Description

BALLOON CATHETER AND MANUFACTURING METHOD THEREOF, AND TREATMENT METHOD

Technical Field

[0001]

The present invention relates to a balloon catheter provided with a crystalline drug on an outer surface of a balloon and a manufacturing method thereof, and a treatment method in which the balloon catheter is used.

Background Art

[0002]

In recent years, balloon catheters have been used for improving lesion affected areas (stenosed parts) in body lumens. A balloon catheter normally includes an elongated shaft portion and a balloon which is provided on the distal side of the shaft portion and is inflatable in the radial direction. After the balloon in a deflated state is brought to a target site in the body by way of a thin body lumen, the balloon is inflated, whereby the lesion affected area can be pushed wide open.

[0003]

If a lesion affected area is forcibly pushed wide open, however, excessive proliferation of smooth muscle cells may occur, causing new stenosis (restenosis) at the lesion affected area. In view of this, recently, drug eluting balloons (DEBs) in which an outer surface of a balloon is coated with a drug for restraining stenosis have been used. The drug eluting balloon, by being inflated, is able to instantaneously release the drug contained in the coating on the outer surface of the balloon to the lesion affected area, thereby restraining restenosis.

[0004]

In recent years, it has been becoming clear that the morphological form of the drug in the coating on the balloon outer surface influences the releasing property of the drug from the balloon surface and/or the tissue transferability of the drug at the lesion affected area. For instance, Patent Document 1 describes a balloon catheter in which crystals of a drug are formed in elongate form on an outer surface of a balloon.

Prior Art Document

Patent Document

[0005]

Patent Document 1: U.S. Patent Application Publication No. 2014/0271775

Summary of Invention

Technical Problem

[0006]

For enhancing a therapeutic effect, a drug eluting balloon catheter is desirably configured in such a manner that the deliverability of the drug on the outer surface of the balloon to living body tissue is high and that the deliverability can be controlled.

[0007]

This invention has been made to solve the above-mentioned problem. It is an object of the invention to provide a balloon catheter by which a drug can be effectively delivered to living body tissue and the deliverability can be controlled and a manufacturing method thereof, and a treatment method.

Technical Solution

[0008]

In order to achieve the above object, a balloon catheter according to the invention is a balloon catheter provided on an outer surface of a balloon with a

plurality of elongate bodies which are crystals of a water-insoluble drug extending while having independent long axes, the balloon catheter including: a base layer having a water-soluble low-molecular compound disposed in a layer form on the outer surface of the balloon, in which at least part of the elongate bodies is located in the inside of the base layer.

Advantageous Effects

[0009]

The balloon catheter configured as above is characterized in that inflation of the balloon causes cracking of the base layer, which facilitates dissolution of the base layer, thereby enabling the elongate bodies as the drug crystals to be easily released from the base layer, so that the drug can be effectively delivered to living body tissue. Furthermore, while the base layer including the water-soluble low-molecular compound is dissolved gradually or rapidly, the elongate bodies in the inside of the base layer make contact with the living body and the drug is thereby delivered to the living body tissue; therefore, the deliverability of the drug can be controlled by the material and thickness of the base layer and the positions of the elongate bodies relative

to the base layer.

[0010]

The elongate bodies may include first elongate bodies of which proximal portions are separate from the outer surface of the balloon and are located in the inside of the base layer. In this case, by adjusting the positions of the proximal portions of the first elongate bodies to be in the inside of the base layer, the deliverability of the drug to living body tissue can be controlled through utilization of the time taken for dissolution of the base layer including the water-soluble low-molecular compound.

[0011]

The elongate bodies may include second elongate bodies extending from the outer surface of the balloon. In this case, the second elongate bodies are eluted from the base layer slowly as the base layer is dissolved, and the drug can be slowly delivered to the living body tissue.

[0012]

The elongate bodies may include third elongate bodies extending from an outer surface of the base layer toward the outside of the surface. In this case, the third elongate bodies as a whole immediately make contact

with the living body tissue, so that the drug can be instantaneously delivered to the living body tissue.

[0013]

The water-insoluble drug may be rapamycin, paclitaxel, docetaxel, or everolimus. In this case, restenosis of a stenosed part in a blood vessel can be favorably inhibited by the elongate bodies of which at least part is located in the inside of the base layer.

[0014]

A method of manufacturing a balloon catheter according to the invention is a method of manufacturing a balloon catheter provided on an outer surface of a balloon with a plurality of elongate bodies which are crystals of a water-insoluble drug extending while having independent long axes, the method including: a step of supplying a coating solution containing the drug, a water-soluble low-molecular compound, an organic solvent, and water from a dispensing tube for supplying the coating solution, while keeping the dispensing tube in contact with the outer surface of the balloon, and giving a physical stimulus to the coating solution to cause formation of crystal nuclei of the water-insoluble drug; a step of volatilizing the organic solvent while leaving water to cause growth of the elongate bodies based on the

crystal nuclei; and a step of evaporating water to form a base layer including the water-soluble low-molecular compound.

[0015]

According to the method of manufacturing a balloon catheter configured as above, volatilization of the organic solvent from the layer including the water-soluble low-molecular compound containing water leads to growth of drug crystals from the crystal nuclei, whereby elongate bodies of which at least part is located in the inside of the base layer can be formed.

[0016]

A treatment method according to the present invention is a treatment method for delivering a drug to a lesion affected area in a body lumen by use of the aforementioned balloon catheter, the treatment method including: a step of inserting the balloon into the body lumen to deliver the balloon to the lesion affected area; a step of inflating the balloon to press the balloon against living body tissue and to bring the elongate bodies into contact with the living body tissue while dissolving the base layer including the water-soluble low-molecular compound; and a step of deflating the balloon and withdrawing the balloon out of the body lumen.

[0017]

According to the treatment method configured as above, inflation of the balloon causes cracking of the base layer, which facilitates dissolution of the base layer, thereby enabling the elongate bodies as the drug crystals to be easily released from the base layer, so that the drug can be effectively delivered to living body tissue. Furthermore, while the base layer including the water-soluble low-molecular compound is dissolved gradually or rapidly, the elongate bodies in the inside of the base layer make contact with the living body tissue and the drug is thereby delivered to the living body tissue; therefore, the deliverability of the drug can be controlled by the material and thickness of the base layer and the positions of the base portions of the elongate bodies relative to the base layer.

Brief Description of Drawings

[0018]

[FIG. 1]

FIG. 1 is a front view of a balloon catheter according to the present embodiment.

[FIG. 2]

FIG. 2 is a sectional view of a distal portion of

the balloon catheter.

[FIG. 3]

FIG. 3 is a schematic perspective view of elongate bodies consisting of drug crystals on an outer surface of a balloon.

[FIG. 4]

FIG. 4 is a schematic view showing the elongate bodies, consisting of the drug crystals, and a base layer on the outer surface of the balloon.

[FIG. 5]

FIG. 5 is a front view of a balloon coating apparatus.

[FIG. 6]

FIG. 6 is a sectional view of a dispensing tube in contact with the balloon.

[FIG. 7]

FIG. 7 is a sectional view showing a state in which a stenosed part of a blood vessel is pushed wide open by the balloon catheter according to the present embodiment.

[FIG. 8]

FIG. 8 is a view showing a base layer in a film-formed amorphous state.

[FIG. 9]

FIG. 9 is a schematic view of the first elongate

bodies and the base layer on the outer surface of the balloon.

