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(57) Abstract: In accordance with the invention a cap for a vessel is provided, the cap comprising an outer tubular element and an inner tubular element located within the outer tubular element, the inner tubular element being separated from the outer tubular element by a cavity, the inner tubular element being attached at an upper end to the outer tubular element; and a septum mounted within the inner tubular element. A vessel assembly comprising the cap, and methods for producing and assembling the cap are also provided.



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VESSEL CAP

FIELD OF THE INVENTION

The present invention relates to sealing systems used for vessels and, more particularly, to a cap incorporating a septum. Sealing systems and caps of this type are particularly applicable to vessels which are accessed using an injection device such as a needle, and where it is important to reduce or prevent contamination of the contents of the vessel. The invention is therefore particularly suited to use in injection ports of vessels employed in biological methods, such as bioreactors.

BACKGROUND OF THE INVENTION

In bioreactors, culture media and cellular products are separated from the ambient environment for reasons of sterility and contamination. Nevertheless access is always required both to withdraw samples for analysis and to feed medium with nutrients, growth factors and other materials required for cell growth. Access for sampling and feeding is usually made by a syringe needle that pierces a flexible and elastic septum.

Typically, the flexible and elastic septum is made of silicone rubber. The septum separates the culture medium and cellular products from the ambient environment and is distinct from the main body of the bioreactor which is usually made of rigid thermoplastic. Septa are usually held in place with a screw cap through which the syringe needle may be inserted by mechanical force.

The septum must serve three functions. First, it must be sufficiently yielding to be pierceable by a standard syringe needle. Second, it must form a seal around the needle to prevent leaks while the injection is effected. Third, it must reseal the bioreactor after the syringe needle has been withdrawn and maintain this seal while the bioreactor is in use. A leak occurring while the needle is in the septum can cause ingress of contaminants. This "injection" leak is difficult to detect because it occurs during the dynamic process of injection and may only be apparent at the end of a multi-day experiment. A failure to seal after the needle is withdrawn is more easily

detected. The resulting "post-injection" leak is evident from leakage of media and loss of media volume.

The screw cap must serve two functions. First, it must be sufficiently robust to screw onto the main body of the vessel and bear down on the rubber septum with sufficient force as to form a tight seal between the septum and the vessel. Second, it must provide an opening through which the syringe needle can be inserted to meet the rubber septum.

Septum deterioration and resulting failure are serious problems. Monitoring a system for leaks can be costly and time consuming. Replacement of seals is inconvenient. Problems of detection and replacement are aggravated in automated systems which may run unattended for as long as 28 days. A failure early in a run can impair the validity of the results and waste the time taken.

Accordingly, it is important to construct the septum arrangement precisely and accurately and to ensure that highest standards are maintained during the assembly of the septum arrangement with the bioreactor.

The manufacture and use of septa and septa caps is known. However, most screw caps and septa are provided as discrete items. This can cause problems with placing or retaining the septum in its correct position over a port of a vessel, particularly when the cap is attached and detached from the vessel. Inaccurate placement of the septum can lead to an inadequate seal and consequent contamination of the vessel.

US 5,088,612 to Storar *et al.* discloses a septum/septum cap construct which may be used for pharmaceutical applications. A vial cap comprises an upper end wall and a skirt portion to press a septum against a neck of the vial and thereby hold the septum in place. However, in this arrangement problems may still occur during removal and attachment the vial cap from the vial.

Another approach is disclosed in US 6,234,335 to Gee *et al.* A septum construct comprises an elastomeric septum fixed to a septum cap by direct bonding. This is disclosed as an alternative to using an adhesive to attach a septum to the cap. The

method involves ionizing a surface upon the elastomer thereby forming a first activated area and ionizing a surface upon the plastic thereby forming a second activated area, then placing the first and second activated areas in contact with one another and applying pressure thereto thereby forming a direct bond between the elastomer and the plastic.

Nevertheless, it is recognised that this and other methods of attaching septa to septa caps may introduce additional unwanted and unregulated materials into close contact with pharmaceutical products. There is therefore a need for an improved septum arrangement in which the septum forms a tight seal over the port of the vessel, without allowing contamination of the vessel and whilst facilitating accurate placement of the septum during removal and refitting of the cap.

A further and related problem is septum deterioration due to the action of the syringe needles used for injection. Syringe needles must be strong enough to pierce the septa without bending or buckling. This strength requirement leads to the use of larger diameter needles. Larger diameter needles require greater insertion force to pierce a septum, which is thus subject to greater wear. The larger needles also make larger holes or tears in the septum, which are harder to reseal after needle withdrawal. Needles of smaller diameter cause less damage to the septum and make resealing easier, but are much more susceptible to bending when piercing a seal.

Syringe needles are made with sharp, bevelled points to slice through the septa with lower force. However, the slicing action of repeated injections with bevelled needles can lacerate a septum, which then begins to leak. In addition, small pieces of rubber torn from a septum by the needles can fall into the reactor. The integrity of the septum may also be affected by the precision of the needle placement by the operator.

