

5 **X-ray markers for scaffolds**

The invention relates generally to a method for producing x-ray markers, an x-ray marker, a semi-finished product for producing an x-ray marker and also to a medical implant comprising at least one such x-ray marker. An implant of this type can have, for example, a
10 framework (also referred to as a scaffold), in particular a stent framework, which is preferably degradable, i.e. after implantation disintegrates in a defined manner in the body of the patient over a specific period of time.

EP 2 457 601 discloses composite markers, which are material combinations of metal
15 marker particles and polymer adhesives. The mass fraction of x-ray-absorbing particles in the composite decisively determines the radiopacity. However, the fraction of said particles cannot be significantly higher than 90 % by weight. At higher fractions the mixture is already so viscous in the uncured state that processing, such as injection into eyelets, is no longer possible. Since, on account of the density differences between polymer adhesives
20 ($\rho < 2 \text{ g/cm}^3$) and x-ray-absorbing metals such as Ta ($\rho > 16 \text{ g/cm}^3$), the volume ratios are precisely the opposite of the mass ratios, a further optimisation of this technology is finite. Even if it were possible to introduce 95 % by weight of x-ray-absorbing particles into a polymer-containing composite and to introduce this also in a defined manner into an eyelet, it would not be possible to achieve radiopacity equal to that of a solid x-ray marker
25 on account of the resultant density of the composite.

In addition, the simple adhesive bonding of solid markers into the eyelets of absorbable scaffolds prevents the formation of corrosion-accelerating local elements only when the adhesive ensures a permanent local separation between marker and scaffold during the
30 entire degradation process, which usually can be achieved only with greater effort. Corrosion-accelerating local elements form when chemically noble and chemically base metals or alloys are in direct electrical contact with one another without interfaces.

EP 2 399 619 also discloses solid markers sheathed by foreign metals. In this variant the risk of local element formation is considerably reduced, however the technical production effort is high here as well.

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The techniques disclosed herein may allow for a method for producing x-ray markers, which method or marker allows an improved handling of the x-ray marker during production.

10 In particular, a method may be provided by means of which x-ray markers can be produced in high quantity with minimal preparative effort.

The x-ray marker should preferably also be arrangeable as close as possible to a metal framework, in particular a stent framework, which is hardly radiopaque and in particular is
15 degradable, without any interactions and the associated corrosion effects between the materials on either side.

This should preferably also be ensured when degradation effects displace the original geometric positions of both components relative to one another - in particular in spite of a
20 polymer adhesive as intermediate medium - and an integral bonding between the x-ray marker and the scaffold cannot be ruled out.

Aspects of the invention are defined in the independent claims. Some optional features of the invention are defined in the dependent claims. A method having the features described
25 herein and also by an x-ray marker having the features may address the issues mentioned above. Further aspects of the invention will also be described hereinafter.

In an exemplary method for producing x-ray markers, it is proposed that at least one material layer is provided, wherein at least one region of the material layer forming the x-
30 ray marker to be produced is pre-cut such that said region is connected to parts of the material layer surrounding said region (in particular merely) via at least one web extended along an extension direction, which web forms a predetermined breaking point. Due to the

connection via a web to the material layer, the x-ray marker is initially prevented from breaking off prematurely from the material layer.

Furthermore, the method may be such that the at least one predetermined breaking point is
5 arranged in a section of the region (said section being formed in particular by the pre-cutting), such that the at least one predetermined breaking point lies further inward in the extension direction of the web (i.e. is closer to the centre of the region) than two outer edge portions of the region, between which the section lies, and wherein the at least one predetermined breaking point is severed in order to release the x-ray marker from said part
10 of the material layer.

In other words, the at least one predetermined breaking point may be arranged offset inwardly towards the core of the region or x-ray marker. Here, the core by way of example can be the centre of mass of the x-ray marker. Due to the arrangement of the at least one
15 predetermined breaking point further inwardly compared to the other outer edges of the x-ray marker, metal-metal contact between the predetermined breaking point and for example the body of an implant and especially a stent strut may be practically ruled out. As a result of this feature, the formation of corrosion-accelerating local elements can therefore be eliminated and ruled out.

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The x-ray marker can be connected in the material layer to at least one web in the form of a predetermined breaking point. However, it can also be necessary for more than one predetermined breaking point to be present between the material layer and x-ray marker. It is therefore part of the present proposal that the x-ray marker can be is connected to the
25 material layer via one, two, three, four, five or, if necessary and expedient, also more predetermined breaking points in the form of webs, as described herein. By way of example, it has been found that an arrangement with two or more predetermined breaking points provides the advantage of a simpler handling during the process of introducing the marker into the eyelet. By way of example, two opposing symmetrically arranged
30 predetermined breaking points can thus constitute tapers of the x-ray marker. During the subsequent process of marker assembly, specially manufactured handling devices can engage in these tapers and can thus ensure a simpler assembly process. These handling

devices can be micro-tweezers or micro-tongs, for example. Furthermore, due to the inward contact face between marker and handling device, is also ensured that potential damage to the marker caused by the handling lies at a point that is not critical for contact corrosion. Such a handling, in addition, can also be carried out when the inward
5 predetermined breaking points do not lie exactly opposite one another, but are arranged offset from one another at a sufficiently large angle, for example as in the case of three predetermined breaking points distanced by 120°.

In the sense of the present disclosure, “pre-cutting” means in particular that a gap
10 surrounding the region and severing the material layer in part is produced and is interrupted at least by the at least one said web. In this respect, the term pre-cutting conveys the idea that the region that will form the x-ray marker, or the x-ray marker itself, is not broken off fully from the material layer, and instead is still connected thereto (via the at least one web with predetermined breaking point).

15 On account of the connection of the x-ray marker to the material layer, the handling of the individual x-ray marker may be improved and protection thereof may be facilitated. In particular, the mechanical strength of the at least one predetermined breaking point may be such that a sufficient transport and storage capability is attained without the marker
20 breaking off prematurely. In that it is possible to process a great number of x-ray markers simultaneously. Depending on the size of the material layer the herein suggested method may facilitate to simultaneous production of hundreds, if not thousands of x-ray markers. As a result an enormous number of x-ray markers can be produced exhibiting the exact same properties due to the simultaneous production. Moreover, the herein suggested
25 method is efficient and elegant as well in that the above outlined great number of x-ray markers can be disconnected from material layer simultaneously as well rendering the production of such a large number of x-ray markers extremely economical.

30 The at least one material layer may be a flat, preferably planar material layer, of which the thickness is preferably significantly smaller than the extent of the material layer perpendicularly to the direction of the thickness of the material layer. Accordingly, the x-ray marker may also have a planar form, wherein a thickness of the x-ray marker is

preferably likewise significantly smaller than an extent of the x-ray marker/region perpendicular to the direction of thickness. In a further arrangement the at least one material layer can be in the form of a tube. Also the tube may have a thickness significantly smaller than the circumference of the tube. Accordingly, the x-ray marker
5 may also have a slightly curved form, wherein a thickness of the x-ray marker is preferably likewise significantly smaller than an extent of the x-ray marker/region perpendicular to the direction of thickness. Cutting from a tube in order to produce the x-ray markers is advantageous in that the volume of the marker may be slightly more compact and may be thereby better x-ray visible. Furthermore, due to the curved form the edges of the marker
10 may better adapt to the form of the eyelet on the round stent resulting the edges to lie more inwardly in the eyelet and extent less or not at all from the eyelet. Moreover, the surface of the marker may be increased resulting a stronger adhesion to the stent when glued on it.

The pre-cutting may be performed by means of laser light (here, the laser light or an
15 appropriate laser light beam can, for example, run over the line to be cut or the gap to be cut, or the material layer is moved relative to a fixedly oriented laser beam). Other suitable methods for pre-cutting the x-ray marker/region are water jet cutting or also punching. In particular, pre-cutting by means of laser light has the advantage that large quantities can be pre-cut very quickly with high precision.

20 The at least one material layer may be a metal foil or a metal foil composite consisting of a number of layers or a tube or tube of a composite material, which in particular is manufactured from one of the following radiopaque materials or comprises one of the following materials: tungsten, tantalum, gold, platinum, iridium, or alloys of the
25 aforementioned materials, such as a platinum-iridium alloy.

The web width, perpendicularly to the extension direction of the web, may lie in the range of from 1 μm to 20 μm , and preferably in the range of from 2 to 10 μm , and in particular is 5 μm . Such a web width is in particular advantageous in respect of a use of the x-ray
30 marker for the visualisation of implants that are the size of vessel supports, since it is possible to prevent the x-ray marker from breaking off prematurely from the material layer during the procedure. This web width also has the advantage that a desired oxidising

through the web during the passivation of the x-ray marker can be quickly achieved, whereby the method can be carried out more quickly.

When pre-cutting, a gap running around the region may be produced (see also above), which gap preferably has a width ranging from 10 μm to 100 μm , preferably ranging from 20 to 60 μm . The advantage of such a gap lies in the fact that the material layer can be cut through in a reliable manner, whilst the material loss is kept low. Furthermore, said gap may be interrupted merely by the at least one said web.

The region or the x-ray marker may be formed in an elongate manner and extends here along a longitudinal axis. Said extension direction of the web may run in this case in particular perpendicularly to the longitudinal axis. However, it is equally possible that the extension direction of the at least one web can run parallel to the longitudinal axis of the marker. Said edge portions may also run on either side of the section or of the web preferably along the longitudinal axis, in particular parallel to the longitudinal axis of the region/x-ray marker. However, the present proposal also includes the situation in which said edge portions can also be introduced at another point.

In particular, the region or x-ray marker can have an oval or elongate form with rounded edges. Due to such an areal increase of the dimensions of the region/x-ray marker in the x- and y-direction of the x-ray marker (z corresponds to the thickness direction), it is possible to replace the double marker used in the case of the present scaffolds with an individual marker. The advantage here lies in particular in the omission of the web separating the two individual markers. Approximately 22% x-ray marker surface may be gained as a result.

Further, the region or the x-ray marker may be formed as a continuous layer which does not contain any holes or other cut-outs within the continuous layer. Holes or other forms of cut-outs within the continuous layer would result of course in material loss and thereby in decrease of the x-ray visibility. Moreover, a solid marker element as described herein may also exhibit an improved x-ray visibility in comparison to discontinuous marker materials such as powders or porous materials.

The material layer with the pre-cut region may be contacted by an acid, in particular is immersed in an acid, such that a burr produced in the region during the pre-cutting preferably disintegrates on account of the chemical attack of the acid and is thus removed. Here, it is particularly advantageous when the acid has an oxidising effect. Here, the term
5 acid also includes a mixture of a number of acids or also a diluted acid or an acid in an organic solvent. In addition, by means of the selection of oxidising or non-oxidising acids, the material attack can be extended to the oxidised boundary layer provided, or (in an oxidising manner) additionally to the substrate therebelow.