[FIG. 10]

FIG. 10 is a schematic view of the second elongate bodies and the base layer on the outer surface of the balloon.

[FIG. 11]

FIG. 11 is a schematic view of the third elongate bodies and the base layer on the outer surface of the balloon.

[FIG. 12]

FIG. 12 is a schematic view showing elongate bodies and a base layer on an outer surface of a balloon.

[FIG. 13]

FIG. 13 is a schematic view showing fixed-side elongate bodies and separate-side elongate bodies as well as a base layer on an outer surface of a balloon.

Mode for Carrying Out the Invention

[0019]

An embodiment of the present invention will be described below referring to the drawings. Note that for convenience of explanation, the dimensional ratios in the drawings may be exaggerated and different from the actual

ratios.

[0020]

As shown in FIGS. 1 and 2, a balloon catheter 10 according to an embodiment of the present invention is a drug eluting type catheter provided with crystals of a drug on an outer surface of a balloon 30. Note that herein the side on which the balloon catheter 10 is inserted into a body lumen will be referred to as “distal end” or “distal side,” while the operator’s hand side on which the balloon catheter 10 is operated will be referred to as “proximal end” or “proximal side.”

[0021]

First, the structure of the balloon catheter 10 will be described. The balloon catheter 10 includes an elongated catheter main body 20, the balloon 30 provided on a distal portion of the catheter main body 20, a drug-containing coating layer 40 provided on the outer surface of the balloon 30, and a hub 26 attached to a proximal end of the catheter main body 20. The balloon 30 provided thereon with the coating layer 40 is covered and protected with a protective sheath 15 until put to use.

[0022]

The catheter main body 20 includes an outer tube 21 which is a tube body opening at distal and proximal ends

thereof, and an inner tube 22 which is a tube body disposed inside the outer tube 21. The inner tube 22 is accommodated in a hollow inside of the outer tube 21, and the catheter main body 20 is of a double tube structure at a distal portion thereof. The hollow inside of the inner tube 22 is a guide wire lumen 24 for passing a guide wire therethrough. In addition, in the hollow inside of the outer tube 21 and on the outside of the inner tube 22, there is formed an inflation lumen 23 for passing therethrough an inflation fluid for the balloon 30. The inner tube 22 is opening to the exterior at an opening portion 25. The inner tube 22 protrudes to the distal side beyond a distal end of the outer tube 21.

[0023]

Of the balloon 30, a proximal-side end portion is fixed to a distal portion of the outer tube 21, and a distal-side end portion is fixed to a distal portion of the inner tube 22. This results in that the inside of the balloon 30 communicates with the inflation lumen 23. With the inflation fluid injected through the inflation lumen 23 into the balloon 30, the balloon 30 can be inflated. The inflation fluid may be a gas or a liquid; for example, gases such as helium gas, CO_2 gas, O_2 gas, N_2 gas, Ar gas, air, mixed gas, etc. and liquids such as physiological

saline solution, a contrast agent, etc. can be used as the inflation fluid.

[0024]

At a central portion in regard of the axial direction of the balloon 30, there is formed a hollow cylindrical straight portion 31 (inflatable portion) having an equal outside diameter when inflated. Tapered portions 33 where the outside diameter gradually varies are formed on both sides of the straight portion 31 in regard of the axial direction. Besides, the coating layer 40 which contains a drug is formed on the whole part of an outer surface of the straight portion 31. Note that the range of the balloon 30 in which the coating layer 40 is formed is not limited only to the straight portion 31; the range may include at least part of the tapered portions 33 in addition to the straight portion 31, or may be only part of the straight portion 31.

[0025]

The hub 26 is formed with a proximal opening portion 27 that communicates with the inflation lumen 23 of the outer tube 21 and functions as a port through which the inflation fluid flows in and out.

[0026]

The length in the axial direction of the balloon 30

is not particularly limited, and is preferably 5 to 500 mm, more preferably 10 to 300 mm, and still more preferably 20 to 200 mm.

[0027]

The outside diameter of the balloon 30 when inflated is not particularly limited, and is preferably 1 to 10 mm, and more preferably 2 to 8 mm.

[0028]

An outer surface of the balloon 30 before the formation of the coating layer 40 is smooth and non-porous. The outer surface of the balloon 30 before the formation of the coating layer 40 may be provided with minute holes that do not pierce through the film of the balloon 30. Alternatively, the outer surface of the balloon 30 before the formation of the coating layer 40 may have both a range of being smooth and non-porous and a range of having minute holes that do not pierce through the film of the balloon 30. The minute holes may be sized to have, for example, a diameter of 0.1 to 5 μm and a depth of 0.1 to 10 μm, and one or more holes may be provided per crystal. Alternatively, the minute holes may be sized to have, for example, a diameter of 5 to 500 μm and a depth of 0.1 to 50 μm, and one or more crystals may be provided per hole.

[0029]

Preferably, the balloon 30 has a certain degree of flexibility and a certain degree of hardness such that the drug can be released from the coating layer 40 provided on the outer surface thereof when the balloon 30 is inflated upon arrival at a blood vessel or tissue or the like. Specifically, the balloon 30 is formed from metal or resin. It is preferable that at least the outer surface of the balloon 30 on which to provide the coating layer 40 is formed of resin. Examples of the material which can be used for forming at least the outer surface of the balloon 30 include thermoplastic resins such as polyolefins (e.g., polyethylene, polypropylene, polybutene, ethylene-propylene copolymers, ethylene-vinyl acetate copolymers, ionomers, or mixtures of two or more of them), flexible polyvinyl chloride resin, polyamides, polyamide elastomers, nylon elastomers, polyester, polyester elastomers, polyurethane, fluororesins, etc., silicone rubbers, and latex rubbers. Among these, preferred are the polyamides. Specifically, at least part of the outer surface of the balloon 30 to be coated with the drug is made of a polyamide. The polyamide is not particularly limited so long as it is a polymer which has an amide linkage. Examples of the polyamide include

homopolymers such as polytetramethylene adipamide (nylon 46), polycaprolactam (nylon 6), polyhexamethylene adipamide (nylon 66), polyhexamethylene sebacamide (nylon 610), polyhexamethylene dodecamide (nylon 612), polyundecanolactam (nylon 11), polydodecanolactam (nylon 12), etc., copolymers such as caprolactam/lauryllactam copolymer (nylon 6/12), caprolactam/aminoundecanoic acid copolymer (nylon 6/11), caprolactam/ω-aminononanoic acid copolymer (nylon 6/9), caprolactam/hexamethylenediammonium adipate copolymer (nylon 6/66), etc., and aromatic polyamides such as copolymers of adipic acid with metaxylenediamine, or copolymers of hexamethylenediamine with m,p-phthalic acid. Further, polyamide elastomers as block copolymers in which nylon 6, nylon 66, nylon 11, nylon 12 or the like constitutes hard segments and a polyalkylene glycol, a polyether, an aliphatic polyester or the like constitutes soft segments can also be used as a material of the balloon 30. The above-mentioned polyamides may be used either singly or in combination of two or more of them. In particular, the balloon 30 preferably has a smooth surface made from polyamide.