Taking into account these considerations, most medical devices that rely on a septum as a means to withdraw samples or add cell growth material use a rubber septum, approximately 3 mm thick and 6-12 mm in diameter. Syringes needles typically used with such septa are 10 microliter total capacity, with a sharp beveled 26 gauge, i.e., 0.48 mm diameter, needle. These are used for both manual injection and for automatic liquid samplers.

Table 1. Needle dimensions

<u>Diameter (Gauge)</u>	<u>Diameter (mm)</u>
25	0.5
26	0.45
27	0.4

There is therefore still a need for a septum arrangement which reduces the problem of laceration of the septum during repeated use.

The present invention aims to address one or more of the above problems and in particular to provide an improved cap for a vessel comprising a septum.

SUMMARY OF THE INVENTION

Accordingly, in one embodiment the present invention provides a cap for a vessel, the cap comprising (a) an outer tubular element and an inner tubular element located within the outer tubular element, the inner tubular element being separated from the outer tubular element by a cavity, the inner tubular element being attached at an upper end to the outer tubular element; and (b) a septum mounted within the inner tubular element.

In a further embodiment, the present invention provides a vessel assembly comprising (a) a vessel having a neck portion; and (b) a cap as defined above; wherein the neck portion of the vessel is located within the cavity separating the inner tubular element from the outer tubular element of the cap.

In a further embodiment, the present invention provides a method for assembling a cap as defined above, comprising forming at least the inner tubular element and outer tubular element, and mounting the septum in the inner tubular element.

In a further embodiment, the present invention provides a method for producing a cap as defined above, comprising forming a first thermoplastic component and a second

thermoplastic component, and joining the first and second thermoplastic components by ultrasonic welding.

In a further embodiment, the present invention provides a cap for a vessel, the cap comprising a septum mounted within the cap and a guide ring positioned above the septum for directing a tip of an injection device to puncture the septum at a defined portion of the septum below the guide ring.

The present inventors found that the process of attaching commercially available screw caps to the body of a vessel such as a bioreactor, whilst ensuring that the septum remained accurately positioned in the screw cap, was problematic. In addition it was found that operators on the production line had considerable difficulty in positioning the septum precisely and accurately within the screw cap and maintaining its position whilst screwing the screw cap/septum arrangement onto the body of the vessel. During use of the bioreactor, particularly charging the bioreactor requires that the cap/septum arrangement is removed from the port to allow charging. During this activity the septum could become separated from the cap and be lost.

This problem is addressed in embodiments of the present invention by mounting the septum within the cap in the inner tubular element referred to above. When the cap is screwed or pushed onto a vessel, the inner tubular element fits within the neck of the vessel and securely positions the septum between the interior of the vessel and the external environment. Preferably the septum forms a water- and/or airtight seal between the interior of the vessel and the external environment. The cap is firmly held in place on the vessel by positioning the neck of the vessel in the cavity between the outer and inner tubular elements. A screw thread can be used to further secure the cap to the neck of the vessel.

Because the septum is securely mounted in the inner tubular element of the cap, the problem of inaccurate placement and loss of the septum during cap removal and refitting is avoided. The septum can be mounted within the inner tubular element by various retaining means without the need for adhesives or other materials which may contaminate the contents of the vessel.

For instance, the septum may be mounted within the inner tubular element by a push-fit arrangement. In one embodiment the septum may be mounted by means of an annular groove cut into an internal surface of the inner tubular element. In another embodiment the septum may be mounted by means of one or more flanges extending away from an internal surface of the inner tubular element. A single flange element may run around the entire internal circumference of the inner tubular element, or alternatively a plurality of smaller flanges at discrete positions may be provided.

The vessel to which the cap is to be fitted is preferably a bioreactor. The vessel may comprise one or more ports or neck portions to which a cap of the present invention may be fitted. The vessel may also be adapted to ensure accurate and secure fixing of the septum, for example in one embodiment by providing a lip within the vessel neck which abuts the septum when the cap is positioned on the vessel. In this embodiment, engagement of a screw thread on the outer tubular element with a matching thread on the neck of the vessel may lead to pressure being exerted on the septum by the lip to produce a seal. In further embodiments, a combination of a groove, flange(s) and/or lip may be used to position and secure the septum.

The septum may be formed from any suitable material. Typically the septum is formed from a flexible and elastic material which can be perforated by a needle to permit injection or aspiration of a fluid there through. The septum may be formed from *silicone rubber or a similar material*.

The inner tubular element has a diameter smaller than and is located at least partially within the outer tubular element. However, in some embodiments the inner tubular element need not necessarily be fully disposed within the outer tubular element, for instance in the sense that the inner tubular element may be longer than the outer tubular element. Thus in one embodiment a lower end of the inner tubular element may extend below a lower end of the outer tubular element, i.e. the inner tubular element may extend further into the vessel to which the cap is fitted.

