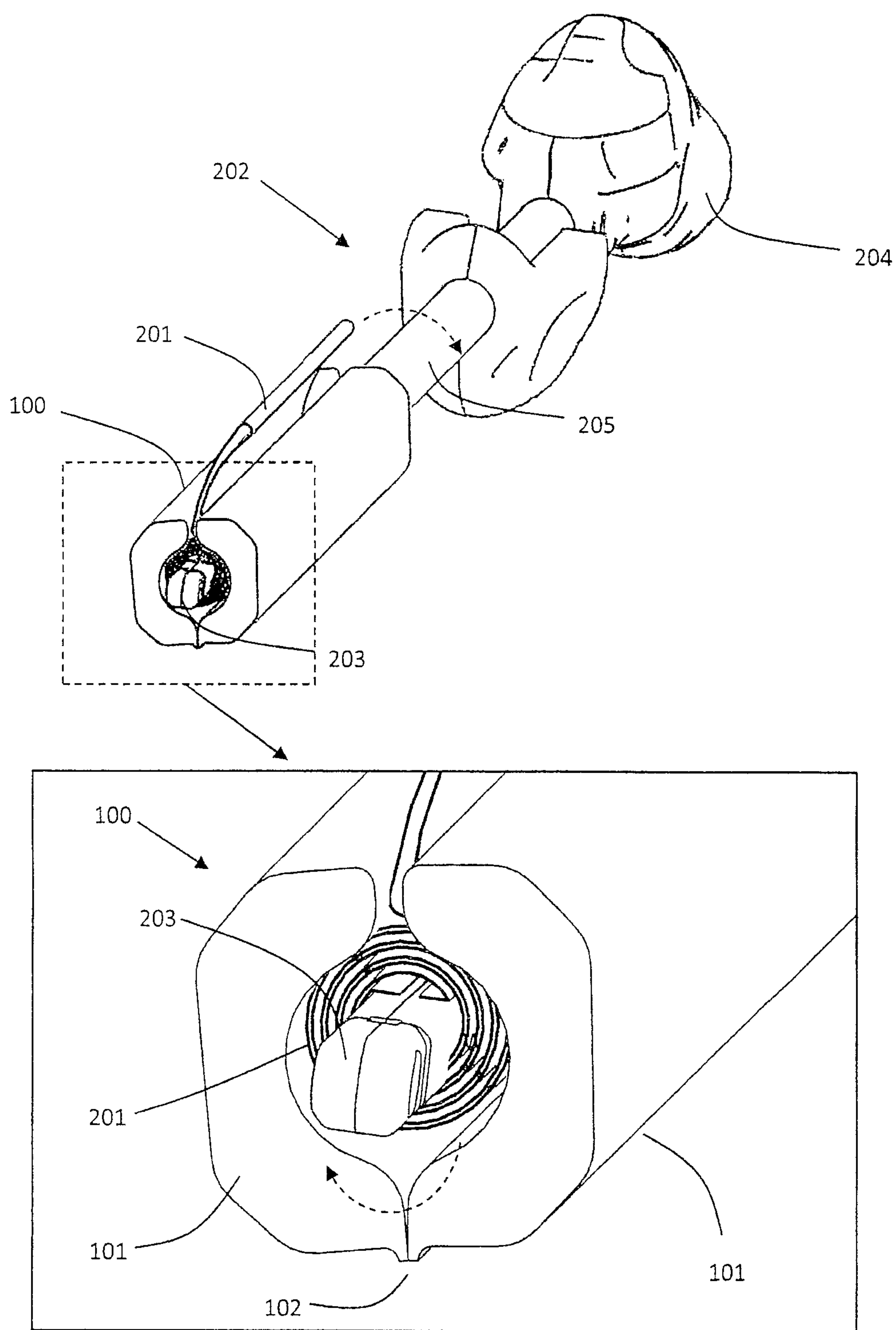


Fig. 2C

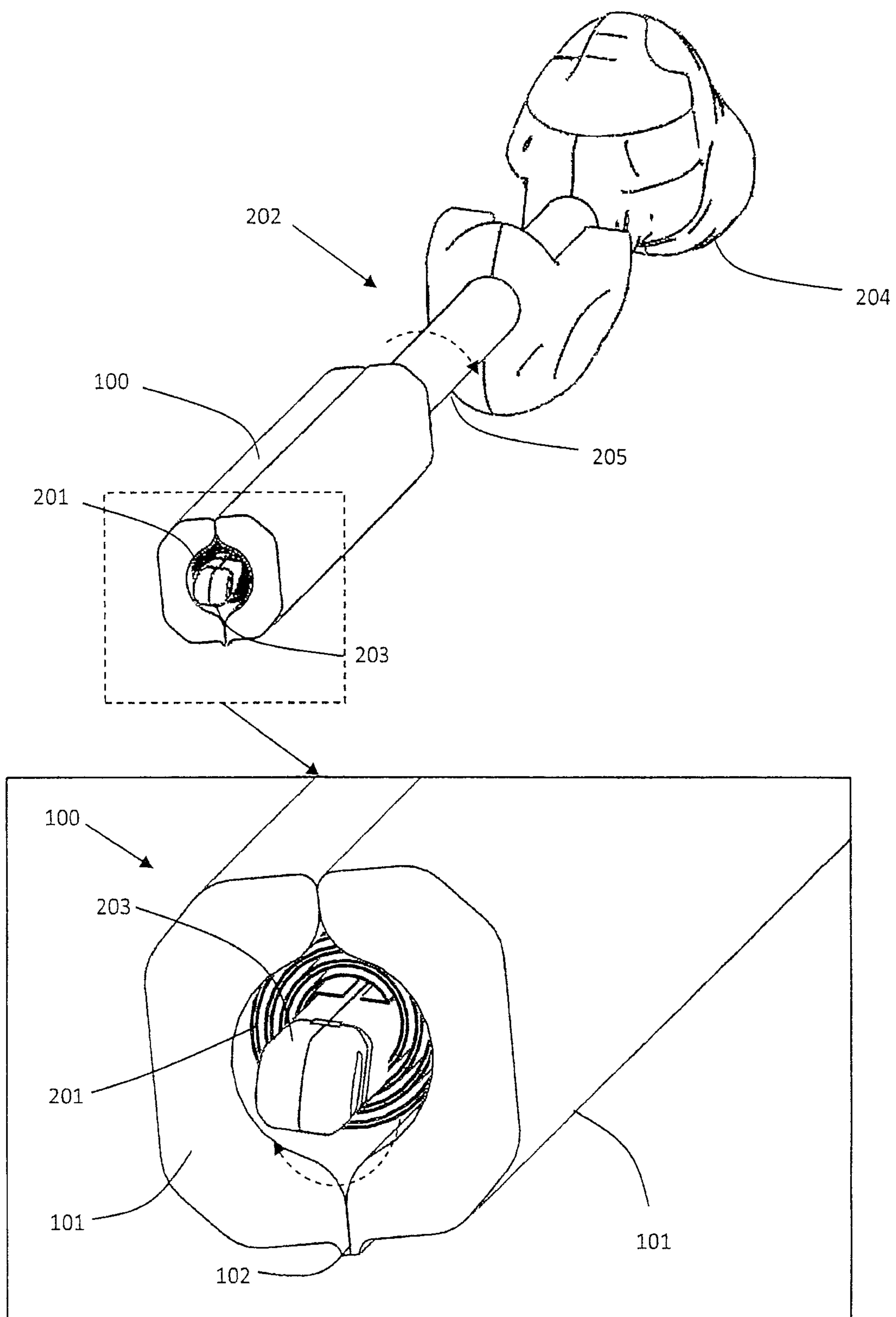


Fig. 2D