- 10 The reduction or in the best case scenario removal of the burr has the advantage of minimising the risk that material contact with the scaffold can be produced more easily after the assembly due to protruding parts of the burr.

By contacting the material layer with the acid, in particular the cut gap may be widened
15 and/or said width of the web may be reduced (for example from approximately 8 μm to approximately 3 μm).

The composition of the used acid or acid mixture may be dependent in particular on the material of the x-ray marker. With use of pure tantalum an acid mixture consisting of 80
20 volume % concentrated HNO_3 and 20 volume % concentrated HF can be used. In the case of gold, a mixture of concentrated hydrochloric acid and concentrated nitric acid in a ratio of 3:1 may be used. The same acid mixture may also be used in the case of tungsten and platinum, wherein this has to be heated to temperatures between 60 and 80°C in order to produce material abrasions in the above-mentioned scope within a period from a few
25 minutes to hours.

The material layer may be treated with the acid together with the pre-cut region is rinsed, primarily with water, in order to remove acid residues.

- 30 The material layer together with the region fixed thereto may be oxidised in order to generate a passivation of a surface of the region or x-ray marker. The oxidation is preferably carried out until the web, as predetermined breaking point has, been oxidised

through over the entire diameter, such that the web, after the oxidation, consists exclusively of oxidised material and no longer of metal or a metal alloy.

During the oxidation, the predetermined breaking point may be severed by being oxidised through completely, and the former integral bond is no longer sufficient to hold the region or x-ray marker at the web. Following complete oxidation of the web, possibly also electrochemical oxidation, and once the x-ray marker has broken off from the material layer, the x-ray marker can be captured and filtered off by a suitable means, for example a vessel encased by mesh.

As a result of this preferred arrangement, a very economical method may be achieved, because two method steps can be carried out simultaneously. On the one hand, the x-ray marker may be provided with a fixedly adhering and cohesive passivation layer, which provides an insulation of the x-ray marker with respect to corrosion-accelerating local elements. Furthermore, the corrosion of the web may mean that the predetermined breaking point is weakened to such an extent that the x-ray marker can be easily broken off from the material layer. In particular, the present method, by means of a suitable choice of the web width, provides the possibility to carry out the method in a self-regulating manner. Here, self-regulating is understood to mean that the complete oxidation of the web can define a maximum oxidation time. The oxidation period can thus be determined as well by the thickness of the web. By suitable selection of the web width, the web can be oxidised through and can separate from the material layer at a moment in time when the oxidation layer to be formed has an ideal and advantageous thickness on the x-ray marker. An optimal oxidation thickness layer can thus be regulated by the web width.

Alternatively, there is the possibility to continue the oxidation of the x-ray marker only until the predetermined breaking point still has a minimal integral bond to the rest of the x-ray marker. In this arrangement the predetermined breaking point is severed during or after rinsing processes in distilled water, under the action of a mechanical stimulus, such as ultrasound, and the marker, which is then separated, falls onto the base of the rinsing vessel, from which it can then be easily removed, for example by being filtered off. Other stimuli can consist in swinging, rinsing out, or rinsing off.

The complete or approximately complete oxidation of the at least one web described herein in particular has the advantage that no further mechanical or other steps, such as breaking out or renewed laser cutting, have to be carried out in order to separate the x-ray marker from the material layer. It is also highly advantageous that, by means of the method proposed herein, an x-ray marker which has a uniform, completely cohesive, passivated surface can be provided in an automatic production process. When breaking out or cutting off an x-ray marker from a corresponding material layer, the x-ray marker might have bare metal at the breaking or cutting point on the outer side, and the passivation layer might potentially be provided with scratches, which also expose bare metal. A point with bare metal would have the significant disadvantage that local elements can form much more easily at such a point following application of the x-ray marker to an implant and can promote corrosion of the implant and can significantly reduce the service life of the implant. However, as a result of the disclosed method, an x-ray marker may be provided which has no such points with bare metal. In addition, a uniform x-ray marker of this type can be produced automatically in high numbers during a single process step.

The oxidation of the surface of the material layer and of the region/x-ray marker may be performed plasma-chemically in an electrolyte.

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The x-ray marker may be rinsed (for example with distilled water) after the oxidation in order to remove the electrolyte.

Alternatively, for passivation of the surface of the region or x-ray marker by plasma-chemical treatment, primarily in electrolyte, the surface can be contacted with an aqueous silicate mixture in order to produce an electrically insulating layer on the surface, wherein said layer comprises sodium silicate of the composition $M_2O \cdot n SiO_2$ with $n = 1$ to 4 , wherein M here can be Na, K or Li. Alternatively, other anionic mixtures can also be used, such as carbonate, sulphate, or phosphate mixtures, primarily with calcium as cation. This method step is preferably performed at increased temperature in order to achieve a sufficient passivation. In one arrangement the passivation step is performed at temperatures of from 30 to 80°C and preferably at temperatures ranging from 40 to 60°C .

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In a further variant, a passivation layer can also be achieved by gas-phase deposition of dielectric materials, such as SiO_2 .

5 A further alternative lies in the use and application of coatings having a high barrier effect. By way of example, diamond-like carbon (DLC), SiC or TiN can be applied. Routine methods are known to a person skilled in the art. In addition, a coating with parylene (preferably parylene C), which is a plastic with high barrier effect to aqueous media, primarily as a complete layer, is advantageous. This material can be applied to the
10 substrate as pore-free and transparent polymer film in a vacuum by condensation from the gas phase. A separation of the x-ray marker from the material layer may be achieved in this arrangement by a suitable mechanical stimulus, such as ultrasound.

After this, the predetermined breaking point is preferably severed by the action of a force,
15 in particular a periodic force, and therefore the region/x-ray marker may be separated from the part of the material layer surrounding the region. In particular, ultrasonic waves can be used for this purpose, which are coupled into the predetermined breaking point.

The plasma-chemical oxidation can be performed in an electrolyte for example, in that the
20 material layer is contacted with a metal conductor (for example titanium wire) and is immersed in an electrolyte, which for example comprises a mineral acid and ethanol, wherein an electrode acting as cathode made of a preferably rust- and acid-resistant metal (for example a suitable rust- and acid-resistant steel) is arranged in the electrolyte or in an electrolyte container receiving the electrolyte. In this plasma-chemical process, an x-ray
25 marker surface may be oxidised in particular up to a depth of approximately 2 to 4 μm . Insulating oxide layers can already be arrived from a depth of 0,5 μm on. This (process carried out under plasma-chemical conditions) in particular may also cause the oxidation of the predetermined breaking point itself, so that this is preferably oxidised through once the plasma-chemical process is complete. A loss of the material cohesion and a breaking-off of
30 the x-ray marker from the connection to the material layer or from the foil or tube composite result. The separated x-ray marker may then be captured, for example by means

of a (in particular net-like) capturing device made of plastic, which was placed beforehand in the electrolyte or in the container.

5 The x-ray marker may then be removed from the electrolyte and rinsed. Once the rinsing process (for example in distilled water) is complete, a surface-passivated x-ray marker free from electrolyte residues may be present, which can then be fixed to a medical implant (see below as well) once dried (for example in warm air).

10 Alternatively to the through-oxidation when the plasma-chemical oxidation process is complete, the x-ray marker can also remain in the foil/tube connection once the plasma-chemical process is finished. Separation may then occur only with rinsing in distilled water in a container into which ultrasonic waves for example are coupled. Here the ultrasonic influence may be dosed so that there is no damage caused to the layer. Other mechanical stimuli specified herein can be suitable, equally.

15 This procedure on the one hand advantageously may rule out mechanical damage to the x-ray marker surfaces and on the other hand may lead to a negligibly small remaining metal fracture area of the predetermined breaking point. This remaining fracture area is advantageously significantly smaller than one that would have been produced by
20 mechanical break-off, for example by bending. In addition, the predetermined breaking point may be placed inside the x-ray marker. This may rule out direct contact with the eyelet.

25 Due to the use of a material layer, the method may advantageously allow a parallelisation of the x-ray marker production.

A plurality of regions in the material layer may be pre-cut, wherein the regions each form an x-ray marker to be produced.

30 The individual regions can then be treated in the manner described herein simultaneously, such that, at the end of the process, a corresponding multiplicity of x-ray markers may be produced (simultaneously).

As also described herein there is an x-ray marker which has been produced by the disclosed method.

5 As also described herein there is an x-ray marker which has at least one section which is arranged such that a contact face has a breaking point severed in order to produce the x-ray marker or has a breaking point produced by severing at least one predetermined breaking point, which breaking point is arranged in the section of the x-ray marker such that the breaking point lies further inward (i.e. is disposed closer to the centre of the x-ray marker)
10 than two outer edge portions of the region, between which the section lies (see also above). Further, such x-ray marker may be provided with an insulating layer, preferably a layer of at least one oxide or silicate of the material the material layer is formed of. In one arrangement the oxide or silicate layer has a thickness of more than 0.5 μm . In a preferred arrangement the oxide or silicate layer has a thickness in the range of 1 to 8 μm , and more
15 preferably in the range of 2 to 5 μm .

As also described herein there is a semifinished product for producing an x-ray marker, wherein the semifinished product is formed by the material layer, in particular in the form of a metal foil or a tube (see also above), into which at least one region of the material
20 layer forming the x-ray marker to be produced is pre-cut such that said region is connected to the part of the material layer surrounding the region (in particular merely) via at least one web extended along an extension direction, which web the forms a predetermined breaking point. The at least one predetermined breaking point is preferably arranged in an section (formed in particular by the pre-cutting) of the region such that the predetermined
25 breaking point lies further inwardly in the extension direction of the web than two edge portions of the region, between which the section lies.

The material layer is preferably formed here such that the web width perpendicularly to the extension direction of the web lies in the range of from 1 μm to 20 μm and preferably in
30 the range of from 2 to 10 μm and in particular in the range of 5 to 7 μm .

The predetermined breaking point may also be formed in particular such that in acid medium it corrodes through much more quickly than the other material layer. In keeping the web in the above defined ranges and having the web connected to the x-ray marker located inwardly and directed to the centre of the marker element as suggested herein the
5 herein suggested method for producing x-ray markers for scaffolds may be highly advantageously influenced, because the production can be carried out extremely efficient. Not only is it possible that a great number of x-ray markers can be processed simultaneously while still being connected via the web to the material layer after cutting, it is moreover possible to completely passivate the x-ray markers, polish the x-ray markers
10 and disconnect the x-ray markers from the material layer in one step. In comparison to common procedures where the marker disconnection from a material layer is done by another cutting step, the x-ray markers would still be provided with an open spot exhibiting fresh and open marker material which needs to be insulated in order to avoid local elements which highly influence the performance of the x-ray marker and the scaffold.
15 Hence, it is thereby provided a very elegant production procedure x-ray markers for scaffolds facilitated by the specific examples of the marker elements themselves and the semifinished product as suggested herein.

A plurality of regions may be pre-cut into the material layer, wherein the regions each form
20 an x-ray marker to be produced. The regions can again be connected individually in the above-described manner to the corresponding surrounding part of the material layer, in each case via at least one web.