Embodiments of the invention also address the problem of septum deterioration, by ensuring that the needle is placed more precisely over the septum and enabling cleaner penetration. Accordingly in some embodiments the cap comprises an

alignment element which can guide an injection device such as a syringe needle into the same puncture hole on repeated injections. In certain preferred embodiments, the alignment element is disposed at least partially, or more preferably fully within the inner tubular element. However in alternative embodiments the inner alignment element may extend at least partially outside the inner tubular element, for instance the alignment element may extend at least partially above an upper end of the inner tubular element. By ensuring that the needle enters the septum at a more precise location, injection after injection, the septum reseals more easily even after multiple injections. Furthermore, the septum is less likely to fragment and less septum material will enter the vessel.

Thus the problem of coring or laceration can be addressed by using a septum having a predefined path for needle penetration. For example, the cap incorporates an alignment element or needle guide. In one embodiment, the needle guide comprises a guide ring defining an opening or aperture at an upper end of the cap, the guide ring and aperture being positioned above the septum. The guide ring may be held in position above the surface of the septum by integrated supports or arms which link the guide ring to, for example, the inner tubular element or the top portion of the cap.

Because the syringe needle is precisely positioned on the septum, a sharp needle can be inserted with low force through the septum many times without tearing or crumbling the rubber. The septum forms an effective seal about a syringe needle so leaks do not occur during injection. By this method contamination of the culture is eliminated. Post-injection leaks are reduced and the volume of media is conserved. Embodiments of the present invention employing a cap incorporating an integral needle guide may be advantageous over needle guides that are supplied separately, since according to the present invention the needle guide is already accurately positioned over the septum and does not need to be fitted or adjusted by the user.

In one embodiment of the present invention, a septum cap construct includes a septum retained in the septum cap, and a cap comprising a syringe guide with an aperture therein for introduction of a syringe needle. The element which performs the primary function of guiding the needle into the septum may be referred to as the "alignment element", "needle guide" or, more specifically, as the "syringe needle guide". The

needle guide may be integrated with the septum cap and may be formed of a single piece of material, such as a thermoplastic resin.

As the septum cap incorporates the syringe guide, the septum cap serves to guide the needle into the aperture in the cap so that the septum suffers minimal misalignment stress and tear. In one embodiment, the cap comprises a needle guide with an upper capture section and a lower guide section. The (lower) guide section may be generally cylindrical or tubular, although this section may also be conical in shape. Typically the lower guide section has a diameter greater than the needle diameter but less than 130% of the needle diameter, in order to limit lateral misalignment. Needle misalignment can be further limited by a high aspect ratio (height/diameter) of the guide section. Preferably, this aspect ratio is at least 2:1.

In certain embodiments, alignment element or needle guide may further comprise an upper capture section. In alternative embodiments, the needle guide comprises only a guide section as described above. The capture section of the needle guide, where present, is designed to capture the needle as it is inserted and align it with the guide section. Accordingly, the capture section can be wide at its top and narrow at its bottom. Preferably, the guide section is conical, with diameters subtending an angle of at most 60 degrees. Preferably, the top (maximum) diameter is at least 5-10 times that of the guide section.

Typically the alignment element is positioned centrally within the inner tubular element of the cap, i.e. coaxially with the inner tubular element and outer tubular element. The alignment element may be supported in position by any suitable arrangement, for instance by one or more arms extending radially between a guide ring of the alignment element and the inner tubular element. For instance, the septum cap may comprise a tripod arrangement integral to the cap and comprising 3 arms supporting the guide, so that the guide is centred above the aperture of the cap.

The cap of the present invention may be manufactured by any suitable method. The portions of the cap other than the septum (i.e. the inner and outer tubular elements, the top portion, the alignment element and other associated components) are typically formed from a thermoplastic material. In one embodiment, a plastic cap is

manufactured by injection moulding. The various thermoplastic elements may, in one embodiment, be manufactured as a single injection-moulded component.

Alternatively, two or more component parts may be manufactured in separate injection moulding steps and the components assembled to form the cap. The components may be joined by any suitable technique. In one embodiment two or more components are joined by ultrasonic welding. The various injection-moulded components may be formed from the same thermoplastic material in order to facilitate ultrasonic welding.

Ultrasonic welding is a well-known technique which involves the use of high frequency sound energy to soften or melt the thermoplastic at the joint. Parts to be joined are held together under pressure and are then subjected to ultrasonic vibrations usually at a frequency of 20, 30 or 40 kHz. The ability to weld a component successfully is governed by the design of the equipment, the mechanical properties of the material to be welded and the design of the components.

In one embodiment the cap comprises a first thermoplastic component joined to a second thermoplastic component at an interface region by an ultrasonic weld. The interface region may be located within the top portion and/or an upper part of the inner tubular element. Thus in one embodiment the first component comprises primarily the outer tubular element and alignment element. The second component comprises primarily a lower part of the inner tubular element. After injection moulding of the first and second components from the same material, the first and second components may be held together and ultrasonically welded at the top portion and/or upper part of the inner tubular element.