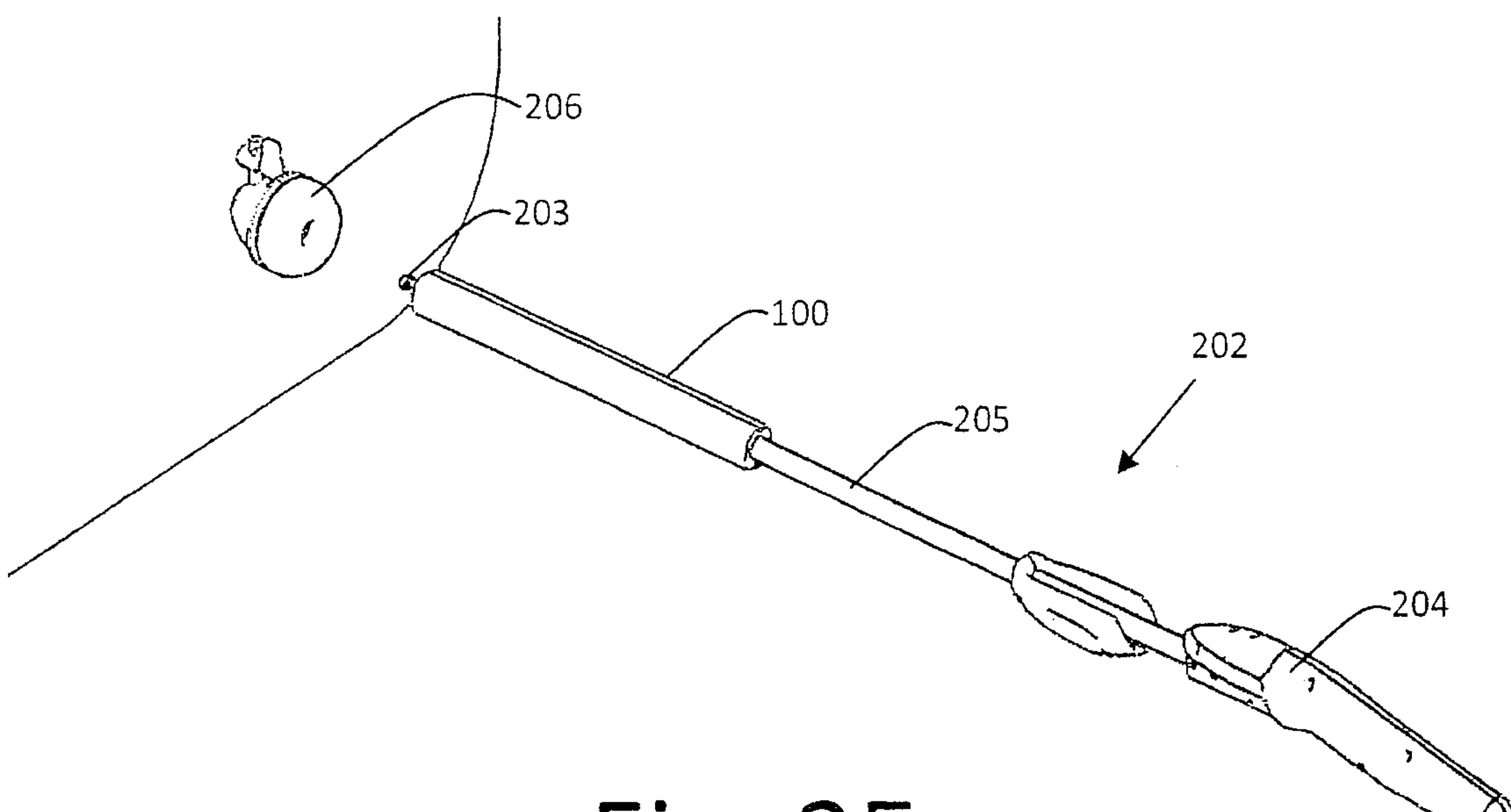


Fig. 2E

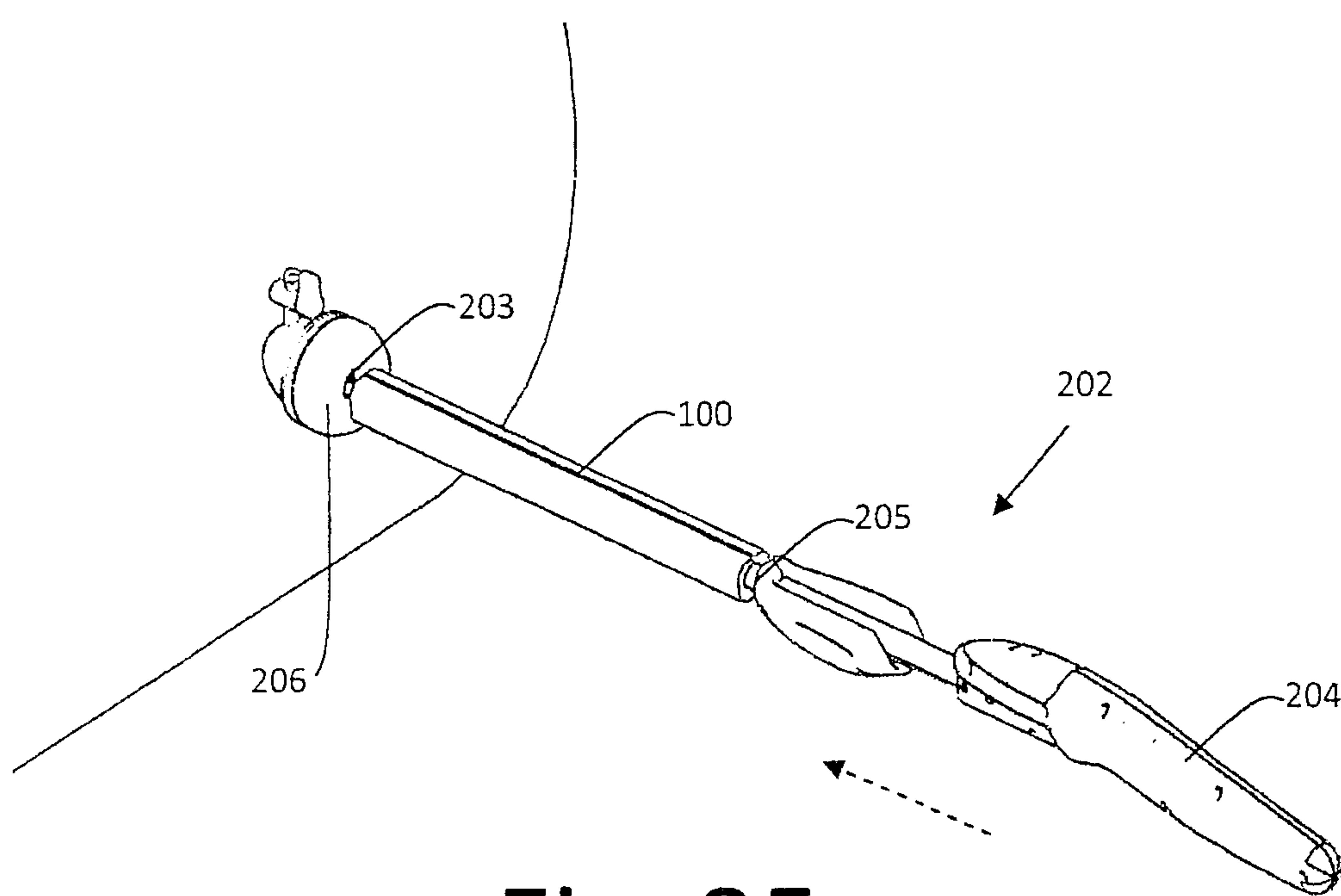
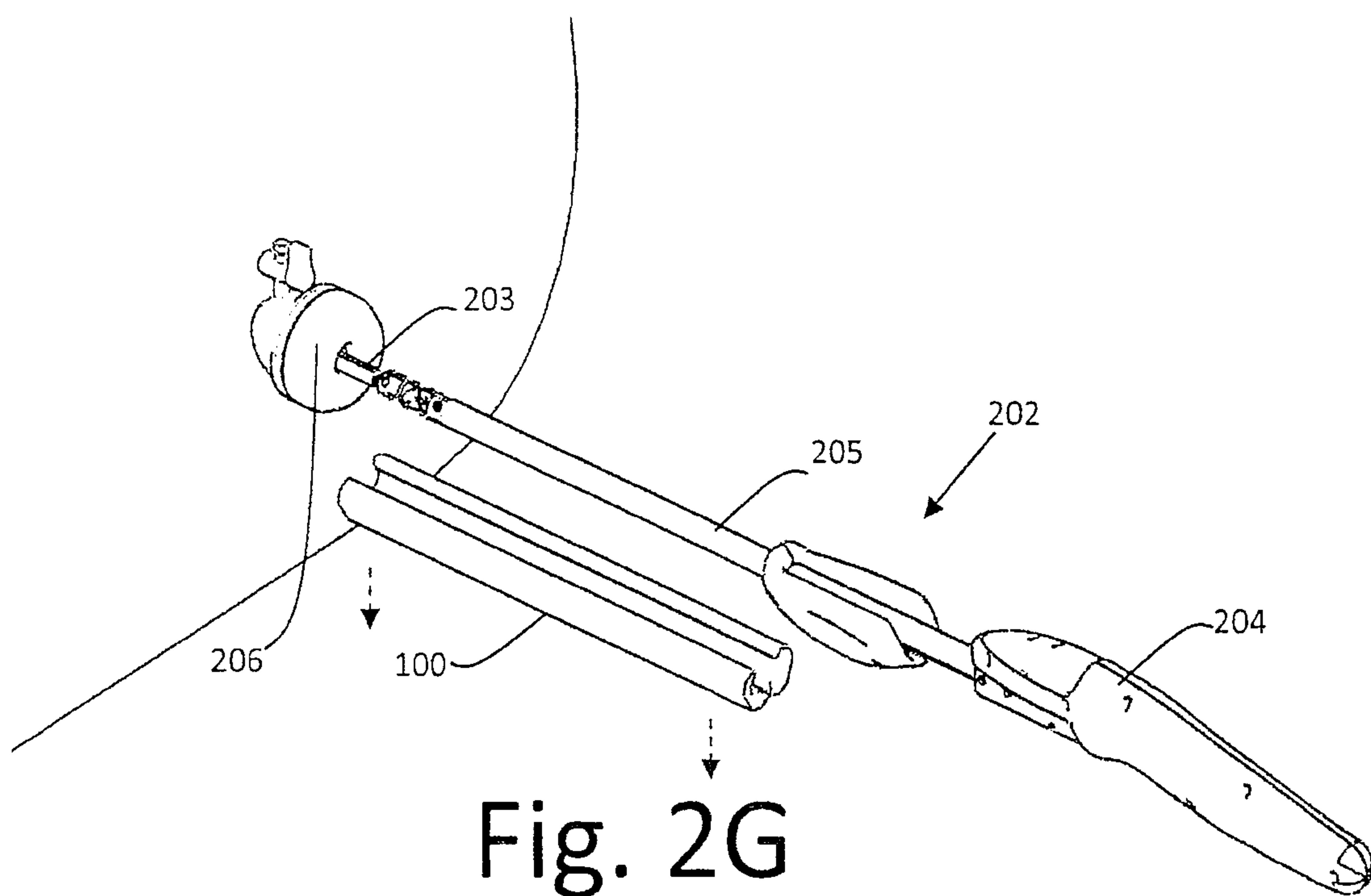