[0030]

The balloon 30 is formed with the coating layer 40

on the outer surface thereof, either directly or through a pre-treatment layer such as a primer layer therebetween, by a method which will be described later. As shown in FIGS. 3 and 4, the coating layer 40 includes a base layer 41 (excipient) which is an additive layer including a water-soluble low-molecular compound disposed in a layer form on the outer surface of the balloon 30, and a plurality of elongate bodies 42 which are crystals of a water-insoluble drug extending while having independent long axes. The elongate bodies 42 include first elongate bodies 42A extending from the inside of the base layer 41 to the outside of the base layer 41, second elongate bodies 42B extending from the outer surface of the balloon 30 to the outside of the base layer 41 by penetrating the base layer 41, and third elongate bodies 42C extending from the outer surface of the base layer 41 to the outside of the surface. In other words, base portions 45 of the elongate bodies 42 may make direct contact with the outer surface of the balloon 30, or may not make direct contact with the outer surface of the balloon 30 because an excipient constituting the base layer 41 is present between the base portions 45 and the outer surface of the balloon 30. The plurality of elongate bodies 42 may be regularly disposed on the outer

surface of the balloon 30. Alternatively, the plurality of elongate bodies 42 may be irregularly disposed on the outer surface of the balloon 30. The elongate bodies 42A, 42B, and 42C differ from one another in the deliverability of the drug to the living body; therefore, by regulating the positions of the base portions 45 of the crystals of the drug, the deliverability of the drug can be controlled arbitrarily. Preparation may be made such that almost only the elongate bodies 42A exist on the surface of the balloon 30. Preparation may be made such that almost only the elongate bodies 42B exist on the surface of the balloon 30. Preparation may be made such that almost the elongate bodies 42C exist on the surface of the balloon 30. Alternatively, preparation may be made such that a combination of a plurality of types of elongate bodies exists on the surface of the balloon 30. Examples of such combination include a combination of the elongate bodies 42A with the elongate bodies 42B, a combination of the elongate bodies 42B with the elongate bodies 42C, and a combination of the elongate bodies 42C with the elongate bodies 42A. Preparation may be made such that all of the elongate bodies 42A, 42B, and 42C exist on the surface of the balloon 30.

[0031]

The inclination angle α of the elongate bodies 42 relative to the outer surface of the balloon 30 or the base layer 41 is not particularly limited, and it is 45 to 135 degrees, preferably 60 to 120 degrees, more preferably 75 to 105 degrees, and still more preferably approximately 90 degrees.

[0032]

The amount of the drug contained in the coating layer 40 is not particularly limited; the amount in density is 0.1 to 10 μg/mm^2, preferably 0.5 to 5 μg/mm^2, more preferably 0.5 to 3.5 μg/mm^2, and still more preferably 1.0 to 3 μg/mm^2. The amount of the crystals in the coating layer 40 is not particularly limited, and it is preferably 5 to 500,000 crystals/(10 μm^2), more preferably 50 to 50,000 crystals/(10 μm^2), and still more preferably 500 to 5,000 crystals/(10 μm^2).

[0033]

The plurality of elongate bodies 42 in which the crystals have mutually independent long axes may be present in a state where they are combined. The plurality of adjacent elongate bodies 42 may be present in contact with one another while forming different angles therebetween. The plurality of elongate bodies 42 may be located with spaces (spaces in which the crystal is not

contained) therebetween on the balloon surface. Both a plurality of elongate bodies 42 in a combined state and a plurality of elongate bodies 42 in a separate and independent state may exist on the surface of the balloon 30. The plurality of elongate bodies 42 may be arranged in a circumferential and brush-like pattern while having different long axis directions. The elongate bodies 42 each exist independently, each have a certain length, and one end (proximal end) of the length portion of each thereof is fixed to the base layer 41 or the balloon 30. The elongate body 42 does not form a composite structure, and is not interlocked, with the adjacent elongate bodies 42. The long axes of the crystals are almost rectilinear. The elongate bodies 42 form predetermined angles relative to the surface which their long axes intersect and with which their base portions 45 make contact.

[0034]

Preferably, the elongate bodies 42 stand independently, without making contact with one another. The base portions 45 of the elongate bodies 42 may be in contact with other base portions 45 on the substrate of the balloon 30. Besides, the base portions 45 of the elongate bodies 42 may be independent, without making contact with other base portions 45, on the substrate of

the balloon 30.

[0035]

The elongate bodies 42 may be hollow or may be solid. Both hollow elongate bodies 42 and solid elongate bodies 42 may exist on the surface of the balloon 30. Where the elongate body 42 is hollow, at least its portion near the distal end thereof is hollow. A section of the elongate body 42 in a plane perpendicular (orthogonal) to the long axis of the elongate body 42 has a void (hollow portion). In the elongate body 42 thus having a void, the section of the elongate body 42 in a plane perpendicular (orthogonal) to the long axis is polygonal in shape. The polygon here is, for example, a triangle, a tetragon, a pentagon, or a hexagon. Therefore, the elongate bodies 42 are each formed as an elongate polyhedron which has a distal end (or a distal surface) and a proximal end (or a proximal surface) and in which a side surface portion between the distal end (or the distal surface) and the proximal end (or the proximal surface) is composed of a plurality of substantially plain surfaces. Alternatively, the elongate bodies 42 may have a needle-like body. This crystalline morphological form (hollow elongate body crystalline morphological form) constitutes the whole part or at least part of a

plane, at the surface with which the base portions 45 make contact.

[0036]

The length in the long axis direction of the elongate bodies 42 having the long axes is preferably 5 to 20 μm, more preferably 9 to 11 μm, and still more preferably around 10 μm. The diameter of the elongate bodies 42 having the long axes is preferably 0.01 to 5 μm, more preferably 0.05 to 4 μm, and still more preferably 0.1 to 3 μm. Examples of the combination of length in the long axis direction and diameter of the elongate bodies 42 having the long axes include a combination of a diameter of 0.01 to 5 μm when the length is 5 to 20 μm, a combination of a diameter of 0.05 to 4 μm when the length is 5 to 20 μm, and a combination of a diameter of 0.1 to 3 μm when the length is 5 to 20 μm. The elongate bodies 42 having the long axes may be rectilinear in the long axis direction thereof, and may also be curved in curved line forms. Both rectilinear elongate bodies 42 and curved elongate bodies 42 may exist on the surface of the balloon 30.

[0037]

The crystalline morphological form including the crystals having the long axes as above-mentioned accounts

for at least 50% by volume, and more preferably at least 70% by volume, based on the whole of the drug crystals on the outer surface of the balloon 30. The elongate bodies 42 as the crystal particles having the long axes are formed not to lie flat but to stand in relation to the outer surface of the balloon 30 or the base layer 41. The base layer 41 may exist in a region where the elongate bodies 42 are present, and may not exist in a region where the elongate bodies 42 are absent.

[0038]

The base layer 41 is present in the state of being distributed into spaces between the plurality of elongate bodies 42 standing together. In regard of the proportions of the materials constituting the coating layer 40, the crystals of the water-insoluble drug preferably occupy a larger volume than that occupied by the base layer 41. The excipient constituting the base layer 41 does not form a matrix. The matrix is a layer which is configured by continuation of a comparatively high-molecular material (polymer or the like), which forms a network-like three-dimensional structure, and in which minute spaces are present. Therefore, the water-insoluble drug constituting the crystals is not adhered to the inside of a matrix material. Moreover, the water-insoluble drug

constituting the crystals is not embedded in a matrix material.