In certain embodiments, separate injection moulding of component parts and assembly by ultrasonic welding may be favoured. This is particularly the case where injection moulding of the screw cap as a single component is more difficult or expensive due to a complex 3-dimensional shape. For instance, in certain embodiments the alignment element may require more precise fabrication such that it is less straightforward to produce the entire cap (apart from the septum) in a single injection moulding.

In order to assemble the cap, the septum may conveniently be fitted into the assembled plastic components by, for example, pushing the septum into the lower end of the inner tubular element. In certain embodiments the groove and/or flange located towards the lower end of the inner tubular element may assist in positioning and retaining the septum within the cap. If desired (for instance if the septum has deteriorated), the septum may be removed from the cap and replaced with a new septum.

The present inventors determined that the primary cause of loss of the prior art septa with guide and base details was the loose connection between the cap and the septum. Typically, when the cap was removed from the vessel, the loose septum could drop out of the cap or become ill-positioned. Such loss could result in operator frustration and loss of batches. Badly positioned septa could result in leakage and or contamination.

Embodiments of the present invention may provide less leakage and contamination through the septum. This is achieved by improving the positioning of the septum in the inner tubular element.

Embodiments of the present invention may also provide a septum cap which permits better alignment of the needle with the syringe aperture. The integral syringe guide/septum cap of the present invention provides more certain alignment than the prior art arrangement. In particular, the syringe needle guide improves the positioning of the needle above the septum, encourages 'cleaner' breaching of the septum, supports the needle so that it is less likely to deform and enables the operator to concentrate on addition or aspiration of material rather than injection technique.

These and other features and advantages of the present invention are apparent from the description below, which is provided by way of example only with reference to the following specific embodiments and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a longitudinal section through a cap according to an embodiment of the present invention.

Figure 2 shows in longitudinal section a cap according to an embodiment of the invention fitted to a vessel.

Figure 3 shows a top view of the cap.

Figure 4 shows a perspective view of the cap with the septum not present.

Figure 5 shows a perspective view of 2 caps according to an embodiment of the invention fitted to a vessel.

As shown in Fig. 1 and Fig. 4, the cap 1 comprises an outer tubular element 2 and an inner tubular element 3. The outer and inner tubular elements 2 and 3 are coaxial, with the inner tubular element 3 having a smaller diameter than the outer tubular element 3. Thus the inner tubular element 3 is disposed within the outer tubular element 2, the inner tubular element being separated from the outer tubular element by cavity 4. The inner and outer tubular elements are joined at an upper or top end of the cap by a top portion 5. Thus cavity 4 forms an annular space extending in a longitudinal direction away from the top portion 5, surrounding inner tubular element 3 and within outer tubular element 2. As shown in Fig. 3, the top portion 5 forms a ring running around the upper end of the cap 1, such that cavity 4 is closed at its upper end and open at its lower end. An inner wall of the outer tubular element 2 is provided with screw threads 6.

An inner perimeter 10 of the inner tubular element 3 defines an internal bore 9 of the cap 1. An annular groove 8 is provided in the inner perimeter 10, positioned towards a lower end of the cap 1. A disc-shaped septum 7 is mounted in groove 8, and is additionally held in place by flange 11, which forms a rim at the lower end of the cap extending into the internal bore 9 within the inner tubular element 2. Thus the septum 7 extends transversely across the internal bore 9, and forms a seal separating an outer part of the internal bore 9 from a space below the septum 7.

The cap 1 further comprises an alignment element 12. The alignment element 12 is positioned within the inner tubular element 2, towards an upper end of the internal bore 9. Thus the alignment element 12 is located above the septum 7. The alignment

element 12 is of tubular or annular shape and is attached to the inner tubular element 3 and/or top portion 5 by 3 radially extending arms 13, one of which is shown in Figure 1. The alignment element 12 encloses an aperture 14 of a generally cylindrical form.

In Figure 1 the outer tubular portion 2, inner tubular portion 3, top portion 5, alignment element 12 and arm 13 are shown as being formed from two injection-moulded component parts which are held together at an interface region 15 by an ultrasonic weld. The interface region 15 is found within the top portion 5 and an upper part of the inner tubular element 3. Thus a first component provides the outer tubular element 2, alignment element 12, arm 13 and a portion of the upper part of the inner tubular element 3. A second component provides a lower part of the inner tubular element 3 and a portion of the upper part of the inner tubular element. The top portion is partially provided by both the first component and second component.

As shown in Figure 2, in use the cap 1 may be screwed on to a vessel 20 by means of screw threads 6 which mate with screw threads 21 on a neck portion 22 of the vessel 20. Note that for clarity only the neck portion and adjoining parts of vessel 20 are shown in Figure 2. Thus when positioning the cap 1 on the vessel 20, the neck portion 22 of the vessel 20 is introduced into the lower end of cavity 4. The neck portion 22 is held firmly in place between the inner tubular element 3, the outer tubular element 2 and the top portion 5.