Fig. 2F



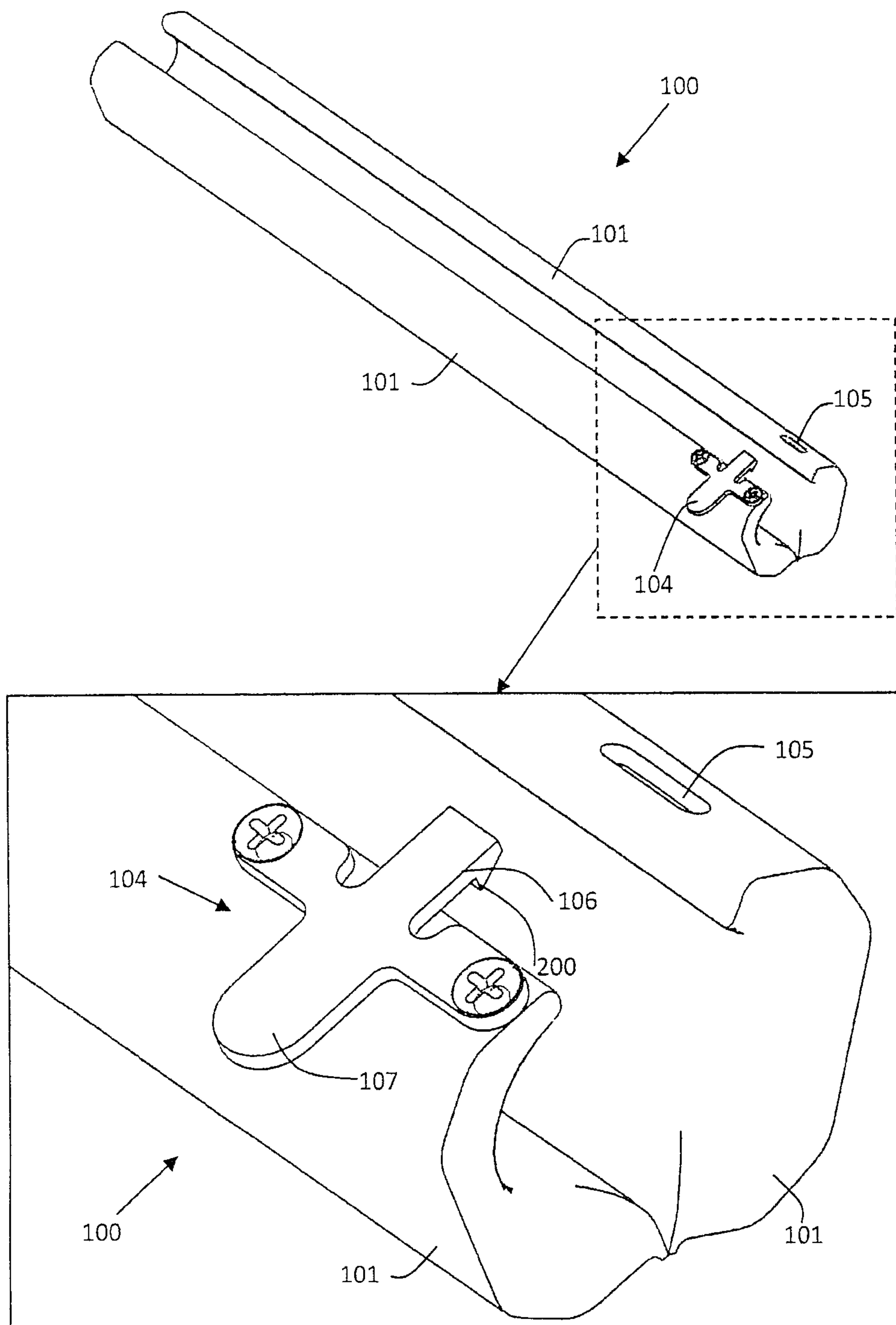


Fig. 3A

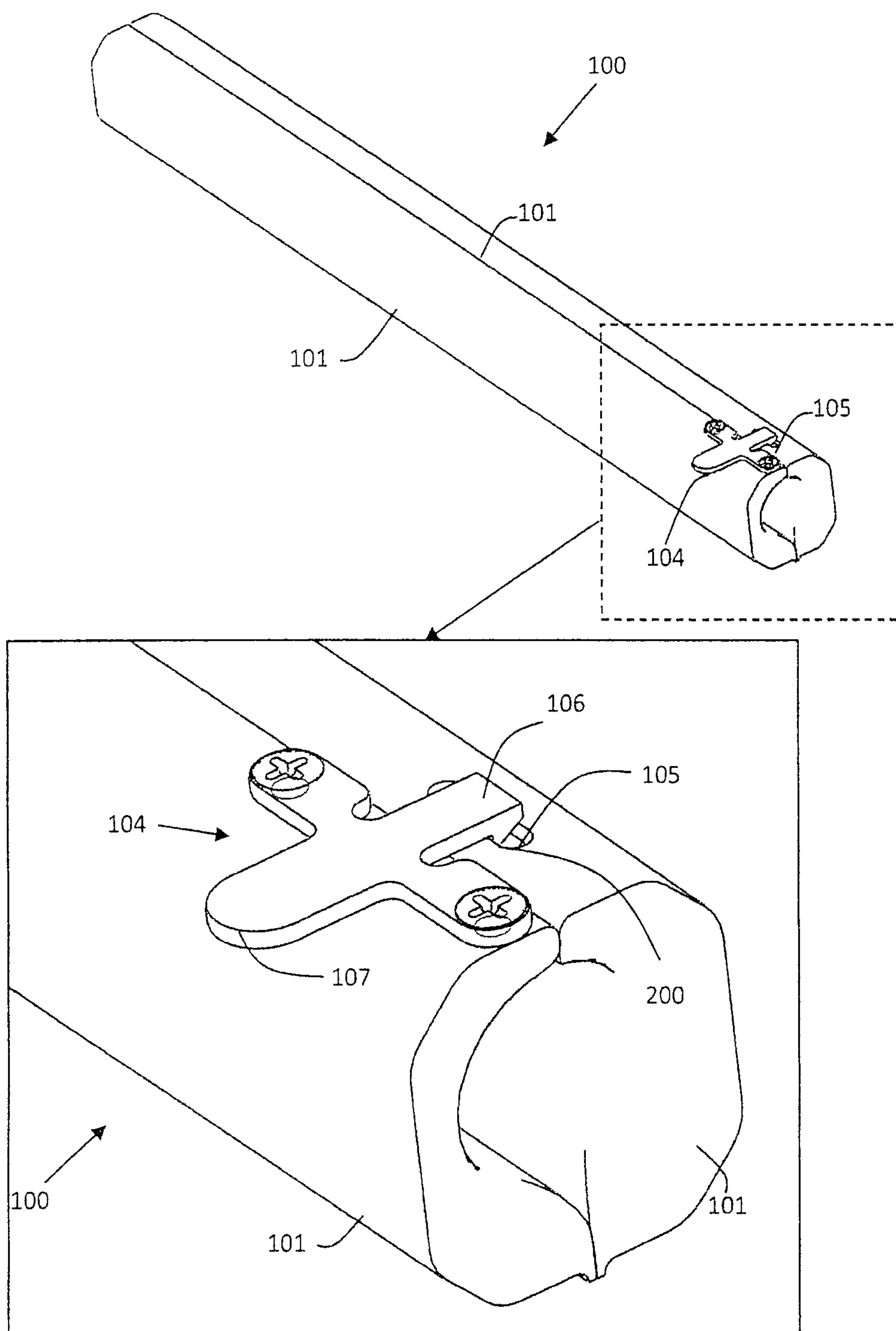


Fig. 3B