[0039]

The base layer 41 is formed as a dried layer, after being applied in an aqueous solution state to the outer surface of the balloon 30. The base layer 41 is amorphous. The base layer 41 may be crystal particles. The base layer 41 may exist as a mixture of an amorphous state with crystal particles. The base layer 41 in FIG. 4 is in a state including crystal particles and/or particulate amorphous portions. The base layer 41 is formed as a layer including the water-insoluble drug. Alternatively, the base layer 41 may be formed as an independent layer that does not include the water-insoluble drug. The thickness of the base layer 41 is 0.1 to 5 μm, preferably 0.3 to 3 μm, and more preferably 0.5 to 2 μm.

[0040]

The layer including the morphological form of the elongate body crystals is low in toxicity and high in stenosis inhibitory effect at the time of delivery into a body. The water-insoluble drug including the hollow elongate body crystalline morphological form has good property of penetration into tissue because of a small crystal unit size upon transfer of the drug to the tissue,

and, since it has good solubility, it acts effectively and can inhibit stenosis. In addition, it is considered that the drug is less liable to remain in the tissue as large lumps and, therefore, shows low toxicity.

[0041]

Besides, the layer including the elongate body crystalline morphological form has a plurality of substantially uniform elongate bodies 42 having the long axes, and the elongate bodies 42 are substantially uniformly standing together on the surface with which their base portions 45 make contact. Therefore, the size (the length in the long axis direction) of the crystals transferred to the tissue is as small as approximately 10 μm. For this reason, the drug uniformly acts on the lesion affected area, with an enhanced property for penetration into the tissue. Furthermore, since the size of the crystals transferred is small, there is no possibility that an excess amount of the drug might remain at the affected area for an excess of time; for this reason, it is considered that the drug can show a high stenosis inhibitory effect, without showing toxicity.

[0042]

The drug in the coating on the outer surface of the balloon 30 may include an amorphous phase. The crystals

and the amorphous phase may be disposed regularly in the coating layer 40. Alternatively, the crystals and the amorphous phase may be disposed irregularly.

[0043]

The protective sheath 15 is a member for inhibiting the drug from falling off the balloon 30, and is removed before the use of the balloon catheter 10. The protective sheath 15 is formed from a flexible material. Examples of the material which can be used include thermoplastic resins such as polyolefins (e.g., polyethylene, polypropylene, polybutene, ethylene-propylene copolymers, ethylene-vinyl acetate copolymers, ionomers, or mixtures of two or more of them), flexible polyvinyl chloride resin, polyamides, polyamide elastomers, polyesters, polyester elastomers, polyurethane, fluororesins, etc., silicone rubbers, and latex rubbers.

[0044]

Now, a balloon coating apparatus 50 for forming the coating layer 40 on the balloon 30 will be described below. As shown in FIGS. 5 and 6, the balloon coating apparatus 50 includes a rotation mechanism section 60 for rotating the balloon catheter 10, and a support base 70 for supporting the balloon catheter 10. The balloon coating apparatus 50 further includes an application

mechanism section 90 provided with a dispensing tube 94 for applying a coating solution to an outer surface of the balloon 30, a movement mechanism section 80 for moving the dispensing tube 94 relative to the balloon 30, and a control unit 99 for controlling the balloon coating apparatus 50.

[0045]

The rotation mechanism section 60 holds the hub 26 of the balloon catheter 10, and rotates the balloon catheter 10 around an axis of the balloon 30 by a drive source, such as a motor, incorporated therein. The balloon catheter 10 is held, with a core member 61 inserted in the guide wire lumen 24, and the core member 61 prevents the coating solution from flowing into the guide wire lumen 24. In addition, in the balloon catheter 10, for operating the flow of a fluid into the inflation lumen 23, a three-way cock capable of operating the opening/closing of a passage or passages is connected to the proximal opening portion 27 of the hub 26.

[0046]

The support base 70 includes a tubular proximal-side support section 71 that accommodates the catheter main body 20 therein and rotatably supports the catheter main body 20, and a distal-side support section 72 that

rotatably supports the core member 61. Note that the distal-side support section 72 may, if possible, rotatably support a distal portion of the catheter main body 20, instead of the core member 61.

[0047]

The movement mechanism section 80 includes a movable base 81 which can be moved rectilinearly in a direction parallel to the axis of the balloon 30, and a tube fixing section 83 to which the dispensing tube 94 is fixed. The movable base 81 can be moved rectilinearly by a drive source, such as a motor, incorporated therein. The tube fixing section 83 fixes an upper end of the dispensing tube 94 relative to the movable base 81. With the movable base 81 moved, therefore, the dispensing tube 94 is moved rectilinearly in a direction parallel to the axis of the balloon 30. In addition, the application mechanism section 90 is mounted on the movable base 81, and the movable base 81 moves the application mechanism section 90 rectilinearly in both directions (both senses) along the axis.

[0048]

The application mechanism section 90 is a section that applies the coating solution to the outer surface of the balloon 30. The application mechanism section 90

includes a container 92 containing the coating solution, a feed pump 93 that feeds the coating solution at an arbitrary feed rate, and the dispensing tube 94 that applies the coating solution to the balloon 30.

[0049]

The feed pump 93 is, for example, a syringe pump. Controlled by the control unit 99, the feed pump 93 can draw the coating solution from the container 92 through a suction tube 91, and feed the coating solution into the dispensing tube 94 through a supply tube 96 at an arbitrary feed rate. The feed pump 93 is disposed on the movable base 81, and can be moved rectilinearly by the movement of the movable base 81. Note that the feed pump 93 is not limited to the syringe pump so long as it can feed the coating solution, and may be, for example, a tube pump.

[0050]

The dispensing tube 94 is a member which communicates with the supply tube 96 and discharges to the outer surface of the balloon 30 the coating solution supplied from the feed pump 93 through the supply tube 96. The dispensing tube 94 is a flexible circular pipe-shaped member. The dispensing tube 94 has its upper end fixed to the tube fixing section 83, extends downward in the

vertical direction from the tube fixing section 83, and is formed with an opening portion 95 at a discharge end 97 which is its lower end. With the movable base 81 moved, the dispensing tube 94 can be moved rectilinearly in both directions (both senses) along the axial direction of the balloon catheter 10, together with the feed pump 93 disposed on the movable base 81. The dispensing tube 94 can supply the coating solution to the outer surface of the balloon 30, in the state of being bent by being pressed against the balloon 30.

[0051]

Note that the dispensing tube 94 may not necessarily be circular pipe-shaped so long as it can supply the coating solution. In addition, the dispensing tube 94 may not necessarily extend in the vertical direction so long as it can discharge the coating solution through the opening portion 95.

[0052]

The dispensing tube 94 is preferably formed from a flexible material such that contact burden on the balloon 30 is reduced and variations in the contact position attendant on the rotation of the balloon 30 can be absorbed by flexure of the dispensing tube 94. Examples of the applicable material for the dispensing tube 94

include polyolefins such as polyethylene, polypropylene, etc., cyclic polyolefins, polyesters, polyamides, polyurethane, and fluororesins such as PTFE (polytetrafluoroethylene), ETFE (tetrafluoroethylene-ethylene copolymer), PFA (tetrafluoroethylene-perfluoroalkyl vinyl ether copolymer), FEP (tetrafluoroethylene-hexafluoropropylene copolymer), etc., but the material is not particularly limited so long as it is flexible and deformable.