A lip 23 is provided within a bore of the neck portion 22 of the vessel 20. The lip 23 is in the form of an upwardly extending ring which is attached to a shoulder portion 24 of the vessel 20. As the neck portion 22 of the vessel 20 is engaged with the cap 1, the lip 23 contacts the septum 7, ensuring that the septum 7 is held firmly in place and that a tight seal is formed between the septum 7, the vessel 20 and the cap 1. The cap 1 thereby isolates an internal space 25 within the vessel 20 from the external space outside of the vessel.

When it is desired to introduce a liquid into or withdraw a liquid from the vessel 20, an injection device such as a needle mounted on a syringe may be used to access internal space 25 according to the following procedure. A distal end or point of the injection device is guided into position by passing through the aperture 14 within

alignment element 12. The point of the injection device then penetrates the septum 7 at a defined position 26, which is located directly below the aperture 14. Thus the alignment element may direct the point of the injection device to puncture the septum in a direction substantially perpendicular to the septum. The septum forms a seal around a barrel of the injection device (e.g. the needle) while liquid is withdrawn or added to the vessel through the injection device. Once the injection device is withdrawn from the vessel, the septum 7 reseals to maintain isolation of the internal space 25 of the vessel.

As shown in Fig. 5, two or more caps 1 may be fitted to a vessel 20 such as a bioreactor.

Various alternatives and modifications of the above specific embodiment will be apparent to a skilled person. For instance in specific alternative embodiments, the cap 1 comprises a flange 11 or groove 8 but not both. It will also be apparent to a skilled person that aperture 14 can be of various lengths and diameters according to the nature of the injection device which is to be used. The aperture 14 may also be conical in shape instead of cylindrical, may vary in diameter or shape along its length or may comprise an upper capture portion where required. For instance the upper diameter of the aperture 14 may be greater than the lower diameter of the aperture 14.

CLAIMS

1. A cap for a vessel, the cap comprising:

an outer tubular element and an inner tubular element located within the outer tubular element, the inner tubular element being separated from the outer tubular element by a cavity, the inner tubular element being attached at an upper end to the outer tubular element; and

a septum mounted within the inner tubular element.

2. A cap according to claim 1, further comprising an alignment element positioned within the inner tubular element above the septum, the alignment element being arranged to guide an injection device to pass through the septum.

3. A cap according to claim 2, wherein the alignment element comprises a guide ring having an aperture for guiding a tip of the injection device to pass through the septum at a portion of the septum directly below the aperture of the guide ring.

4. A cap according to claim 3, wherein the guide ring has a length:diameter ratio of at least 2:1.

5. A cap according to claim 3 or claim 4, wherein the guide ring is attached to the inner tubular element by one or more support arms extending radially away from the guide ring.

6. A cap according to any preceding claim, wherein the inner tubular element and outer tubular element are joined at the upper end by a top portion, such that the cavity is closed at the upper end.

7. A cap according to any preceding claim, wherein an inner wall of the outer tubular element comprises a threaded portion.

8. A cap according to any preceding claim, wherein an inner wall of the inner tubular element comprises an annular groove within which the septum is mounted.
9. A cap according to any preceding claim, wherein an inner wall of the inner tubular element comprises one or more flanges extending away from the inner wall for retaining the septum.
10. A cap according to any preceding claim, comprising a first thermoplastic component and a second thermoplastic component, the first and second thermoplastic components being joined by an ultrasonic welded region.
11. A cap according to claim 10, the first component comprises the outer tubular element and the alignment element, and the second component comprises at least a portion of the inner tubular element.
12. A vessel assembly comprising:
 - (a) a vessel having a neck portion; and
 - (b) a cap as defined in any preceding claim;wherein the neck portion of the vessel is located within the cavity separating the inner tubular element from the outer tubular element of the cap.
13. A vessel assembly according to claim 12, wherein the vessel comprises a lip adjacent to the neck portion, and the lip contacts the septum when the cap is fully engaged with the neck portion.
14. A vessel assembly according to claim 12 or claim 13, wherein the neck portion comprises an external threaded portion which engages the threaded portion of the outer tubular element.
15. A vessel assembly according to any of claims 12 to 14, wherein the vessel comprises a bioreactor.

16. A method for assembling a cap according to any preceding claim, comprising forming at least the inner tubular element and outer tubular element, and mounting the septum in the inner tubular element.
17. A method according to claim 16, wherein the septum is detachably mounted in the cap by push-fitting the septum into a lower end of the inner tubular element.
18. A method for producing a cap according to claim 10 or claim 11, comprising forming the first thermoplastic component and the second thermoplastic component, and joining the first and second thermoplastic components by ultrasonic welding.
19. A method according to claim 18, wherein the first and second thermoplastic components are formed by injection moulding.
20. A cap for a vessel, the cap comprising a septum mounted within the cap and a guide ring positioned above the septum for directing a tip of an injection device to puncture the septum at a defined portion of the septum below the guide ring.