A semifinished product of this type makes it possible advantageously to produce a plurality
25 of x-ray markers in parallel.

As also described herein there is a medical implant, in particular in the form of a framework, wherein the medical implant comprises at least one x-ray marker as described herein, which in particular is arranged in a receptacle (what is known as an eyelet) of the
30 framework. A receptacle of this type can be formed for example on a strut of the framework.

By means of the at least one x-ray marker, it is possible to determine the position of the implanted implant by means of radiography, for example in the body of the patient.

5 The framework is preferably a stent framework, in particular a degradable stent framework, which for example is designed and provided to be implanted into a blood vessel of the patient. Here, the stent framework may have a multiplicity of interconnected struts, which form the cells of the stent framework.

10 Here, the stent framework in particular may have two ends, which surround an inlet opening and outlet opening of the stent framework, through which, respectively, blood can flow into and out again from an interior of the stent framework surrounded by the stent framework.

15 At least at one of the two ends, a receptacle (eyelet) can be provided, which is preferably formed as a through-opening of a strut of the framework or stent framework, wherein an x-ray marker as disclosed herein is fixed in the receptacle. At the other end, a receptacle can also be provided which is preferably formed as a through-opening of a strut of the framework or stent framework, wherein an x-ray marker as disclosed herein can likewise be fixed in the receptacle of the other end.

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Thus, the disclosed techniques may enable the use of solid x-ray markers, the use of which previously with degradable scaffold materials, such as magnesium or magnesium alloys, would have resulted in increased corrosion rates and therefore in a significantly reduced service life.

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The process of laser cutting a large number of markers from a material layer/foil/tube may be very economical in terms of production compared to the production of individual markers, since all measures for individual contacting are spared.

30 The passivation of entire material layer portions/foil/tube portions having pre-cut x-ray markers may facilitate the process steps of pickling and passivation by advantages brought about on account of the omission of the individual contacting.

There are no disadvantages, for example as occur in the case of the coating of bulk material, where both adhesion and clumping of the passivation layers with one another and effects resulting from particle abrasion can occur.

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The inward predetermined breaking point may ensure that there is no metal-metal contact, which promotes local element formation and thus increases the risk of corrosion.

10 The detachment of the x-ray marker from the material layers or foil/tube composite caused by the process of plasma-chemical or wet-chemical oxidation is not accompanied by any mechanical loading of the predetermined breaking point. The remaining metal fracture area still present at the predetermined breaking point is thus minimised advantageously to a few μm^2 , if there is any such remaining area at all. Even if there was remaining a metal fracture area local elements would not occur due to the inwardly directed position of the area which
15 excludes direct contact between the metal fracture area and the scaffold material.

In addition, the disclosed techniques may avoid damage to the passivated surface caused by scratches or the like, particularly in the edge regions of the marker, which are particularly susceptible to the formation of local elements, and cannot be ruled out when
20 the markers are pushed out mechanically.

Lastly, when assembling the x-ray markers in non-degradable and insufficiently radiopaque scaffold materials, such as nitinol, complex multi-stage process steps afflicted by high rejection rates (as in the case of galvanic deposition methods for example) are
25 spared.

Further features and advantages of the invention will be explained in the description of the drawings of exemplary embodiments of the invention, provided with reference to the drawings, in which:

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Fig. 1a shows a perspective view of an x-ray marker having a predetermined breaking point;

Fig. 1b shows a perspective view of an x-ray marker having two predetermined breaking points;

5 Fig. 2a shows a plan view of an x-ray marker having a predetermined breaking point;

Fig. 2b shows a plan view of an x-ray marker having two predetermined breaking points;

Fig. 3 shows the detail A from Figure 2;

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Fig. 4a shows an image recorded by scanning electron microscope (SEM) of the x-ray marker still in the material layer or foil material and connected to the material layer via a web;

15 Fig. 4b shows an image recorded by light microscope of the x-ray marker still in the material layer or foil material and connected to the material layer via two webs;

Fig. 5 shows a detailed view, obtained by scanning electron microscope, of an inwardly offset predetermined breaking point that is still intact;

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Fig. 6 shows burr formation at the laser-cutting edges: SEM image before the pickling process, i.e. before contact of the material layer with a suitable acid;

Fig. 7 shows the burr formation at the laser-cutting edges: SEM image after the pickling process;

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Fig. 8 shows an overview of laser-cut x-ray markers in a semifinished product, each marker having an inward predetermined breaking point; and

30 Fig. 9 shows an eyelet with, stuck therein, an x-ray marker having an inward predetermined breaking point (image recorded by light microscope).

Figures 1 to 3 show an x-ray marker 1 which preferably comprises a highly absorbent x-ray marker surface (for example made of tungsten and/or tantalum), which preferably is passivated so that, following assembly in the receptacles (eyelets) 101 (Figure 4) of a degradable or also non-degradable medical implant 100 (for example a framework, in particular a stent framework), there is no occurrence of accelerated corrosion.

In particular, Figure 1a shows a graphical representation of an x-ray marker 1 which extends along the longitudinal direction L and comprises a section 21 in which the predetermined breaking point 23 is disposed inwardly. In the illustration of Figure 1b, an embodiment of the x-ray marker 1 which has two mutually opposed sections 23 is shown in the same illustration.

Figures 2a and 2b now show the x-ray markers 1 from Figures 1a and 1b in a plan view. In both illustrations a region A is marked by a circle and is shown in detail in Figure 3. By way of example, dimensions here in Figures 2a and 2b are specified in millimetres and standard deviations thereof.

Figure 3 shows a detailed view of the region A from Figures 2a and 2b. What can be seen is the position of the predetermined breaking point 21 in the section 23 directed inwardly from the outer side of the x-ray marker 1. The inwardly directed position is visible in particular by the edges 1a and 1b arranged further outwardly in the extension direction E compared to the predetermined breaking point 21. The web 20 provided formerly is indicated in Figure 3 by dashed lines.

This specific arrangement is also visible in Figures 4a and 4b, which show microscopic images of the x-ray marker 1 connected to the material layer 2 via one web (Figure 4a) or two webs (Figure 4b). The gap 24 here separates the x-ray marker 1 from the surrounding material 22 of the material layer 2.

In Figure 5, an image of the region A of Figures 2a and 2b recorded by SEM is shown, wherein here the web 20 is still connected to the x-ray marker 1 via the predetermined

breaking point 21. The inwardly directed position of the predetermined breaking point 21 compared with 1a and 1b is also clearly visible here.

Figure 6 shows an image of the gap 24 recorded by SEM. At the cutting edge, the burr 25 can be seen before this is treated with suitable acid. By way of comparison, the effects of the treatment with a suitable acid on the gap 24 and the burr 25 are shown in Figure 7. By way of comparison it can be seen that the burr 25 has significantly lost roughness and sharp edges, and the treatment with suitable acid results in a material-removing effect.

Figure 8 also shows that the present method is suitable for pre-cutting a multiplicity of x-ray markers 1 into a material layer 2 so as to achieve a high level of automation of the production process. It can be seen that a multiplicity of x-ray markers 1 can be produced simultaneously by the same applied method step.

Figure 9 shows an image recorded by light microscope of an x-ray marker 1 which has been introduced into a receptacle 101 (eyelet) of a strut 102 of a framework 100. In this illustration it can be clearly seen that any metal-metal contact with the strut 102 is ruled out by the inwardly directed position of the predetermined breaking point.

The x-ray marker 1 is preferably produced in that a corresponding region 1 is pre-cut almost fully into a flat material layer 2, which is preferably a metal foil 2, for example by means of a laser (for example see Fig. 4a, 4b or 8).

In order to prevent a premature breaking-off of the markers 1 from the material layer 2, these are provided with at least one geometrically inwardly offset predetermined breaking point 21, as is illustrated for example in Figures 1 to 3 and 5.

Alternatively to a single predetermined breaking point, an embodiment is shown by way of example in Figures 1b, 2b and 4b, in which a second predetermined breaking point opposite the first predetermined breaking point is provided.

Said pre-cutting is carried out in particular so that the region 1 of the material layer 2 is connected via at least one web 20, which is extended along an extension direction E and which forms the (inward) predetermined breaking point 21, to a part 22 of the material layer 2 surrounding the region 1, wherein the predetermined breaking point 21 is “inward”,
5 since it is arranged in a section 23 (formed by the pre-cutting) which is formed or arranged at an outer edge of the region 1 so that the predetermined breaking point 21 or the base of the web 20 lies further inwardly in the extension direction E (for example Figures 2a, 2b and 5) of the web 20 (i.e. closer to the centre of the region/x-ray marker 1) than two edge portions 1a, 1b of the region 1, between which the section 23 is disposed.

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As can be seen in particular from Figures 2a, 2b and 3, provision can be made so that the region 1 or the x-ray marker 1 is formed in an elongate manner and extends along a longitudinal axis L. Said extension direction E of the web 20 runs here primarily

perpendicularly to the longitudinal axis L. Furthermore, said edge portions 1a, 1b run on either side of the section 23 or web 20, preferably along or parallel to the longitudinal axis L of the region 1 or x-ray marker 1. In particular, the region 1 or x-ray marker 1 can have an oval or elongate form with rounded corners or semi-circular ends.

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The web width B of the predetermined breaking point 21 or of the web 20 (see Fig. 3 and 5) is for example approximately 8 μm . The gap 24 (in particular laser cutting gap 24), which is produced during the pre-cutting, is for example between 10 and 100 μm wide. The mechanical strength of the predetermined breaking point 21 is sufficient to attain an adequate transport and storage capability without the marker 1 breaking off prematurely.

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In a subsequent process, the film or material layer 2 is immersed in a suitable acid or acid mixture. The composition of this acid mixture is dependent, as described herein, on the material of the x-ray marker 1. The pickling effect that then occurs results in a chemical levelling or polishing of the very rough burr 25 (see Figures 6 and 7) produced during the pre-cutting or laser cutting, and in particular results in a small widening of the laser cutting gap 24. The web width B is reduced in such a step for example from approximately 8 μm to approximately 3 μm . After an intermediate – preferably two-stage – rinsing process, the foil/material layer 2 is contacted by way of example with a titanium wire and is immersed in a mixture of an electrolyte containing mineral acid and ethanol. The electrolyte container here has an electrode configured as a cathode and made of a rust- and acid-resistant steel.

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A plasma-chemical process is performed, which is described by way of example in some examples detailed further below, wherein, during the course of said process, the x-ray marker surface is oxidised or otherwise passivated, for example to a depth of approximately 2 to 4 μm . This (process (oxidation) preferably carried out under plasma-chemical conditions) at the same time also causes an oxidation of the predetermined breaking point 21 itself. This is preferably oxidised through once the plasma-chemical process is complete. A corresponding loss of the material cohesion and a breaking-off of the marker 1 from the connection of the foil or the material layer 2 results. The separated marker 1 now falls into a capturing device, which for example is net-like (for example

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made of a plastic), which was placed beforehand in the electrolyte. The device is then removed from the electrolyte and rinsed preferably a number of times. Once the rinsing process is complete (preferably in distilled water), x-ray markers that are free from electrolyte residues and that are surface-passivated are present, which are then available –
5 after drying (for example in warm air) – for the assembly process.