[0053]

The outside diameter of the dispensing tube 94 is not particularly limited, and is, for example, 0.1 to 5.0 mm, preferably 0.15 to 3.0 mm, and more preferably 0.3 to 2.5 mm. The inside diameter of the dispensing tube 94 is not particularly limited, and is, for example, 0.05 to 3.0 mm, preferably 0.1 to 2.0 mm, and more preferably 0.15 to 1.5 mm. The length of the dispensing tube 94 is not particularly limited, and is preferably a length of not more than 5 times the balloon diameter, for example, 1.0 to 50 mm, preferably 3 to 40 mm, and more preferably 5 to 35 mm.

[0054]

The control unit 99 is composed, for example, of a computer, and unifyingly controls the rotation mechanism

section 60, the movement mechanism section 80, and the application mechanism section 90. Therefore, the control unit 99 can unifyingly control the rotating speed of the balloon 30, the moving speed of the dispensing tube 94 in the axial direction of the balloon 30, the drug discharge rate from the dispensing tube 94, and so on.

[0055]

The coating solution supplied from the dispensing tube 94 to the balloon 30 is a solution or suspension containing the constituent materials of the coating layer 40, and contains a water-insoluble drug, an excipient, an organic solvent, and water. After the coating solution is supplied to the outer surface of the balloon 30, the organic solvent and water volatilize, whereby a coating layer 40 including a plurality of elongate bodies 42 which are crystals of the water-insoluble drug extending while having independent long axes is formed on the outer surface of the balloon 30.

[0056]

The viscosity of the coating solution is 0.5 to 1,500 cP, preferably 1.0 to 500 cP, and more preferably 1.5 to 100 cP.

[0057]

The water-insoluble drug means a drug which is

insoluble or difficultly soluble in water; specifically, the water-insoluble drug is a drug of which the solubility in water is less than 5 mg/mL at pH 5 to 8. The solubility may be less than 1 mg/mL, or, further, may be less than 0.1 mg/mL. The water-insoluble drug includes fat-soluble drugs.

[0058]

Some preferred examples of the water-insoluble drug include immunosuppressants, e.g., cyclosporines inclusive of cyclosporine, immunoadjuvants such as rapamycin, carcinostatics such as paclitaxel, antiviral or antibacterial agents, antineoplastic agents, analgesic and anti-inflammatory agents, antibiotics, antiepileptics, anxiolytic agents, antiparalytic agents, antagonists, neuron blocking agents, anticholinergic and cholinergic agents, muscarine antagonists and muscarine agents, antiadrenergic agents, antiarrhythmic agents, antihypertensive agents, hormone preparations, and nutritional supplements.

[0059]

The water-insoluble drug is preferably at least one selected from a group composed of rapamycin, paclitaxel, docetaxel, and everolimus. The rapamycin, paclitaxel, docetaxel, and everolimus herein include their analogs

and/or derivatives so long as the analogs and/or derivatives have equivalent drug activity to the original. For example, paclitaxel and docetaxel are in an analog relation. Rapamycin and everolimus are in a derivative relation. Among these, more preferable is paclitaxel.

[0060]

The excipient constitutes the base layer 41 on the balloon 30. The excipient includes a water-soluble low-molecular compound. The molecular weight of the water-soluble low-molecular compound is 50 to 2,000, preferably 50 to 1,000, more preferably 50 to 500, and still more preferably 50 to 200. The amount of the water-soluble low-molecular compound is preferably 5 to 10,000 parts by weight, more preferably 5 to 200 parts by weight, and still more preferably 8 to 150 parts by weight, per 100 parts by weight of the water-insoluble drug. Examples of the applicable constituent material of the water-soluble low-molecular compound include serine ethyl esters, citric acid esters, polysorbates, water-soluble polymers, sugars, contrast agents, amino acid esters, glycerol esters of short-chain monocarboxylic acids, pharmaceutically acceptable salts and surfactants, and mixtures of two or more of these. The water-soluble low-molecular compound is characterized in that it has a

hydrophilic group and a hydrophobic group and is soluble in water. Preferably, the water-soluble low-molecular compound is non-swellable or difficultly swellable. The excipient is preferably amorphous on the balloon 30. The excipient including the water-soluble low-molecular compound has an effect of uniformly dispersing the water-insoluble drug on the outer surface of the balloon 30. The excipient constituting the base layer 41 is preferably not a hydrogel. Being the low-molecular compound, the base layer 41 is rapidly dissolved without being swelled upon contact with an aqueous solution. Further, since the base layer 41 becomes easily soluble upon inflation of the balloon 30 in a blood vessel, the crystal particles of the water-insoluble drug on the outer surface of the balloon 30 becomes easily releasable; thus, the base layer 41 has an effect of increasing the amount of the drug crystal particles adhered to the blood vessel. In the case where the base layer 41 is a matrix composed of a contrast agent such as Ultravist (registered trademark), the crystal particles are embedded in the matrix, and crystals are not produced to extend from the substrate of the balloon 30 toward the outside of the matrix. On the other hand, the elongate bodies 42 according to the present embodiment extend from

the surface of the substrate of the balloon 30 to the outside of the base layer 41. The length of that portion of the elongate body 42 which is located on the outside of the base layer 41 is greater than the length of that portion of the elongate body 42 which is located inside the base layer 41. The base layer 41 is formed in such a manner as to support the base portions 45 of the elongate bodies 42 which are crystals.

[0061]

The organic solvent is not particularly limited, and examples thereof include tetrahydrofuran, acetone, glycerin, ethanol, methanol, dichloromethane, hexane, and ethyl acetate. Among these, preferred are mixed solvents of some of tetrahydrofuran, ethanol, and acetone.

[0062]

Examples of a mixture of an organic solvent with water include a mixture of tetrahydrofuran and water, a mixture of tetrahydrofuran and ethanol and water, a mixture of tetrahydrofuran and acetone and water, a mixture of acetone and ethanol and water, and a mixture of tetrahydrofuran and acetone and ethanol and water.

[0063]

A method of forming crystals of the water-insoluble drug on the outer surface of the balloon 30 by use of the

above-mentioned balloon coating apparatus 50 will be described below.

[0064]

First, the inflation fluid is supplied into the balloon 30 through the three-way cock connected to the proximal opening portion 27 of the balloon catheter 10. Next, in a state where the balloon 30 is inflated, the three-way cock is operated to seal up the inflation lumen 23, thereby maintaining the balloon 30 in the inflated state. The balloon 30 is inflated with a pressure (e.g., 4 atm) lower than a pressure (e.g., 8 atm) at the time of use in a blood vessel. Note that the coating layer 40 can also be formed on the outer surface of the balloon 30 without inflating the balloon 30, and, in that case, it is unnecessary to supply the inflation fluid into the balloon 30.

[0065]

Subsequently, in a condition where the dispensing tube 94 does not make contact with the outer surface of the balloon 30, the balloon catheter 10 is rotatably disposed on the support base 70, and the hub 26 is interlocked to the rotation mechanism section 60.

[0066]

Next, the position of the movable base 81 is

adjusted to position the dispensing tube 94 in relation to the balloon 30. In this instance, the dispensing tube 94 is positioned to a position on the most distal side in a surface region of the balloon 30 where to form the coating layer 40. As an example, the extending direction (discharge direction) of the dispensing tube 94 is opposite to the rotating direction of the balloon 30. Therefore, at the position where the dispensing tube 94 is put in contact with the balloon 30, the balloon 30 is rotated in the direction opposite to the discharge direction in which the coating solution is discharged from the dispensing tube 94. By this, a physical stimulus can be given to the coating solution, whereby formation of crystal nuclei of the drug crystal can be promoted. Since the extending direction (discharge direction) of the dispensing tube 94 toward the opening portion 95 is opposite to the rotating direction of the balloon 30, the crystals of the water-insoluble drug formed on the outer surface of the balloon 30 are liable to be formed assuming a morphological form in which the crystals include a plurality of elongate bodies 42 having mutually independent long axes. Note that the extending direction of the dispensing tube 94 may not necessarily be opposite to the rotating direction of the balloon 30, and, hence,

may be the same as or perpendicular to the rotating direction.