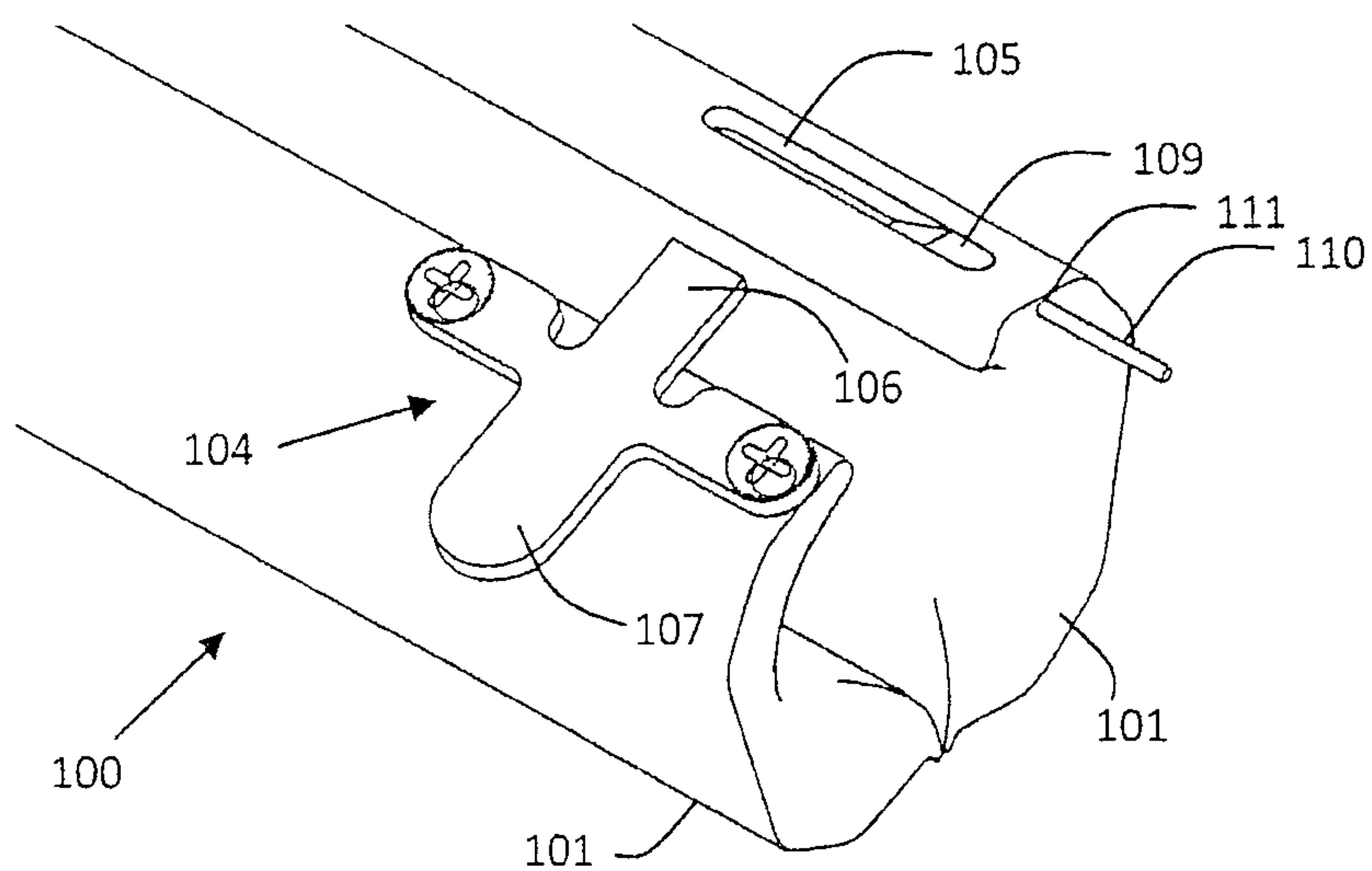


Fig. 3C

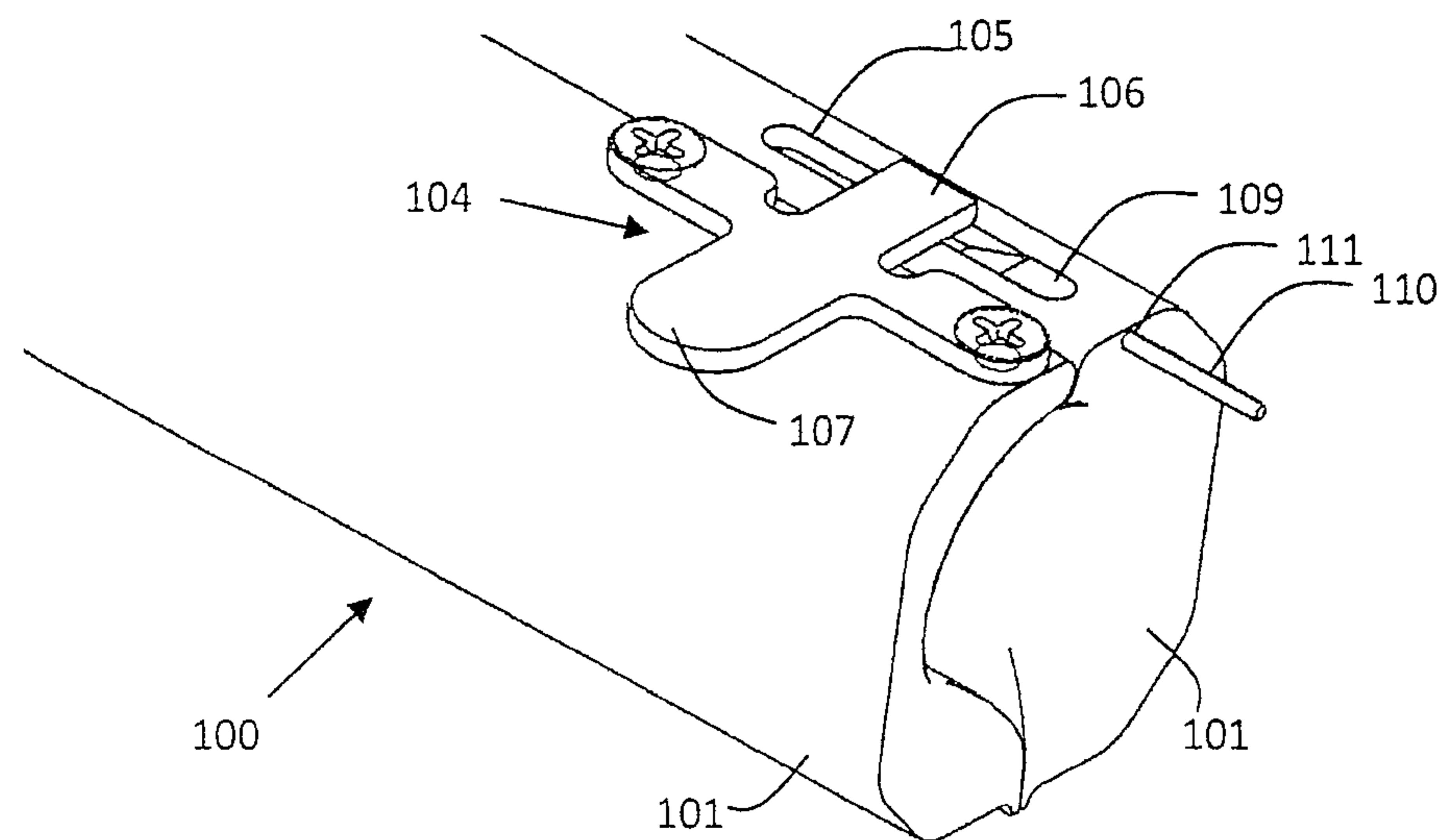


Fig. 3D

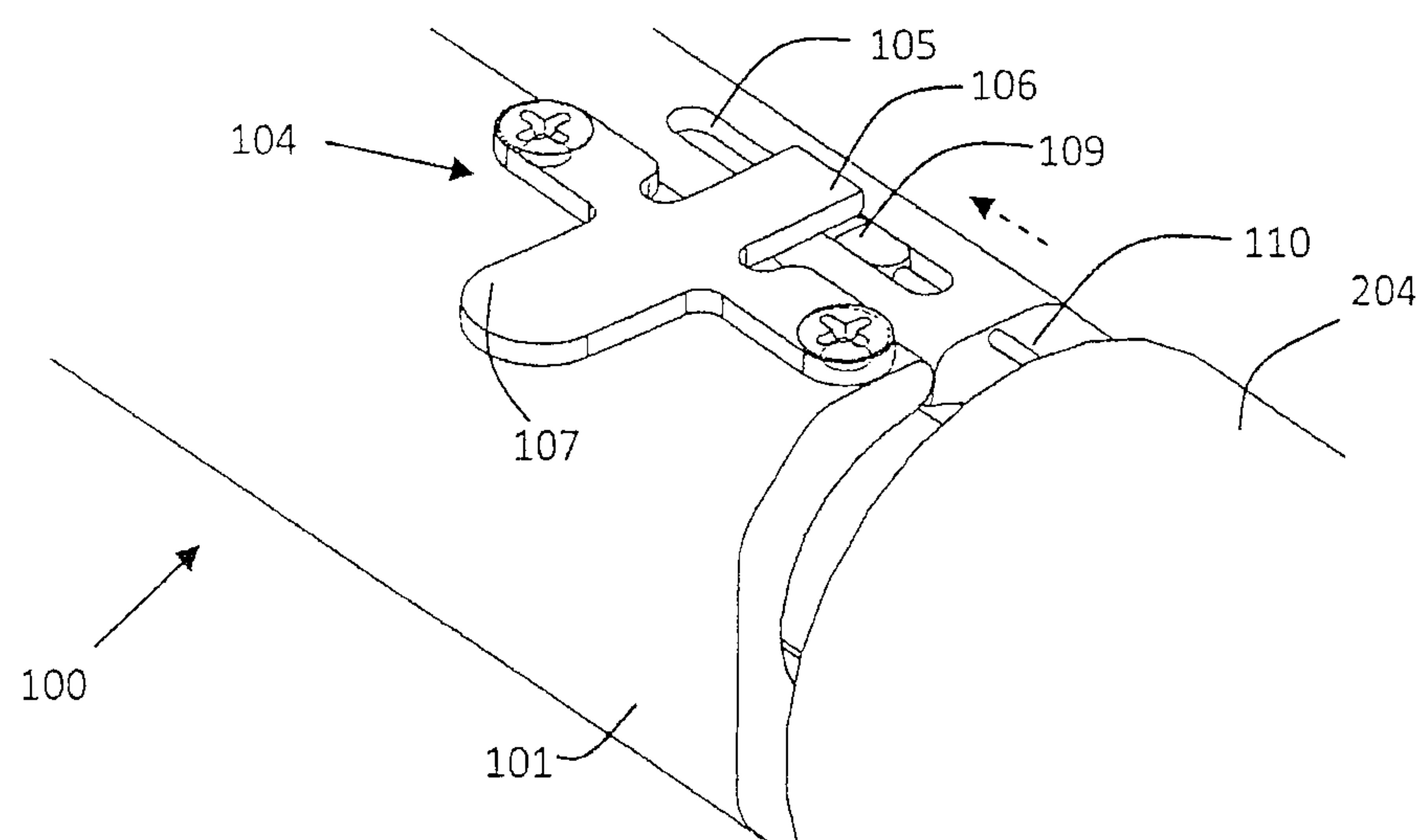