In this method, preferably material layers 2 or semifinished products 200 are used, as shown in Figure 10. Here, a number of regions 1/x-ray markers 1 are pre-cut (in the above-described way) into a material layer 2 (metal foil 2) so that a number of x-ray markers 1
10 can be produced in parallel.

A finished x-ray marker 1 is preferably glued in accordance with Figures 6 and 9 into a receptacle (what is known as an eyelet) 101, which for example is formed as a through-opening 101 in a strut 102 of a medical implant 100. An implant 100 of this type is
15 preferably a framework 100, in particular a stent framework 100, which is preferably degradable. The x-ray marker 1 can of course also be used with non-degradable frameworks/stent frameworks 100.

Some detailed examples will be described hereinafter.

Example 1

A framework (scaffold) 100 made of a degradable magnesium alloy (see Fig. 6) has a receptacle (eyelet) at a distal end and at a proximal end, which receptacle is provided for
25 assembly with x-ray markers 1. The diameters of the oval eyelet 101 are approximately 800 μm and approximately 350 μm . Oval undersized solid markers 1 made of tungsten with inward predetermined breaking points 21 are assembled in these eyelets 101 (see Figures 1 and 2). The thickness of this tungsten marker 1 is in particular identical to the wall thickness of the scaffold 100, and for example is 100 μm . The undersize relative to
30 the corresponding eyelet dimensions is in each case 20 to 30 μm , for example. The tungsten marker 1 has a predetermined breaking point 21 in relation to the rest of the foil 2 (see Figures 3 and 5) and has therefore been cut out beforehand from a foil 2 by means of a

laser light beam (see Figures 4 and 5). The cutting gap 24 is for example between 10 and 100 μm . The burr 25 produced during the laser cutting is removed by pickling in a mineral acid, for example an acid mixture having a temperature of 30°C formed from nitric and hydrochloric acid, over 2 to 5 min (see Figures 7 and 8). This is followed by a three-stage
5 rinsing process in distilled hot water having a temperature of 80°C.

After being dried in air, the foil material 2 is plasma-chemically oxidised with the laser-cut x-ray markers 1 in an electrolyte containing sulphuric acid and phosphoric acid. The oxidation of the chemically stable element tungsten is brought about by the locally limited
10 plasma discharges at bath voltages above 180 V. Here, individual plasma discharges scan the tungsten surface systematically. The surface of the marker 1 thus obtains a method-typical porous surface, which consists predominantly of WO_3 , which is electrically non-conductive and is practically insoluble in water. The oxide layer thickness is between 2 and 4 μm . On account of the conversion nature, i.e. the temporarily fused surface produced by
15 the plasma discharges, the original external geometry of the marker 1 is retained and the oxide layer has a high adhesive strength on account of the material bonding to the underlying metal substrate. Since the plasma-chemical oxidation effect is also effective at the predetermined breaking point 21, which is approximately 3 μm wide, said predetermined breaking point is oxidised through. The separated marker 1 falls into a net-
20 like capturing device, which was placed previously in the electrolyte. A subsequent pickling effect in the electrolyte does not take place, since the previously plasma-chemically oxidised surface has a sufficiently high corrosion resistance compared to a maximum residence time in the electrolyte of two minutes. The x-ray marker 1 is then removed from the electrolyte and then subjected to a multi-stage rinsing process in hot
25 water at a temperature of 80°C. Once the rinsing process in distilled water is complete, x-ray markers 1 that are free of electrolyte residues and that are surface-passivated are now provided and are then dried in warm air and are available for assembly processes.

The assembly process, i.e. the connecting of the x-ray marker(s) 1 to the corresponding
30 implant 100 starts with the wetting or immersion of the x-ray marker 1 in a silicone adhesive, for example: NUSIL Med 2. In parallel thereto, the inner sides of the eyelet (see Figure 6) are wetted with the aid of a thin plastic needle, which has been immersed

previously in the silicone adhesive. The x-ray marker 1 is then placed in the eyelet 101 using tweezers or another suitable handling device. Another option is to push the x-ray marker directly from the material layer into the receptacle. The silicone adhesive is then cured in a hot-air oven at 150°C over a period of time of 15 min. The finished, assembled
5 x-ray marker 1 is illustrated in Figure 9.

Example 2

According to Example 2, the scaffold 100 is provided with an x-ray marker 1 made of
10 tantalum, which has a microporous surface made of tantalum oxide, produced by means of plasma-chemical oxidation.

The scaffold 100 made of a degradable magnesium alloy (see Fig. 6) again has an eyelet 101 at the distal end and at the proximal end, which eyelets are provided for assembly with
15 x-ray markers 1. The diameters of the corresponding oval eyelet 101 are approximately 800 µm and approximately 350 µm. Oval undersized solid markers 1 made of tantalum with inward predetermined breaking points 21 are assembled in these eyelets 101 (see Figures 1 and 2). The thickness of this tantalum marker 1 is identical to the wall thickness of the scaffold 100 and for example is 100 µm. The undersize relative to the corresponding
20 eyelet dimensions is in each case 20 to 30 µm. The tantalum marker 1 has a predetermined breaking point 21 in relation to the rest of the foil 2 (see Figures 3 and 5) and has therefore been cut out beforehand from a foil 2 by means of a laser light beam (see Figures 4 and 5). The cutting gap 24 is between 10 and 100 µm in this case as well.

25 The burr 25 produced during the laser cutting is removed by pickling in a mixture formed from nitric acid and hydrofluoric acid at room temperature, over 1 to 3 min. This is followed by a three-stage rinsing process in distilled hot water having a temperature of 80°C.

30 After being dried in air, the foil material 2 is plasma-chemically oxidised with the laser-cut x-ray markers 1 in an electrolyte containing phosphoric acid. The oxidation of the chemically stable element tantalum is brought about by the locally limited plasma

discharges at bath voltages above 180 V. Here, individual plasma discharges scan the tantalum surface systematically. The surface of the marker 1 thus obtains a method-typical porous surface, which consists predominantly of Ta_2O_5 and Ta phosphates, which are electrically non-conductive. The oxide layer thickness is between 0.5 and 4 μm . On account of the conversion nature of the temporarily melted surface produced by the plasma discharges, the original external geometry of the marker 1 is retained and the oxide layer has a high adhesive strength on account of the material bonding to the underlying metal substrate. Since the plasma-chemical oxidation effect is also effective at the predetermined breaking point 21, which is approximately 3 μm wide, said predetermined breaking point is oxidised through. The separated marker 1 falls into a net-like capturing device, which was placed previously in the electrolyte. A subsequent pickling effect in the electrolyte does not take place, since the previously plasma-chemically oxidised surface has a sufficiently high corrosion resistance compared to a maximum residence time in the electrolyte of a few minutes. The x-ray marker 1 is then removed from the electrolyte and then subjected to a multi-stage rinsing process in hot water at a temperature of 80°C. Once the rinsing process in distilled water is complete, x-ray markers 1 that are free of electrolyte residues and that are surface-passivated are now provided and are then dried in warm air and are available for assembly processes.

The assembly process starts again with the wetting or immersion of the x-ray marker 1 in a silicone adhesive, for example NUSIL Med 2. In parallel thereto, the inner sides of the eyelet 101 (see Figure 6) are wetted with the aid of a thin plastic needle, which has been immersed previously in the silicone adhesive. The x-ray marker 1 is then placed in the eyelet 101 using tweezers or another suitable handling device. The silicone adhesive is then cured in a hot-air oven at 150°C over a period of time of 15 min. The finished, assembled x-ray marker 1 is constructed as illustrated in Figure 9.

Example 3

According to Example 3, a scaffold 100 made of nitinol is provided with an x-ray marker 1 made of gold having a predetermined breaking point 21 approximately 5 μm wide.

The scaffold 100 made of a nickel-titanium alloy nitinol (see Fig. 6) has an eyelet 101 at the distal end and at the proximal end, which eyelet is provided for assembly with an x-ray marker 1. The diameters of the corresponding oval eyelet 101 are approximately 800 μm and approximately 350 μm . Oval undersized solid markers 1 made of gold with inward predetermined breaking points 21 are assembled in these eyelets 101 (see Figures 1 and 2). The thickness of this gold marker 1 is identical to the wall thickness of the scaffold 100 and for example is 100 μm . The undersize relative to the corresponding eyelet dimensions is in each case 20 to 30 μm . The gold marker 1 has a predetermined breaking point 21 in relation to the rest of the foil 2 (see Figures 3 and 5) and has therefore been cut out beforehand from a foil 2 by means of a laser light beam (see Figures 4 and 5). The cutting gap 24 is between 50 and 100 μm in this case as well.

The burr 25 produced during the laser cutting is removed by pickling diluted aqua regia (1 part HNO_3 + 3 parts HCl). After a treatment time of approximately 1 min., the foil 2 is removed from the pickling bath and is freed of adhering pickling residues in a three-stage rinsing process in distilled hot water having a temperature of 80°C.

The film 2 is then immersed in an aqueous sodium-silicate mixture or lithium-silicate mixture (waterglass). This mixture has a temperature of approximately 50°C. After a treatment time of approximately 5 min., an electrically insulating layer formed of silicates and approximately 2 to 5 μm thick is deposited on the gold surfaces, which for example can have the following empirical formulas, such as $\text{Na}_2\text{O}_7\text{Si}_3$, $\text{Na}_2\text{O}_3\text{Si}$, $\text{Na}_2\text{O}_5\text{Si}_2$ or $\text{Na}_4\text{O}_4\text{Si}$ or in the case of the lithium silicate Li_2O , SiO_2 or Li_2SiO_3 . The following two method steps can then be performed:

a) After being dried in air, the foil material 2 with the laser-cut x-ray markers 1 and the dielectric layer now provided is brought into a plastic container filled with distilled water, which container is exposed to ultrasound in the frequency range between 25 and 50 kHz. The x-ray markers 1 are set in mechanical vibration, meaning that they break off at the predetermined breaking point, break off from the connection to the foil, and drop into the

vessel, without the surface being damaged. The water is then removed from the plastics container and the separated x-ray markers are dried in air.

b) After being dried in air, the foil material 2 with the laser-cut x-ray markers 1 and the dielectric layer now provided is brought into a slightly alkaline, diluted NaOH solution. The pH value is between 8 and 9. The plastic container with the x-ray markers 1 now coated with sodium silicate is brought into an ultrasonic bath. By applying ultrasound in the frequency range between 25 and 50 kHz, the foil material is set in slight vibration, which causes the individual markers 1 to break off from the connection to the foil 2 at the predetermined breaking point 21. The separated markers 1 can then be removed from the container and dried in air.