[0067]

Subsequently, the coating solution is supplied to the dispensing tube 94 while adjusting the feed rate by the feed pump 93, the balloon catheter 10 is rotated by the rotation mechanism section 60, and the movable base 81 is moved so that the dispensing tube 94 is gradually moved proximally along the axial direction of the balloon 30. The coating solution discharged from the opening portion 95 of the dispensing tube 94 is applied to the outer surface of the balloon 30 while drawing a spiral, since the dispensing tube 94 is moved relative to the balloon 30.

[0068]

The moving speed of the dispensing tube 94 is not particularly limited, and is, for example, 0.01 to 2 mm/second, preferably 0.03 to 1.5 mm/second, and more preferably 0.05 to 1.0 mm/second. The discharge rate of the coating solution from the dispensing tube 94 is not particularly limited, and is, for example, 0.01 to 1.5 μL/second, preferably 0.01 to 1.0 μL/second, and more preferably 0.03 to 0.8 μL/second. The rotating speed of the balloon 30 is not particularly limited, and is, for

example, 10 to 300 rpm, preferably 30 to 250 rpm, and more preferably 50 to 200 rpm. The diameter of the balloon 30 when coated with the coating solution is not particularly limited, and is, for example, 1 to 10 mm, and preferably 2 to 7 mm.

[0069]

Thereafter, the organic solvent contained in the coating solution applied to the outer surface of the balloon 30 volatilizes earlier than water. Therefore, the organic solvent volatilizes in a condition where the water-insoluble drug, the water-soluble low-molecular compound and water are left on the outer surface of the balloon 30. When the organic solvent thus volatilizes with water left in the coating, the water-insoluble drug is precipitated inside the water-soluble low-molecular compound that contains water, and crystals gradually grow from crystal nuclei, so that drug crystals of a morphological form in which the crystals include a plurality of elongate bodies 42 having mutually independent long axes are formed on the outer surface of the balloon 30. The base portions 45 of the elongate bodies 42 are located on the outer surface of the balloon 30, on the surface of the base layer 41, or in the inside of the base layer 41 (see FIG. 4). After the organic

solvent has volatilized and the drug crystals are precipitated as the plurality of elongate bodies 42, water evaporates more slowly than the organic solvent, and the base layer 41 including the water-soluble low-molecular compound is formed. The time taken for evaporation of water is appropriately set in accordance with the kind of the drug, the kind of the water-soluble low-molecular compound, the kind of the organic solvent, the ratios of the amounts of the materials, the coating amount of the coating solution, and the like, and is, for example, approximately 1 to 600 seconds.

[0070]

Then, while rotating the balloon 30, the dispensing tube 94 is gradually moved in the axial direction of the balloon 30, whereby the coating layer 40 is gradually formed on the outer surface of the balloon 30 along the axial direction of the balloon 30. After the coating layer 40 including the elongate bodies 42 is formed over the whole range of coating for the balloon 30, operations of the rotation mechanism section 60, the movement mechanism section 80, and the application mechanism section 90 are stopped.

[0071]

Thereafter, the balloon catheter 10 is removed from

the balloon coating apparatus 50, to complete the coating of the balloon 30. Thereafter, the inflation fluid is discharged from the balloon 30, whereby the balloon 30 is deflated and folded. Next, the balloon 30 is covered with the tubular protective sheath 15 (see FIG. 1), to complete the manufacture of the balloon catheter 10. The protective sheath 15 is a member for inhibiting the drug from falling off the balloon 30, and it is removed before use of the balloon catheter 10.

[0072]

A method of using the balloon catheter 10 according to the present embodiment will be described below, taking as an example a case of treating a stenosed part in a blood vessel.

[0073]

First, by a known method such as Seldinger method, the operator percutaneously punctures a blood vessel and places an introducer (not shown) indwelling. Next, the protective sheath 15 is removed from the balloon catheter 10, priming is performed, and thereafter a guide wire 200 (see FIG. 7) is inserted into the guide wire lumen 24. In this state, the guide wire 200 and the balloon catheter 10 are inserted into the blood vessel through the inside of the introducer. Subsequently, the balloon catheter 10

is moved forward, with the guide wire 200 preceding, and the balloon 30 is delivered to a stenosed part 300. Note that a guiding catheter may be used for delivering the balloon catheter 10 to the stenosed part 300.

[0074]

Subsequently, a predetermined quantity of an inflation fluid is injected from the proximal opening portion 27 of the hub 26 by use of an indeflator or syringe or the like, and the inflation fluid is fed through the inflation lumen 23 into the balloon 30. By this, as shown in FIG. 7, the folded balloon 30 is inflated, and the stenosed part 300 is pushed wide open by the balloon 30. In this instance, the coating layer 40 containing the drug crystals provided on the outer surface of the balloon 30 makes contact with the stenosed part 300.

[0075]

When the balloon 30 is inflated and the coating layer 40 is thereby pressed against the living body tissue, the base layer 41 composed of the water-soluble low-molecular compound contained in the coating layer 40 is dissolved gradually or rapidly, and, while the dissolution proceeds, the drug is delivered to the living body. Since the first elongate bodies 42A, the second

elongate bodies 42B, and the third elongate bodies 42C which are crystals of the drug differ in the position of their base portions 45 relative to the base layer 41, they differ in tissue deliverability as the base layer 41 is dissolved gradually or rapidly. In addition, the inflation of the balloon 30 causes cracking of the base layer 41, which facilitates dissolution of the base layer 41, thereby enabling the elongate bodies 42 as the drug crystals to be easily released from the base layer 41. For this reason, where the first elongate bodies 42A, the second elongate bodies 42B and the third elongate bodies 42C differing in solubility are provided by adjusting the positions of the base portions 45 of the elongate bodies 42, the deliverability of the drug can be arbitrarily set.

[0076]

Thereafter, the inflation fluid is discharged by drawing it via the proximal opening portion 27 of the hub 26, whereby the balloon 30 is deflated and put into a folded state. Thereafter, the guide wire 200 and the balloon catheter 10 are withdrawn out of the blood vessel through the introducer, to complete the procedure.

[0077]

As has been described above, the balloon catheter 10 according to this embodiment is a catheter provided on

the outer surface of the balloon 30 with the plurality of elongate bodies 42 which are the crystals of the water-insoluble drug extending while having independent long axes, in which the balloon catheter 10 has the base layer 41 including the water-soluble low-molecular compound disposed in a layer form on the outer surface of the balloon 30, and at least part of the elongate bodies 42 is located in the inside of the base layer 41. In the balloon catheter 10 configured in this way, inflation of the balloon 30 causes cracking of the base layer 41, which facilitates dissolution of the base layer 41, thereby enabling the elongate bodies 42 as the drug crystals to be easily released from the base layer 41, so that the drug can be effectively delivered to the living body tissue. Furthermore, while the base layer 41 including the water-soluble low-molecular compound is dissolved gradually or rapidly, the elongate bodies 42 inside the base layer 41 make contact with the living body tissue, and the drug is delivered to the living body tissue; therefore, the deliverability of the drug can be controlled by the material and thickness of the base layer 41 and the positions of the base portions 45 of the elongate bodies 42 relative to the base layer 41.