Fig. 3E

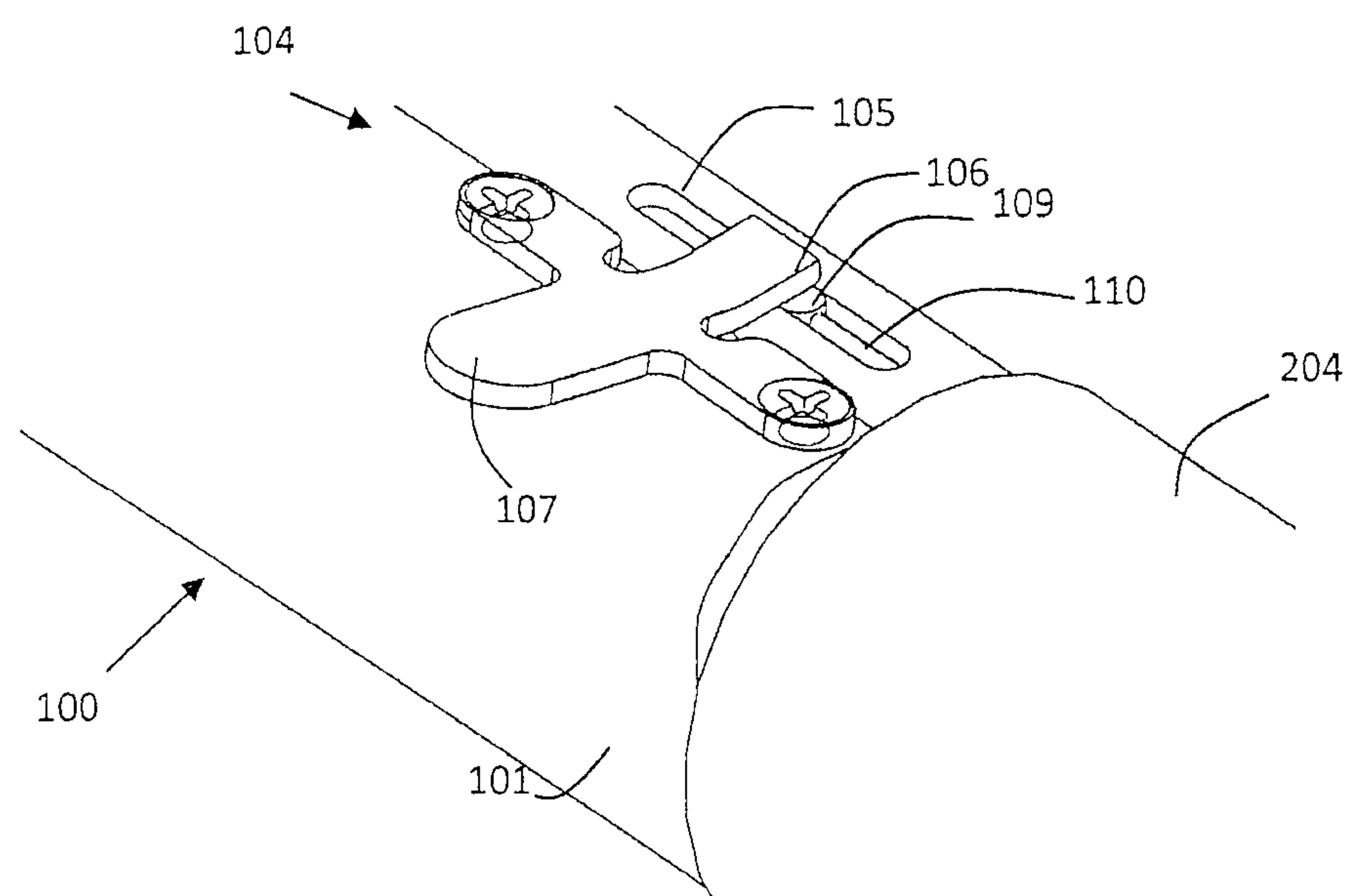


Fig. 3F

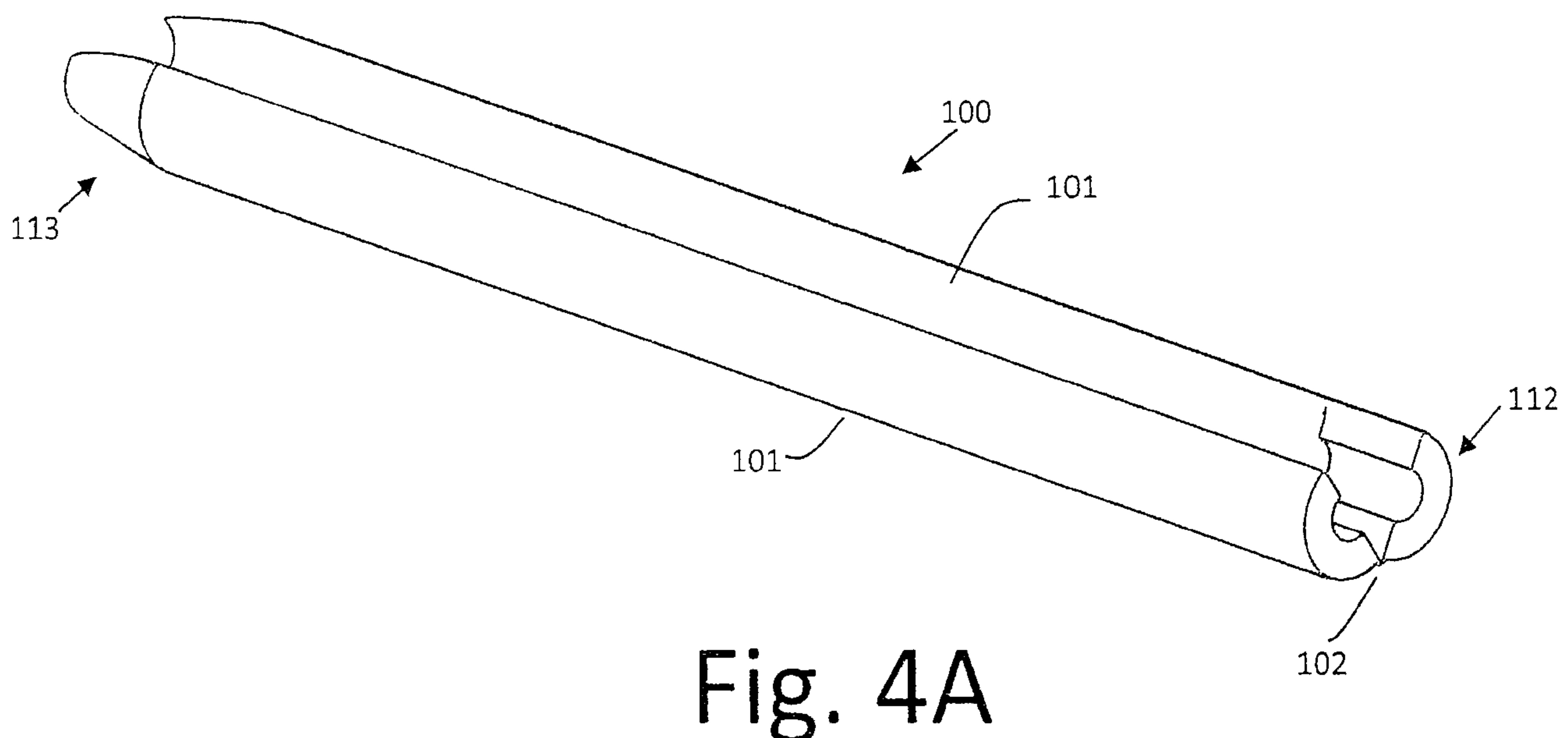