By both variations a) and b) plastic deformations as well as surface damages too were avoided.

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The assembly process starts again with the wetting or immersion of the x-ray marker 1 in a silicone adhesive, for example NUSIL Med 2. In parallel thereto, the inner sides of the eyelet 101 (see Figure 6) are wetted with the aid of a thin plastic needle, which has been immersed previously in the silicone adhesive. The x-ray marker 1 is then placed in the eyelet 101 using tweezers or another suitable handling device. The silicone adhesive is then cured in a hot-air oven at 150°C over a period of time of 15 min. The finished, assembled x-ray marker 1 is again constructed as illustrated in Figure 9.

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Patent claims

1. A method for producing x-ray markers, wherein at least one region of a material layer forming the x-ray marker to be produced is pre-cut, such that said region is connected
5 via at least one web, which forms a predetermined breaking point, to a part of the material layer surrounding the region,
wherein the predetermined breaking point is arranged in a section of the region such that the predetermined breaking point lies further inward in an extension direction of the web than two edge portions of the region between which the section is
10 disposed, wherein the predetermined breaking point is severed in order to detach the x-ray marker from said part of the material layer.
2. The method according to claim 1, wherein the material layer is a metal foil or a metal tube made of radiopaque metal.
- 15 3. The method according to any one of the preceding claims, wherein a width of the web perpendicularly to the extension direction is pre-cut in a range of from 1 μm to 20 μm .
4. The method according to any one of the preceding claims, wherein during the pre-cutting, a gap surrounding the region is produced and in particular has a width ranging
20 from 10 μm to 100 μm .
5. The method according to any one of the preceding claims, wherein the material layer together with the pre-cut region is contacted with an acid, such that a burr produced
25 during the pre-cutting at the region is reduced, in particular is polished.
6. The method according to claim 6, wherein the material layer treated with the acid is rinsed together with the pre-cut region after the contacting with the acid.
- 30 7. The method according to any one of the preceding claims, wherein an outer surface of the region connected to the material layer is passivated for protection against corrosion, in particular by one of the following measures:

- oxidation of the surface, wherein in particular the oxidation is a plasma-chemical oxidation, which in particular is carried out in an electrolyte; or
 - coating with a dielectric layer, wherein in particular a gas-phase deposition produces thin silicon oxide layers; or
 - 5 - contacting of the surface with an aqueous silicate mixture for producing an electrically insulating layer on the surface, wherein said layer comprises sodium silicates; or
 - application of a complete layer of parylene.
- 10 8. The method according to claim 7, wherein the region, in particular after the passivation, is separated from the part of the material layer surrounding the region, in particular by one of the following measures:
- by the oxidation performed for passivation, wherein the predetermined breaking point is fully oxidised and is thus severed; or
 - 15 - by vibrating the predetermined breaking point, in particular by exposing the predetermined breaking point to ultrasonic waves.
9. An x-ray marker, wherein the x-ray marker has a section including a web extended along an extension direction,
- 20 a contact face which is formed at a breaking point when the web is severed in order to produce the x-ray marker, and
- wherein the contact face lies further inward in the extension direction of the web than two edge portions of the x-ray marker between which the section is disposed.
- 25 10. The x-ray marker according to claim 9, wherein the marker has an oxide or silicate layer with a thickness of more than 0.5 μm .
11. A semifinished product for producing an x-ray marker, in particular an x-ray marker according to claims 9 or 10, wherein the semifinished product is formed by a material
- 30 layer, into which at least one region of the material layer forming the x-ray marker to be produced is pre-cut, such that said region is connected via a web, which is extended

along an extension direction and forms a predetermined breaking point, to the part of the material layer surrounding the region,

wherein the predetermined breaking point is arranged in a section of the region so that the predetermined breaking point lies further inward in the extension direction of the web than two edge portions of the region between which the section is disposed.

12. The semifinished product according to claim 11, wherein a width of the web perpendicular to the extension direction lies in the range of from 1 μm to 20 μm .
13. A medical implant, in particular in the form of a framework, wherein the medical implant comprises at least one x-ray marker according to any one of claims 9 to 10.