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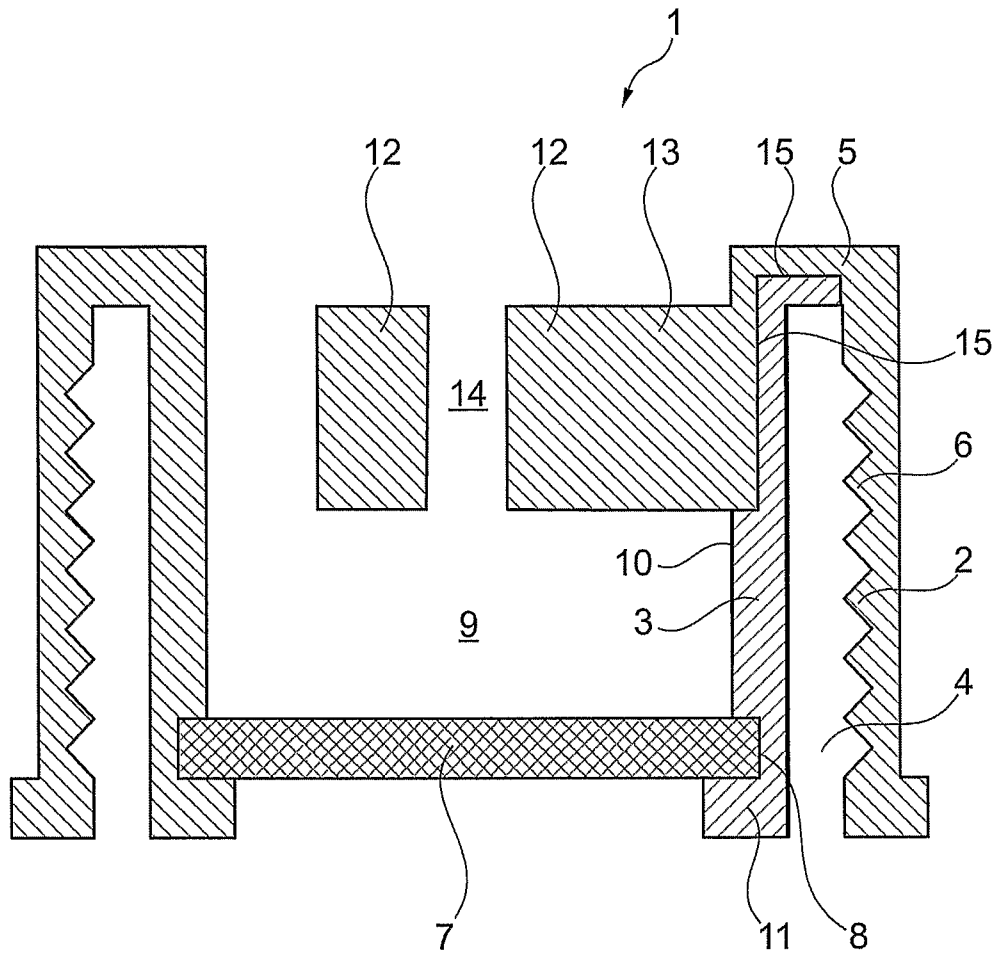


Fig. 1

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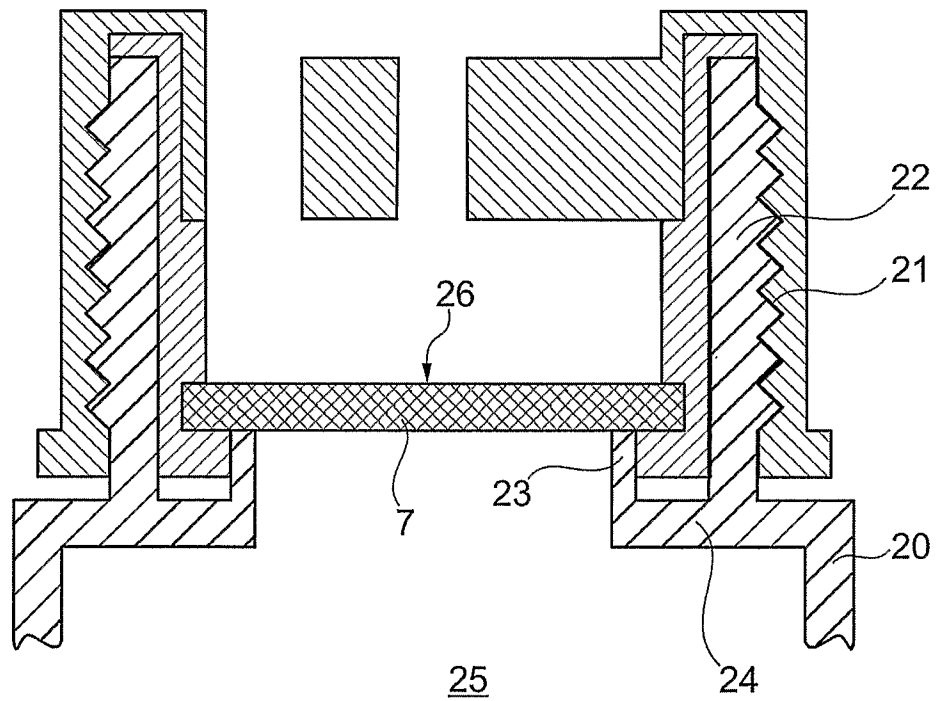