Fig. 4A

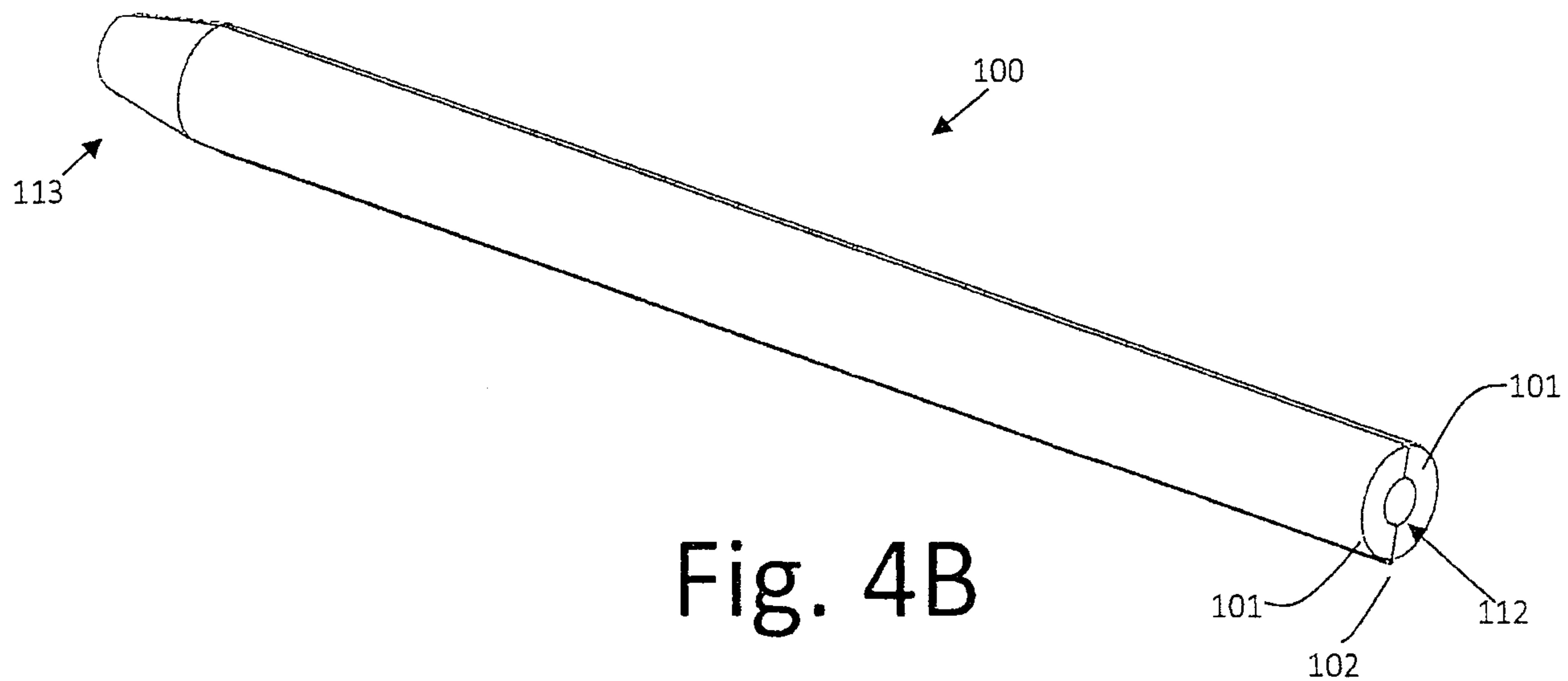


Fig. 4B

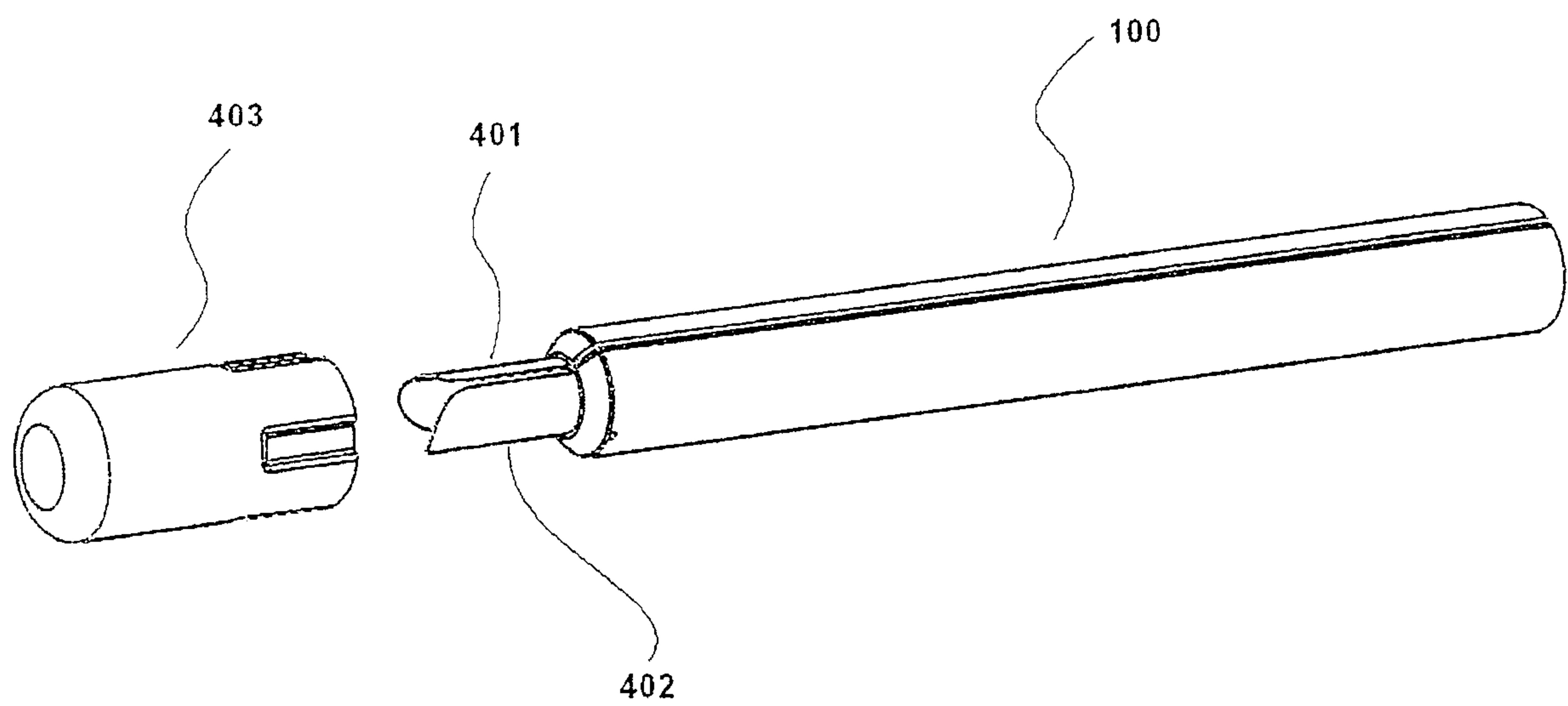


Fig. 4C