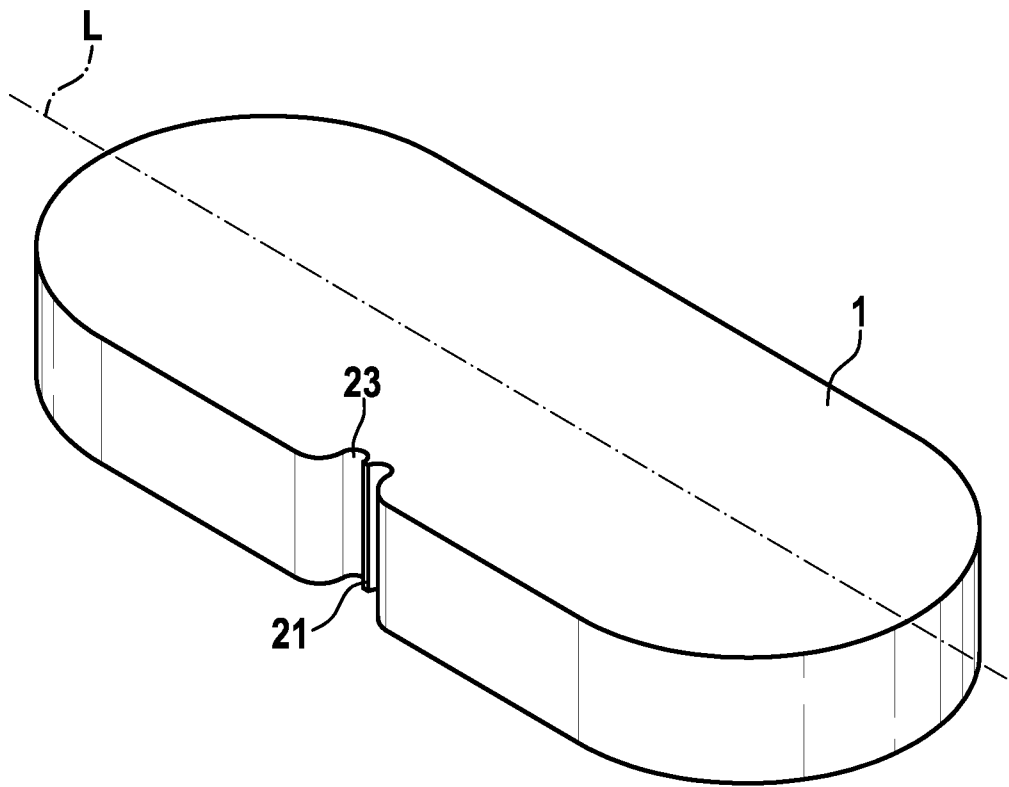


FIG. 1A

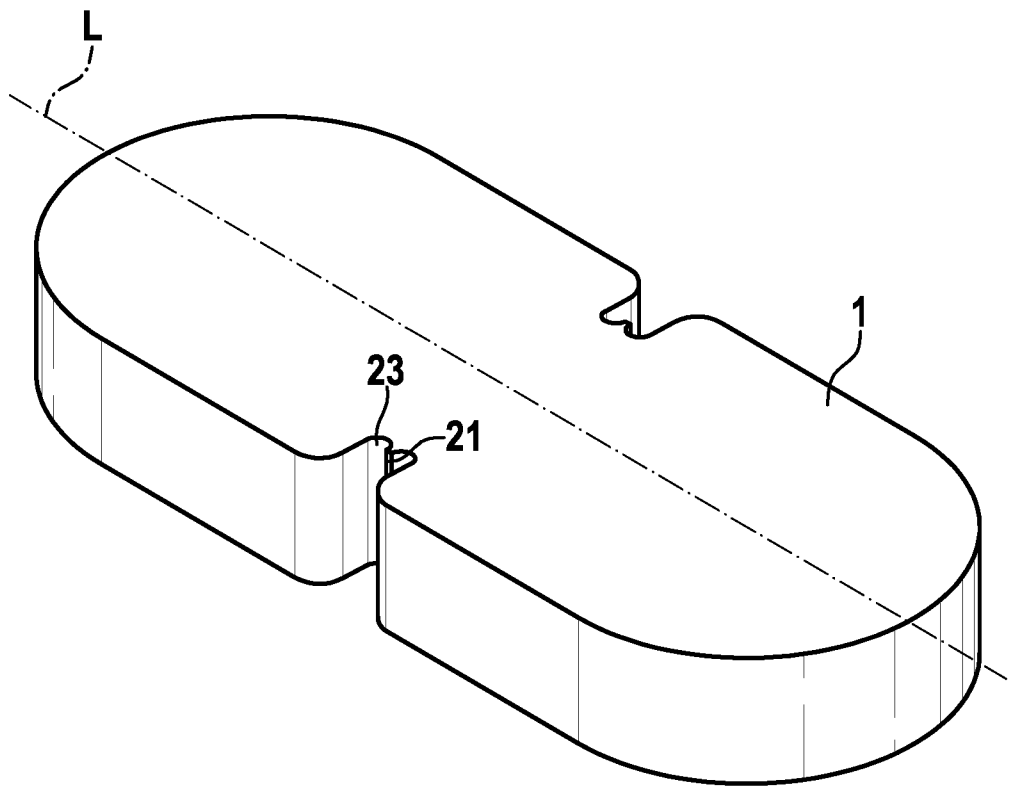


FIG. 1B

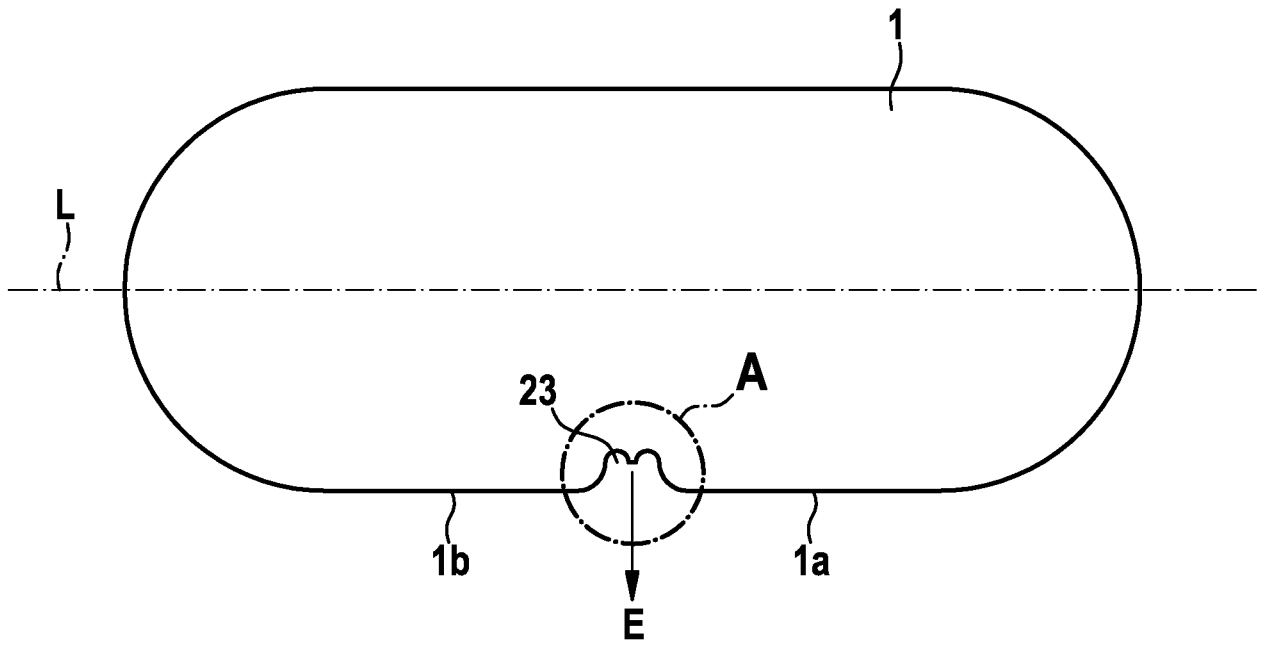


FIG. 2A

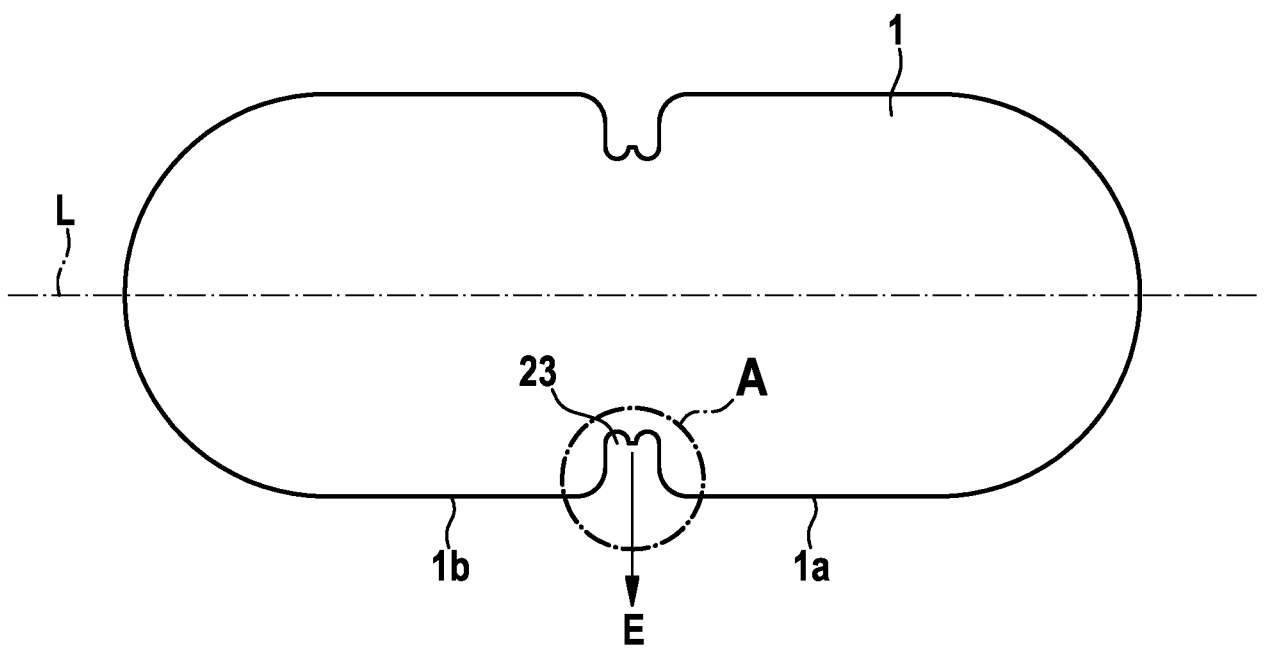


FIG. 2B