[0078]

In addition, the elongate bodies 42 include the first elongate bodies 42A that have their base portions 45 separate from the outer surface of the balloon 30 and located in the inside of the base layer 41. This ensures that by regulating the positions of the base portions 45 of the first elongate bodies 42A in the inside of the base layer 41, the deliverability of the drug to the living body tissue can be controlled through utilization of the time taken for dissolution of the base layer 41 including the water-soluble low-molecular compound.

[0079]

Besides, the elongate bodies 42 include the second elongate bodies 42B extending from the outer surface of the balloon 30. This ensures that the second elongate bodies 42B extending from the outer surface of the balloon 30 are slowly eluted from the base layer 41 as the base layer 41 including the water-soluble low-molecular compound is dissolved, whereby the drug can be slowly delivered to the living body tissue.

[0080]

Further, the elongate bodies 42 include the third elongate bodies 42C extending from the outer surface of the base layer 41 toward the outside of the surface. This ensures that the third elongate bodies 42C as a whole

immediately make contact with the living body tissue, whereby the drug can be instantaneously delivered to the living body tissue.

[0081]

In addition, the water-insoluble drug may be rapamycin, paclitaxel, docetaxel, or everolimus. In this case, restenosis of a stenosed part in a blood vessel can be favorably inhibited by the elongate bodies 42.

[0082]

Besides, the method of manufacturing the balloon catheter 10 according to the present embodiment is a method of manufacturing the balloon catheter 10 provided on the outer surface of the balloon 30 with the plurality of elongate bodies 42 which are crystals of the water-insoluble drug extending while having independent long axes. The manufacturing method includes: the step of supplying a coating solution containing the drug, a water-soluble low-molecular compound, an organic solvent and water from the dispensing tube 94 for supplying the coating solution, while keeping the dispensing tube 94 in contact with the outer surface of the balloon 30, and giving a physical stimulus to the coating solution to cause formation of crystal nuclei of the water-insoluble drug; the step of volatilizing the organic solvent while

leaving water to cause growth of the elongate bodies 42 on the basis of the crystal nuclei; and the step of evaporating water to form the base layer 41 including the water-soluble low-molecular compound. According to the method of manufacturing the balloon catheter 10 configured as above, the organic solvent volatilizes from the layer of the water-soluble low-molecular compound containing water, whereby the drug crystals grow from the crystal nuclei, and the elongate bodies 42 of which at least part is located in the inside of the base layer 41 can be formed.

[0083]

In addition, the present invention also includes the treatment method (therapeutic method) for delivering a drug to a lesion affected area in a body lumen by use of the aforementioned balloon catheter 10. The treatment method includes: the step of inserting the balloon 30 into the body lumen and delivering the balloon 30 to the lesion affected area; the step of inflating the balloon 30 to press the balloon 30 against the living body tissue and to bring the elongate bodies 42 into contact with the living body tissue while dissolving the base layer 41 including the water-soluble low-molecular compound; and the step of deflating the balloon 30 and withdrawing the

balloon 30 out of the body lumen. According to the treatment method configured in this manner, the inflation of the balloon 30 causes cracking of the base layer 41, which facilitates dissolution of the base layer 41, thereby enabling the elongate bodies 42 as the drug crystals to be easily released from the base layer 41, so that the drug can be effectively delivered to the living body tissue. Furthermore, while the base layer 41 including the water-soluble low-molecular compound is dissolved gradually or rapidly, the elongate bodies 42 in the inside of the base layer 41 make contact with the living body tissue, and the drug is delivered to the living body tissue; therefore, the deliverability of the drug can be controlled by the material and thickness of the base layer 41 and the positions of the base portions 45 of the elongate bodies 42 in relation to the base layer 41.

[0084]

Note that the present invention is not limited to the aforementioned embodiment, and various modifications can be made by those skilled in the art within the technical thought of the present invention. For instance, while the balloon catheter 10 according to the above embodiment is of the rapid exchange type, the balloon

catheter may be of the over-the-wire type.

[0085]

As has been described above, the base layer 41 exists as an amorphous phase, crystal particles, or a mixture thereof. While the base layer 41 shown in FIG. 4 is in the state of crystal particles and/or particulate amorphous portions, the base layer 41 may be in a film-formed amorphous state as depicted in FIG. 8. As shown in FIG. 9, the first elongate bodies 42A extend from the inside of the base layer 41 to the outside of the base layer 41. As depicted in FIG. 10, the second elongate bodies 42B extend from the outer surface of the balloon 30 to the outside of the base layer 41 by penetrating the base layer 41. As shown in FIG. 11, the third elongate bodies 42C extend from the outer surface of the base layer 41 toward the outside of the surface.

[0086]

In addition, as shown in FIG. 12, the base layer 41 as an additive layer may have a rugged pattern (recesses and projections). The height of the rugged pattern is 0.1 to 5 μm. The elongate bodies 42 as crystals project from projected portions 43 constituting the rugged pattern of the base layer 41. In other words, the projected portions 43 of the base layer 41 support the elongate bodies 42 as

the crystals. Note that the base layer 41 may have projected portions 43 from which the elongate bodies 42 do not project. The elongate bodies 42 as the crystals may project from recessed portions 44 constituting the rugged pattern of the base layer 41. The base layer 41 may include both the projected portions 43 that support the elongate bodies 42 and the projected portions 43 that do not support the elongate bodies 42. The base layer 41 may include both the recessed portions 44 that support the elongate bodies 42 and the recessed portions 44 that do not support the elongate bodies 42. Besides, the base layer 41 may include both the projected portions 43 that support the elongate bodies 42 and the recessed portions 44 that support the elongate bodies 42. The elongate bodies 42 may project obliquely from the base layer 41 such as to be inclined relative to the outer surface of the balloon 30. The base layer 41 may have both the elongate bodies 42 that are substantially perpendicular to the outer surface of the balloon 30 and the elongate bodies 42 that are inclined relative to the outer surface of the balloon 30. The base portions 45 of the elongate bodies 42 may be in direct contact with the outer surface of the balloon 30. Alternatively, the base portions 45 of the elongate bodies 42 may not be in contact with the

outer surface of the balloon 30 but be located in the inside of the base layer 41. The base layer 41 may have both the elongate bodies 42 that are in direct contact with the outer surface of the balloon 30 and the elongate bodies 42 that are not in contact with the outer surface of the balloon 30.