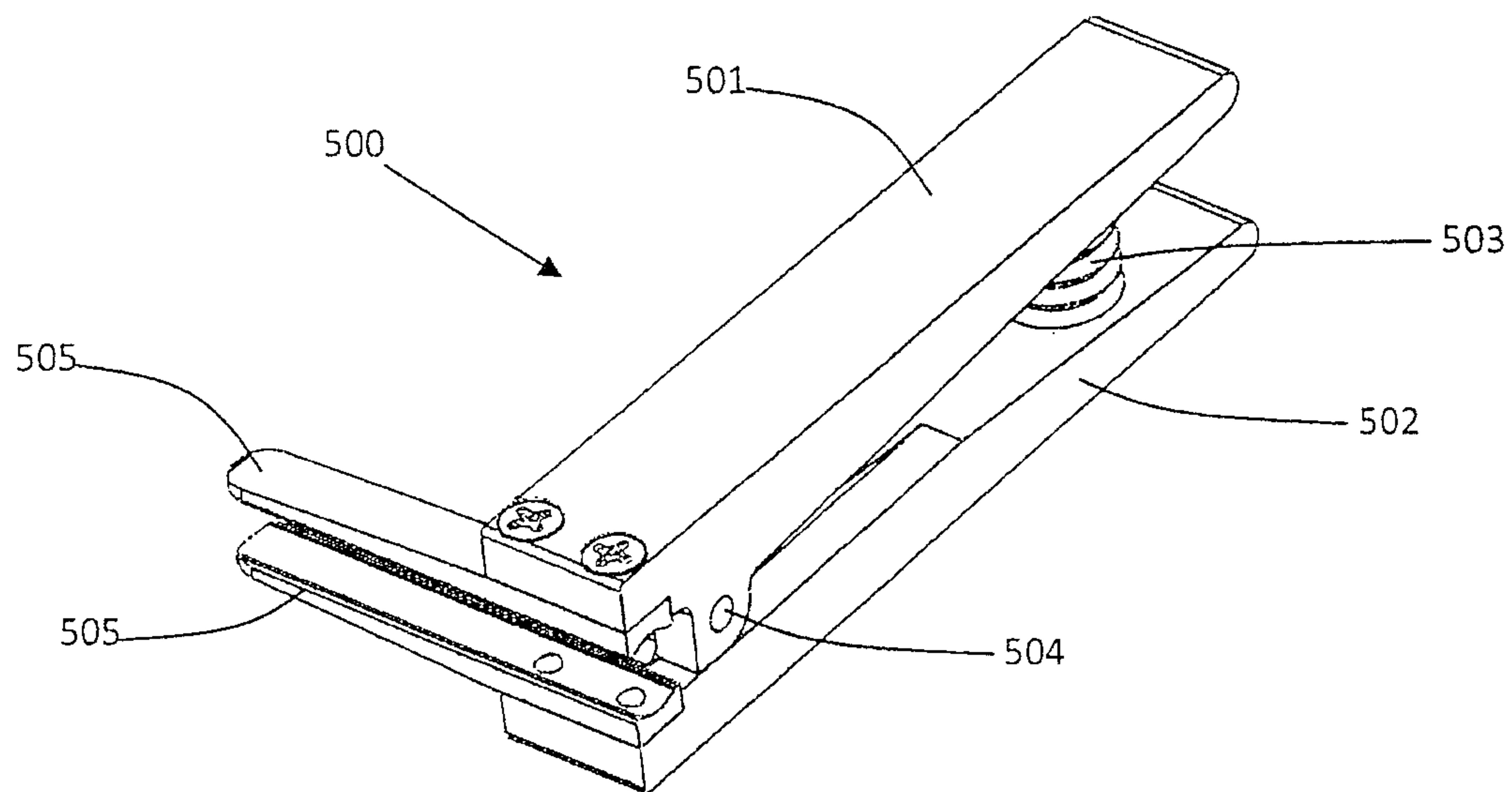


Fig. 5A

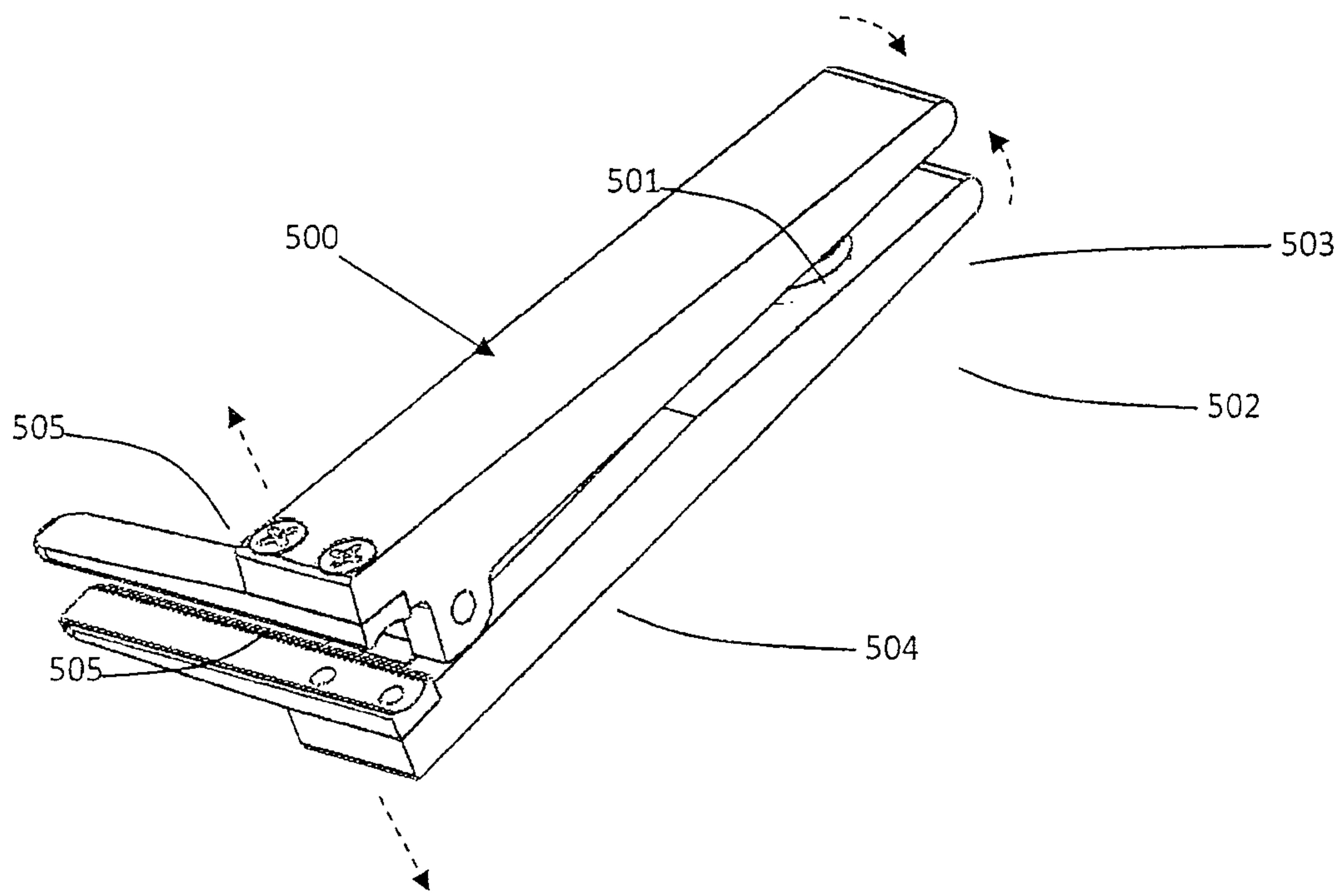


Fig. 5B

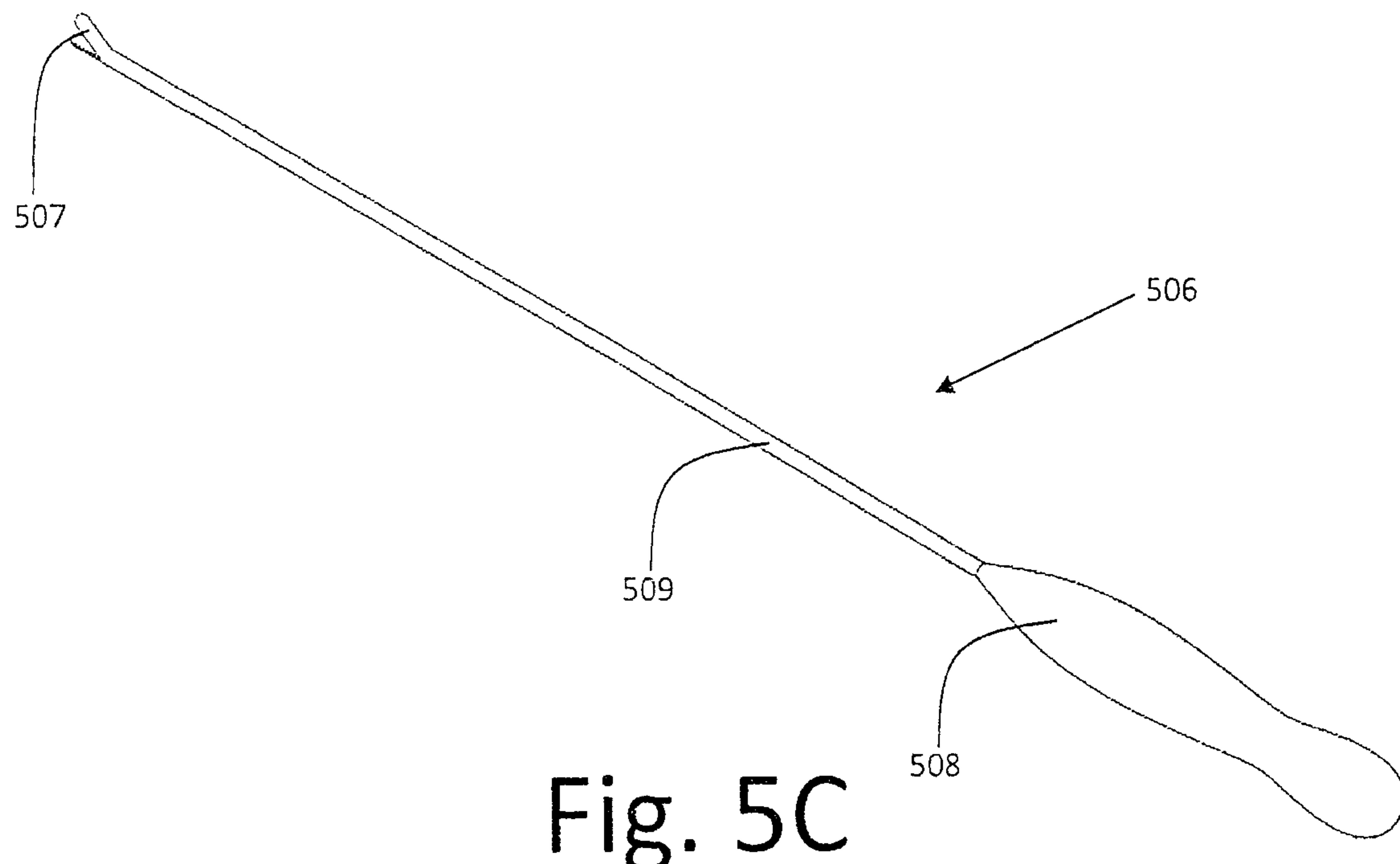