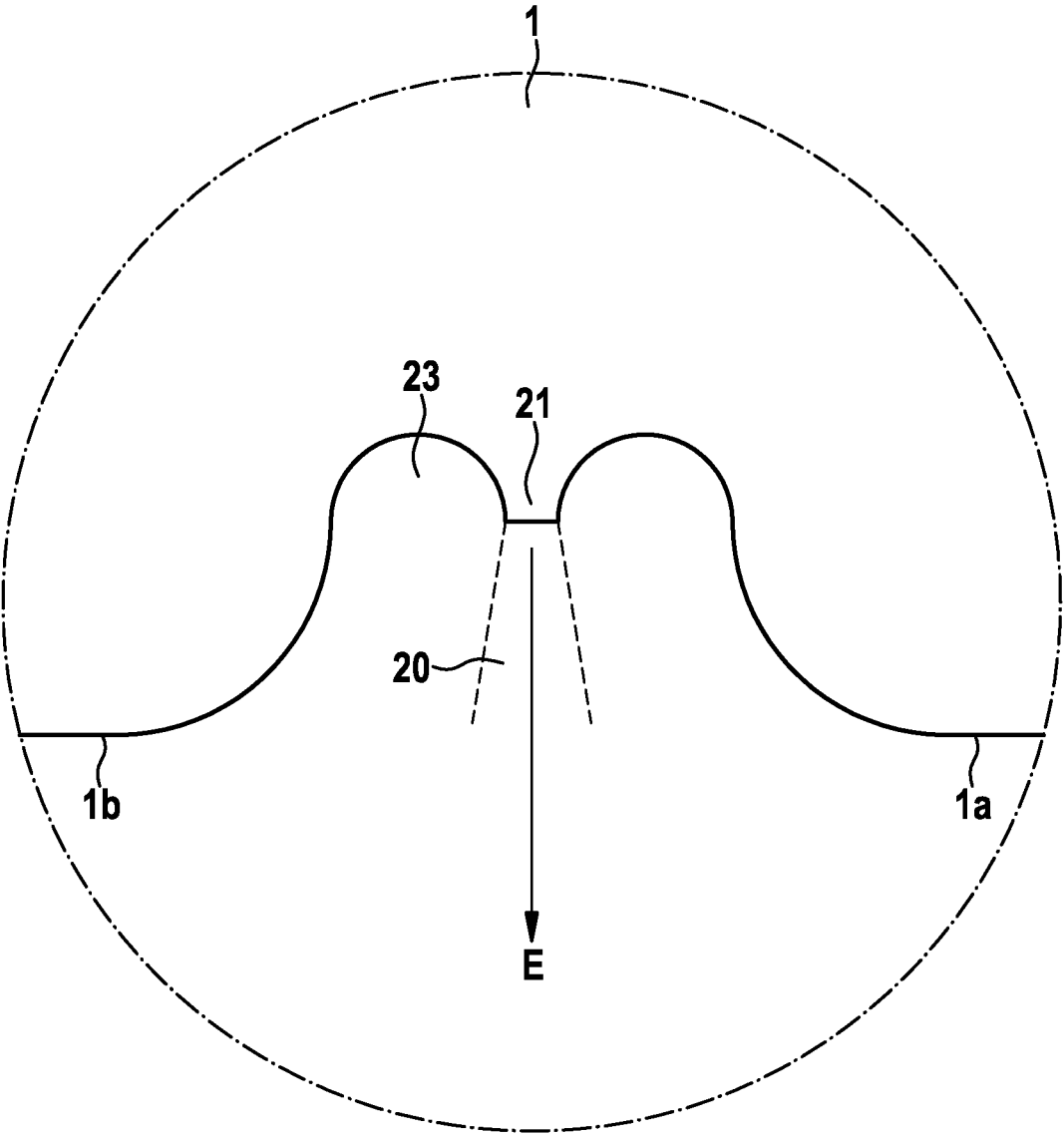


FIG. 3

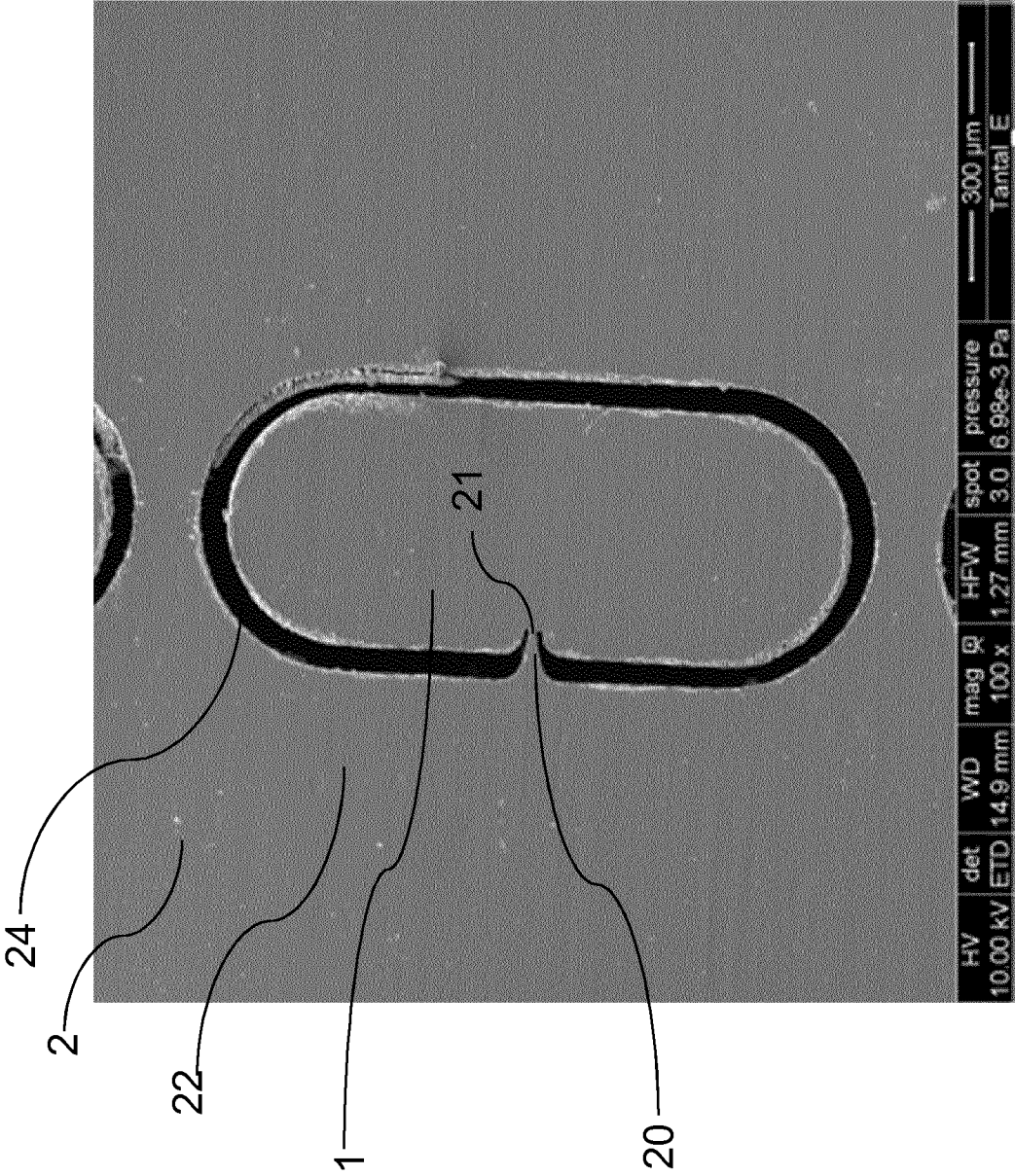


FIG. 4A

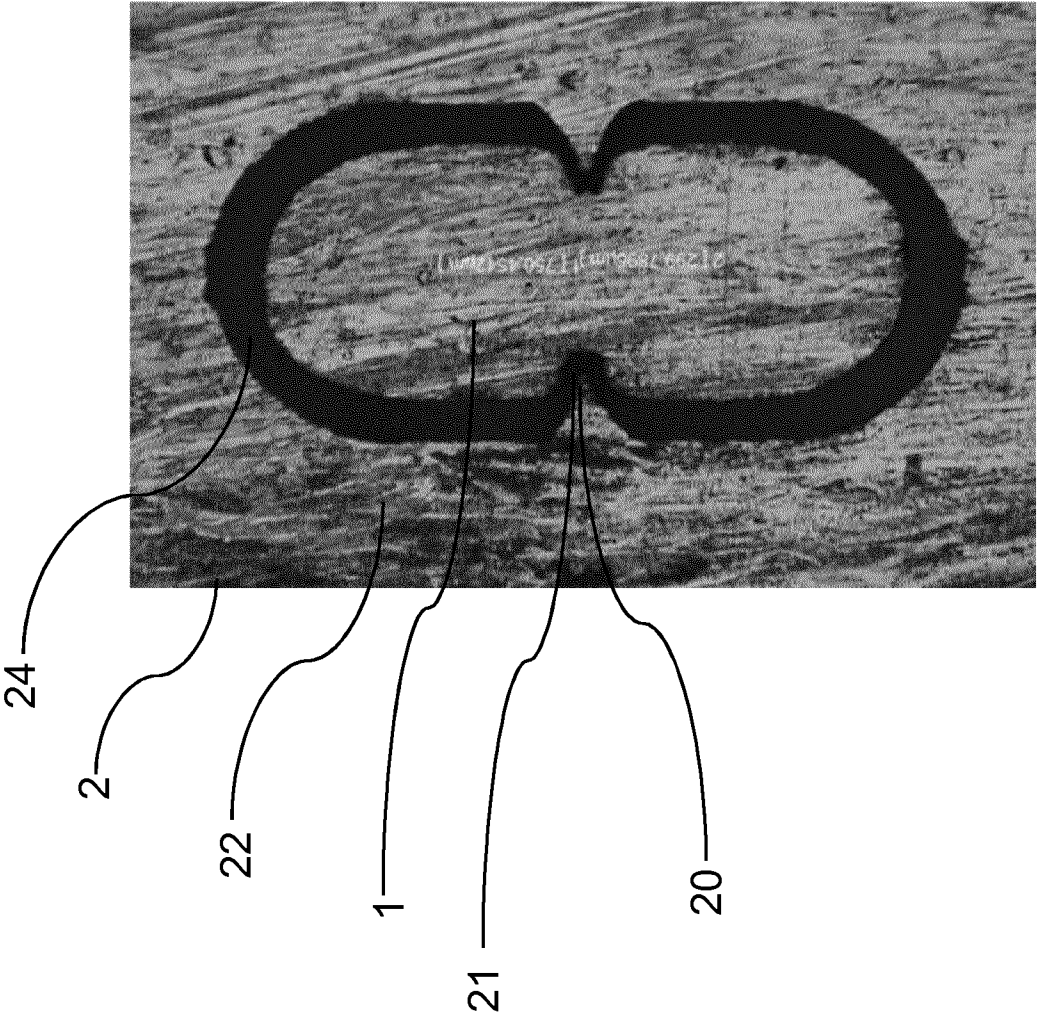


FIG. 4B

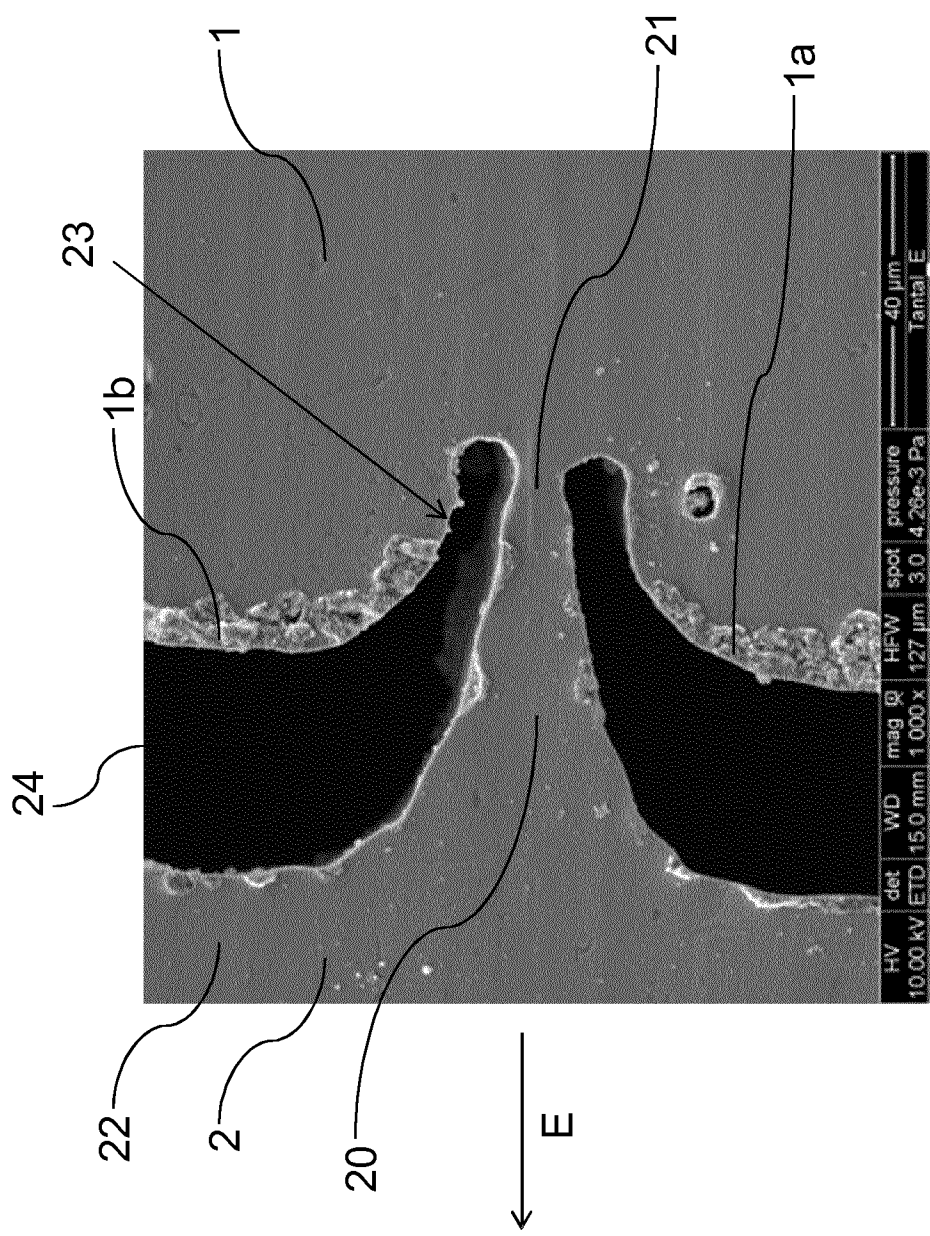


FIG. 5