Fig. 2

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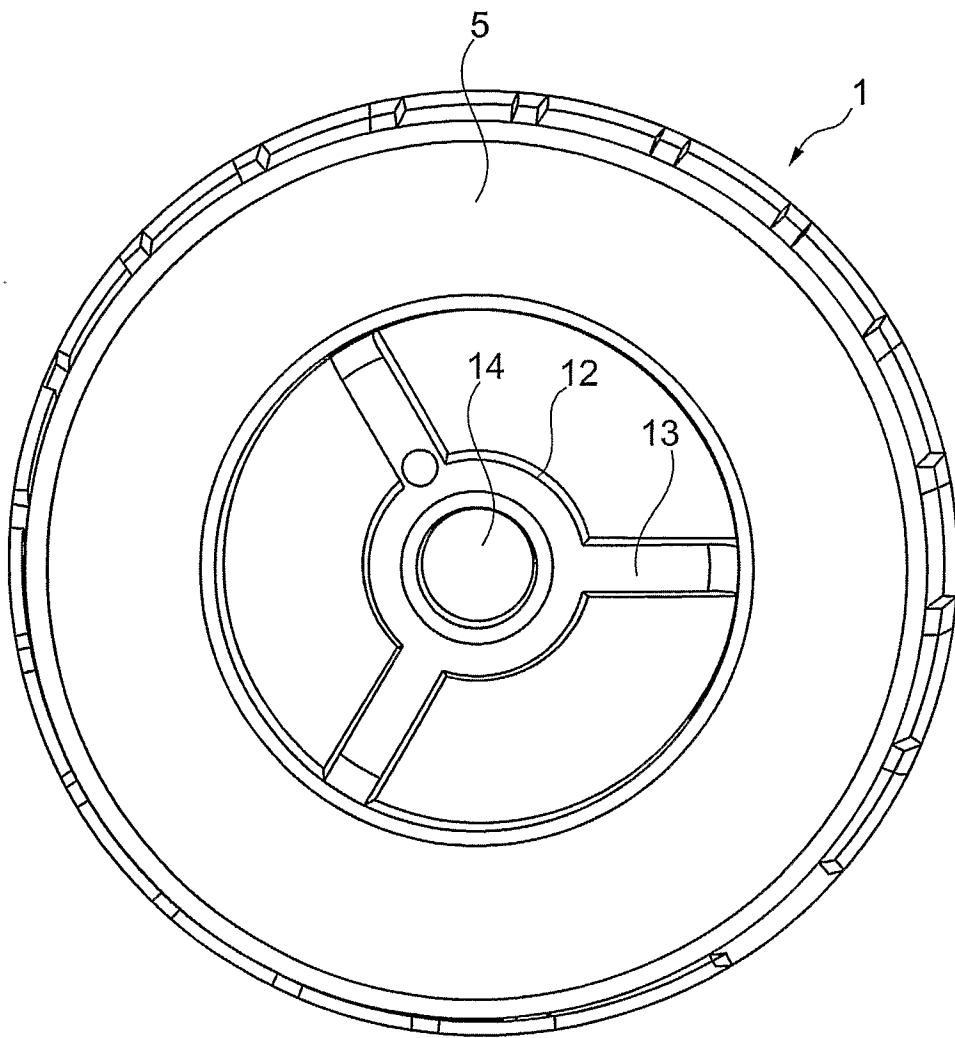