Fig. 5C

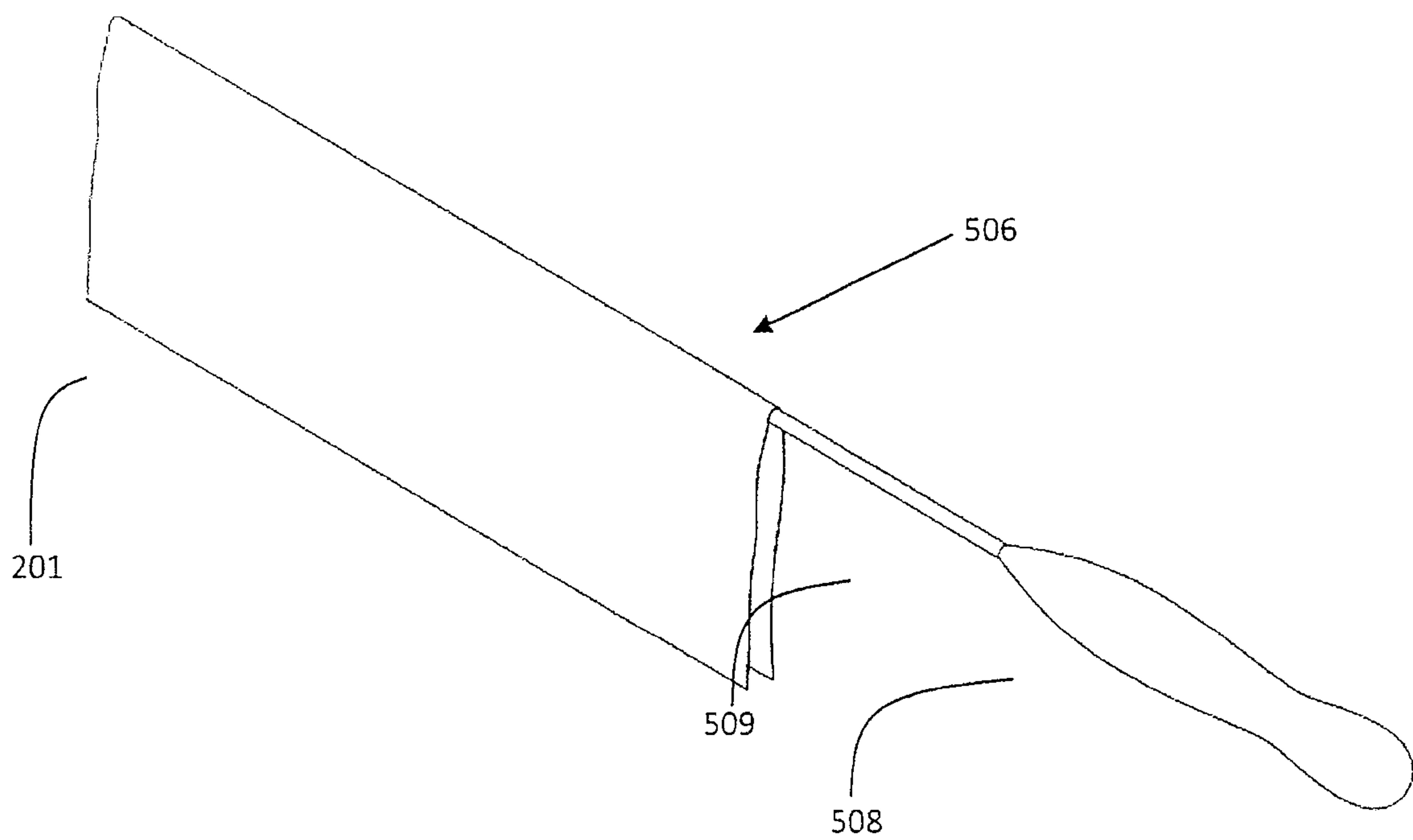


Fig. 5D

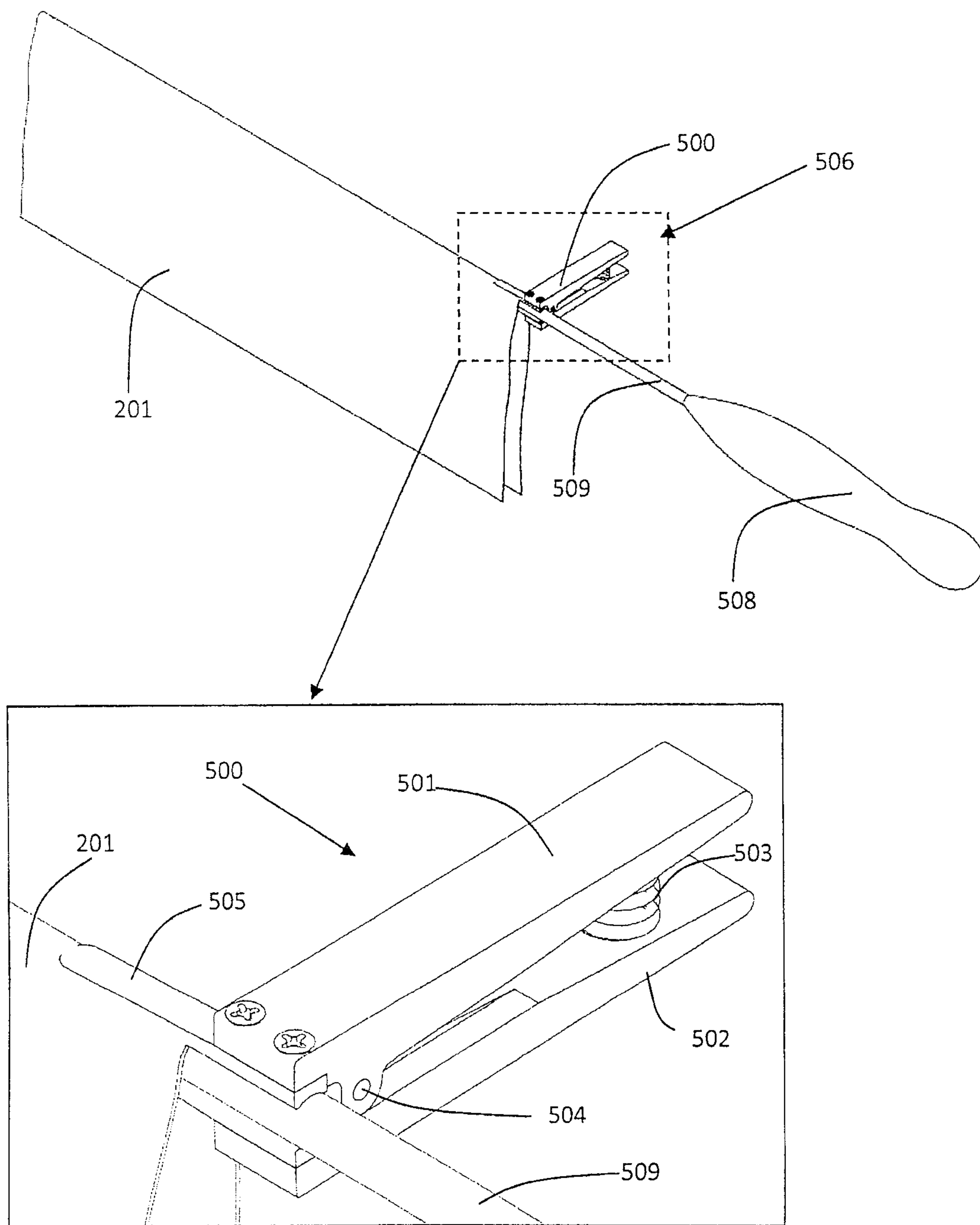


Fig. 5E