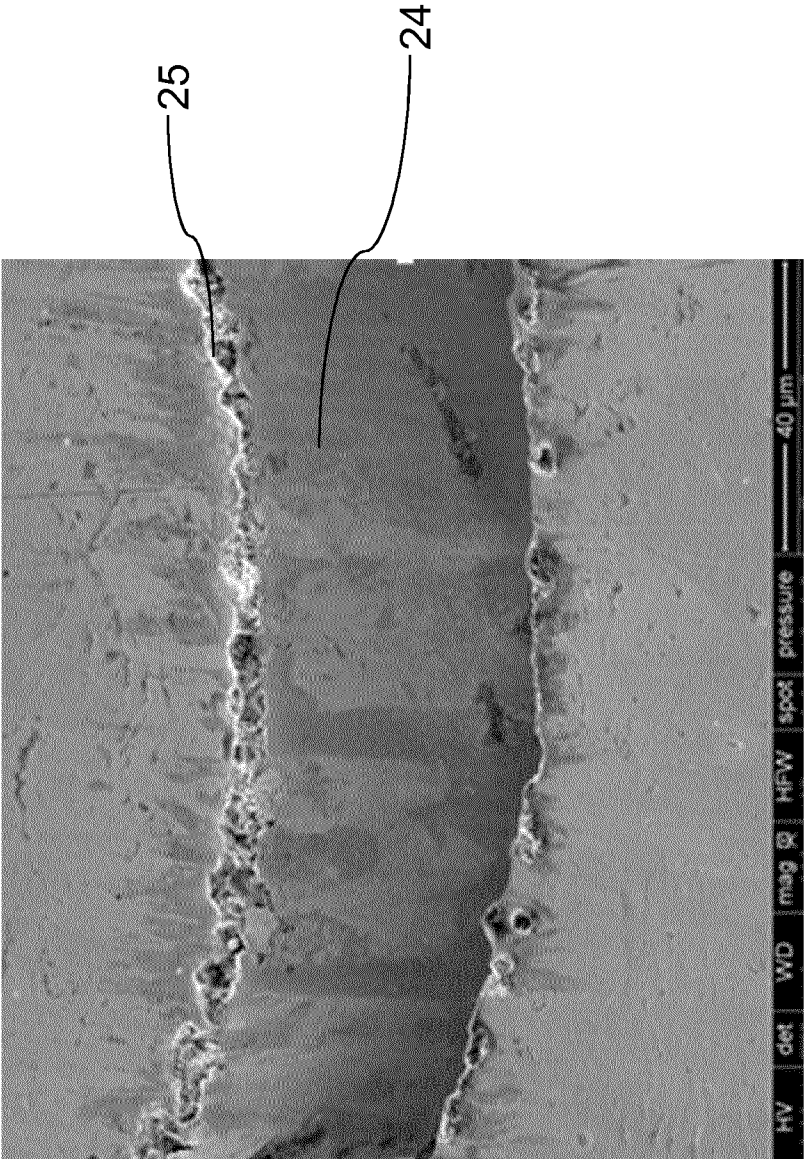


FIG. 6

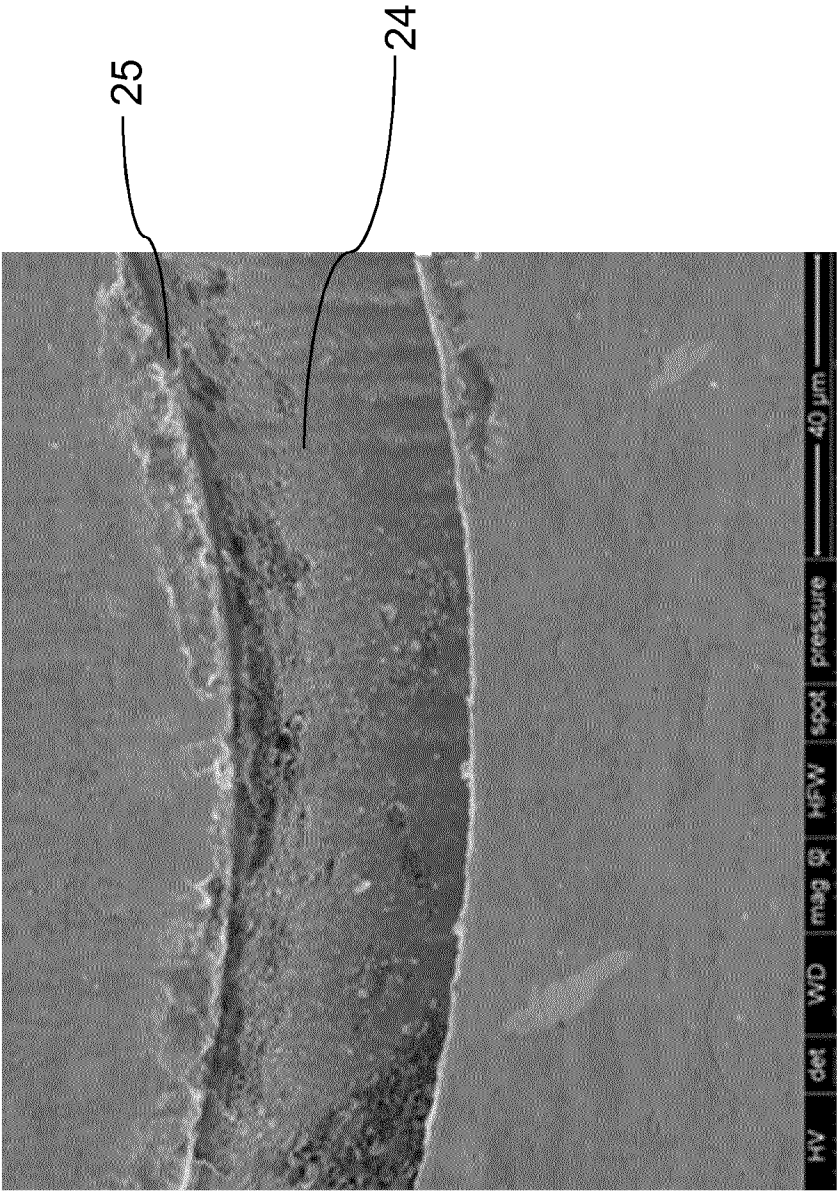


FIG. 7

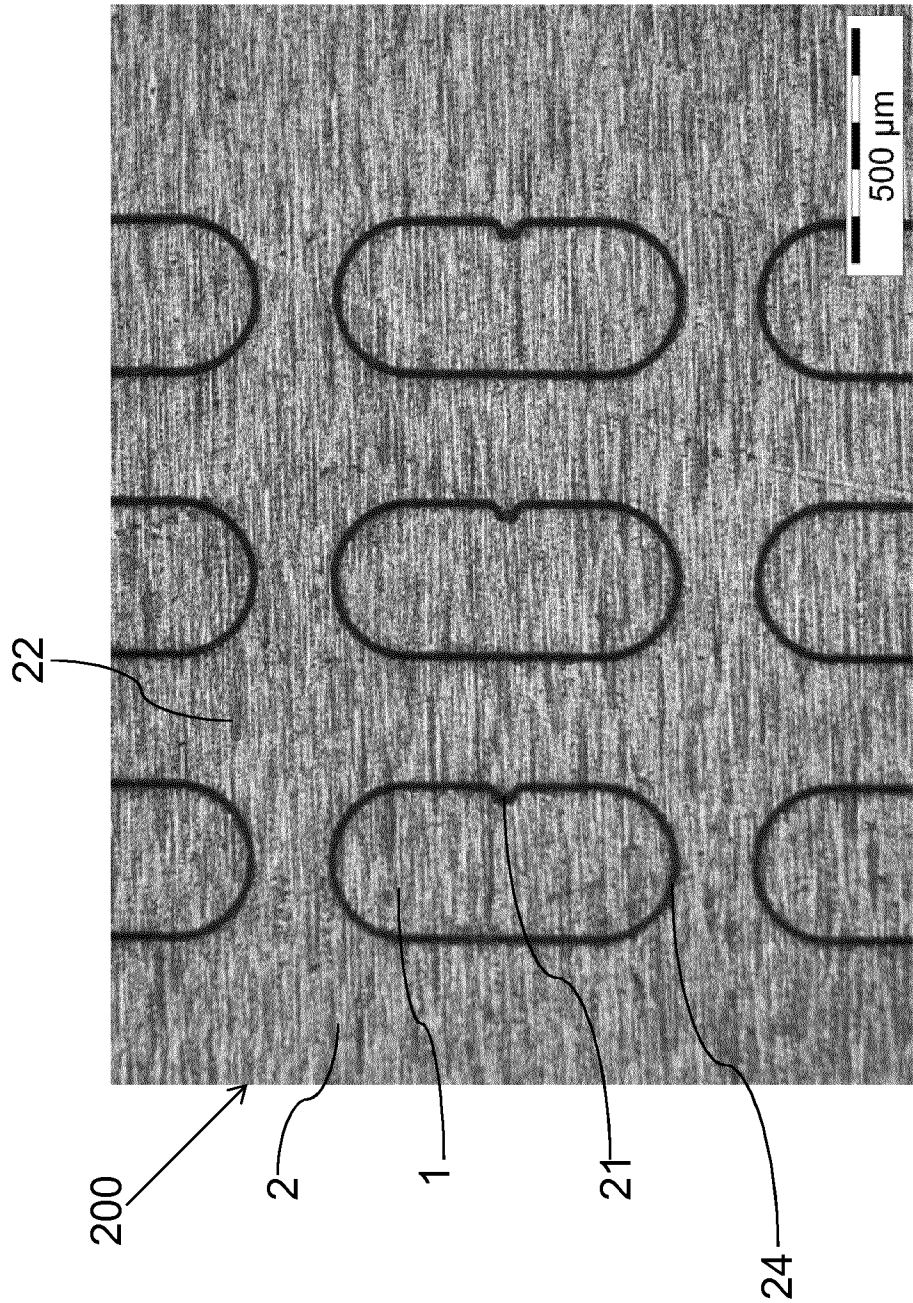


FIG. 8

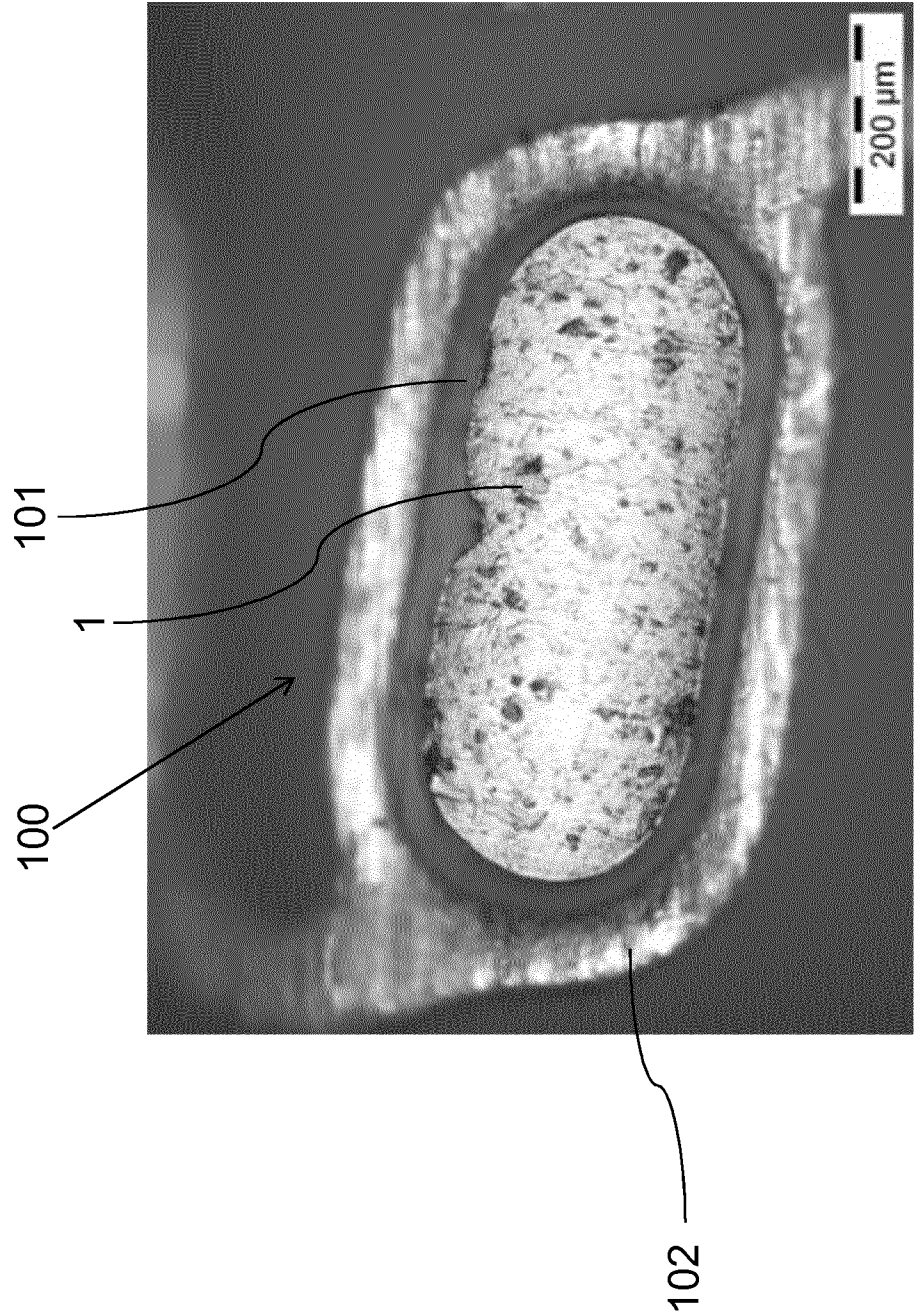


FIG. 9