Fig. 3

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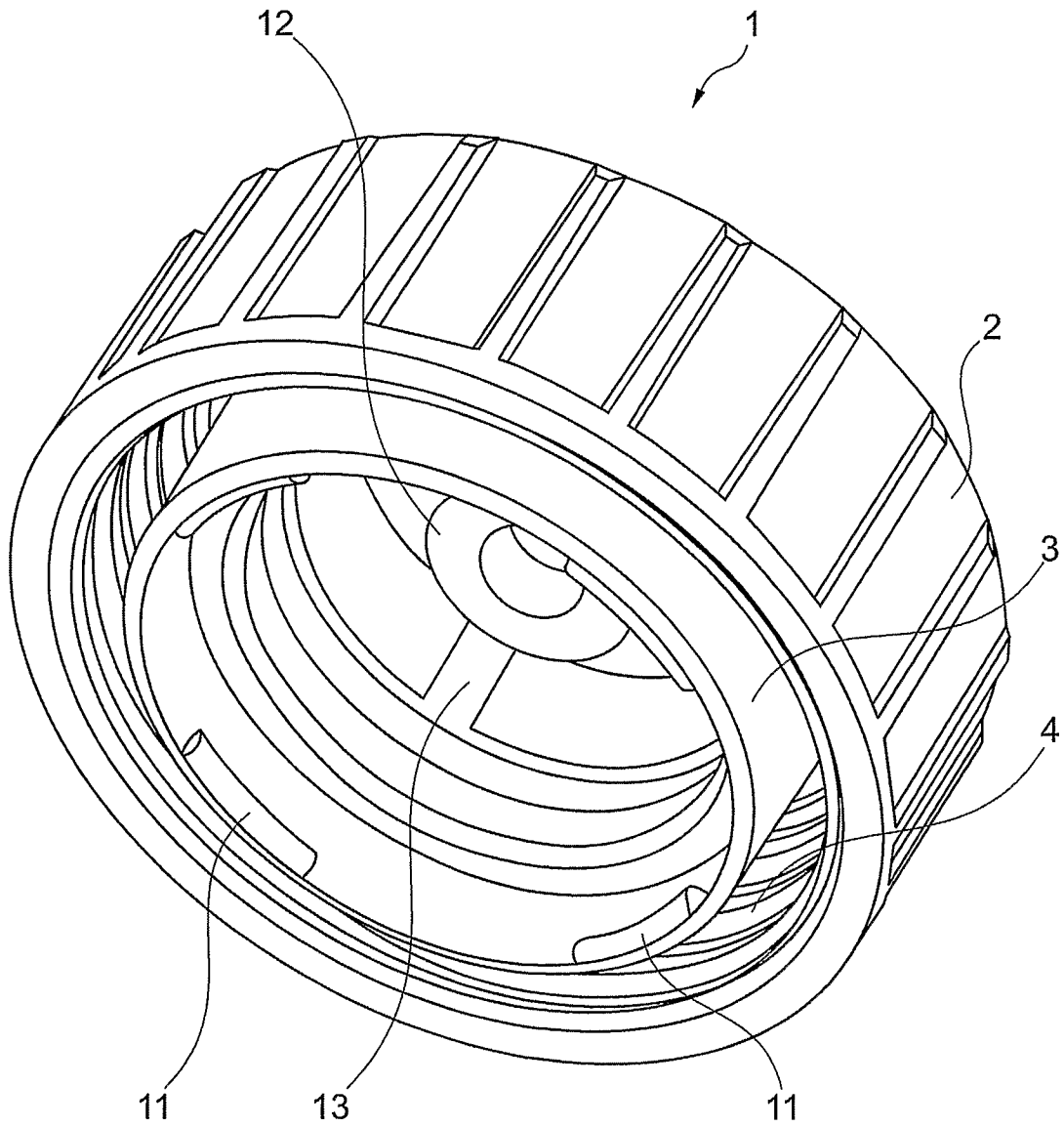


Fig. 4

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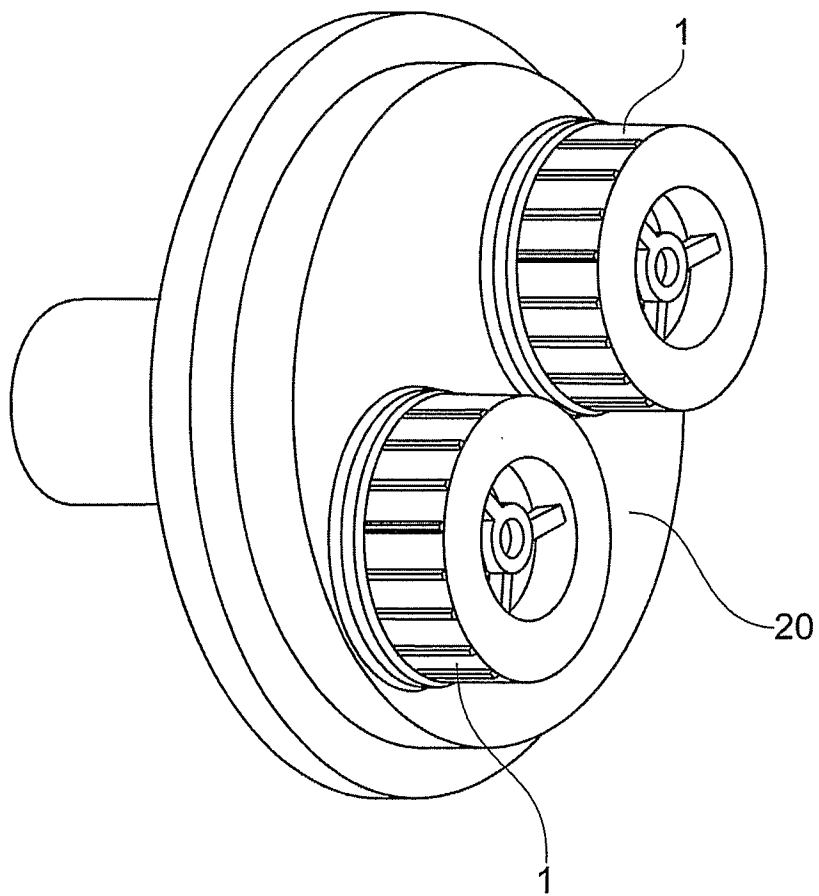


Fig. 5