[0087]

Besides, as illustrated in FIG. 13, the crystals may include fixed-side elongate bodies 46 (balloon substrate contacting crystal particles) that originally project from the base layer 41, and separate-side elongate bodies 47 (balloon substrate non-contacting crystal particles) that are separate from the fixed-side elongate bodies 46. The amount of the fixed-side elongate bodies 46 is greater than the amount of the separate-side elongate bodies 47. The separate-side elongate bodies 47 are formed by being separated from the fixed-side elongate bodies 46 upon breaking of the elongate crystals when the balloon 30 is folded in the manner of being wrapped around the inner tube 22. Of the separate-side elongate body 47, at least part of a distal portion, a proximal portion, and a portion between the distal portion and the proximal portion is in contact with the base layer 41. Part of the separate-side elongate body 47

may be embedded in the base layer 41. The presence of the base layer 41 ensures that the fixed-side elongate bodies 46 and the separate-side elongate bodies 47 are prevented from easily falling off the balloon 30 during transportation, by interactions thereof with the base layer 41. The fixed-side elongate bodies 46 and the separate-side elongate bodies 47 are easily released through dissolution of the base layer 41 when the balloon 30 is inflated and the base layer 41 comes into contact with water (blood). The fixed-side elongate bodies 46 and the separate-side elongate bodies 47, which differ in form, are different in releasing property, which is preferable from the viewpoint of action on the living body. The fixed-side elongate bodies 46 may be formed through breaking of crystal, or may be formed without breaking of crystal. The base layer 41 may have both the fixed-side elongate bodies 46 that are formed through breaking of crystal and the fixed-side elongate bodies 46 that are formed without breaking of crystal. The fixed-side elongate bodies 46 may be standing from the base layer 41, or may be lying along the base layer 41. The base layer 41 may have both the fixed-side elongate bodies 46 that are standing from the base layer 41 and the fixed-side elongate bodies 46 that are lying along

the base layer 41.

[0088]

The length of the crystals fixed to the base layer 41, before breaking of crystal, is, for example, 5 to 20 μm, and the length after breaking of crystal is, for example, 3 to 20 μm. The length of the fixed-side elongate bodies 46 formed through breaking of crystal is, for example, 5 to 20 μm. The length of the separate-side elongate bodies 47 is, for example, 3 to 10 μm.

[0089]

Note that the present application is based on Japanese Patent Application No. 2016-058030 filed on March 23, 2016, the contents of which are incorporated herein by reference in entirety thereof.

Description of Reference Symbols

[0090]

10 Balloon catheter

20 Catheter main body

21 Outer tube

22 Inner tube

30 Balloon

40 Coating layer

41 Base layer

42 Elongate body

42A First elongate body

42B Second elongate body

42C Third elongate body

46 Fixed-side elongate body (balloon substrate contacting crystal particle)

47 Separate-side elongate body (balloon substrate contacting crystal particle)

50 Balloon coating apparatus

94 Dispensing tube

Claims

1. A balloon catheter provided on an outer surface of a balloon with a plurality of elongate bodies which are crystals of a water-insoluble drug extending while having independent long axes,

wherein the balloon catheter has a base layer including a water-soluble low-molecular compound disposed in a layer form on the outer surface of the balloon, the water-soluble low molecular compound having a molecular weight of 50 to 2,000, being dissolved in water in an amount of not less than 5 mg/mL, and being dissolved in water without swelling,

at least part of the elongate bodies is located inside of the base layer, and

the elongate bodies include a first elongate body whose proximal end portion is separate from the outer surface of the balloon, the outer surface being smooth and non-porous, and is located inside of the base layer.

2. The balloon catheter according to claim 1, wherein the elongate bodies include a second elongate body extending from the outer surface of the balloon and/or a third elongate body extending from an outer surface of the base layer toward an outside of the

surface.

3. A balloon catheter provided on an outer surface of a balloon with a plurality of elongate bodies which are crystals of a water-insoluble drug extending while having independent long axes,

wherein the balloon catheter has a base layer including a water-soluble low-molecular compound disposed in a layer form on the outer surface of the balloon, the water-soluble low molecular compound having a molecular weight of 50 to 2,000, being soluble in water in an amount of not less than 5 mg/mL, and being soluble in water without swelling,

at least part of the elongate bodies is located inside of the base layer, and

the elongate bodies include a second elongate body extending from the outer surface of the balloon, the outer surface being smooth and non-porous.

4. The balloon catheter according to claim 3, wherein the elongate bodies include a first elongate body whose proximal end portion is separate from the outer surface of the balloon and is located inside of the base layer and/or a third elongate body extending from an outer surface of the base layer toward an outside of the

surface.

5. The balloon catheter according to any one of claims 1 to 4, wherein the water-soluble low molecular compound is at least one of serine ethyl ester, citric acid esters, polysorbates, sugars, amino acid esters, or glycerol esters of short-chain monocarboxylic acids.

6. The balloon catheter according to any one of claims 1 to 5, wherein the balloon is formed by using a polyamide.

7. The balloon catheter according to any one of claims 1 to 6, wherein the water-soluble low-molecular compound included in the base layer is a crystal, an amorphous phase or a mixture of them.

8. The balloon catheter according to any one of claims 1 to 7, wherein the water-insoluble drug is rapamycin, paclitaxel, docetaxel, or everolimus.

9. The balloon catheter according to any one of claims 1 to 8, wherein the base layer has a rugged surface.

10. The balloon catheter according to any one of claims 1 to 9, wherein the outer surface of the balloon has a portion which is not covered with the base layer but is exposed to an outside, in at least part of a region where the elongate bodies are not provided.

11. The balloon catheter according to any one of claims 1 to 10, wherein adjacent ones of the elongate bodies are structurally separate from each other.

12. The balloon catheter according to any one of claims 1 to 10, wherein adjacent ones of part of the plurality of elongate bodies are in contact with each other.

13. A method of manufacturing a balloon catheter provided on an outer surface of a balloon with a plurality of elongate bodies which are crystals of a water-insoluble drug extending while having independent long axes, the method comprising:

a step of supplying a coating solution containing the drug, a water-soluble low-molecular compound which has a molecular weight of 50 to 2,000, is soluble in water in an amount of not less than 5 mg/mL and is soluble in water without swelling, an organic solvent, and water from a dispensing tube for supplying the coating solution, while keeping the dispensing tube in contact with the outer surface of the balloon which outer surface is smooth and non-porous, and giving a physical stimulus to the coating solution to cause formation of crystal nuclei of the water-insoluble drug;

a step of volatilizing the organic solvent while

leaving water to cause growth of the elongate bodies based on the crystal nuclei; and

a step of evaporating water to form a base layer including the water-soluble low-molecular compound.

14. The method of manufacturing a balloon catheter according to claim 13, wherein the water-insoluble low-molecular compound is at least one of serine ethyl ester, citric acid esters, polysorbates, sugars, amino acid esters, and glycerol esters of short-chain monocarboxylic acids.

15. The method of manufacturing a balloon catheter according to claim 13 or 15, wherein the balloon is formed by using a polyamide.

16. The method of manufacturing a balloon catheter according to any one of claims 13 to 15, wherein the water-soluble low-molecular compound included in the base layer is a crystal, an amorphous phase or a mixture of them.

17. The method of manufacturing a balloon catheter according to any one of claims 13 to 16, wherein the elongate bodies include at least one of a first elongate body whose proximal end portion is separate from the outer surface of the balloon, the outer surface being smooth and non-porous, and is located inside of the base

layer, a second elongate body extending from the outer surface of the balloon, or a third elongate body extending from an outer surface of the base layer toward an outside of the surface.

Abstract

BALLOON CATHETER AND MANUFACTURING METHOD THEREOF, AND TREATMENT METHOD

There are provided a balloon catheter by which a drug can be effectively delivered to living body tissue and the deliverability can be controlled and a manufacturing method thereof, and a treatment method. Disclosed is a balloon catheter (10) provided on an outer surface of a balloon (30) with a plurality of elongate bodies (42) which are crystals of a water-insoluble drug extending while having independent long axes. The balloon catheter (10) has a base layer (41) including a water-soluble low-molecular compound disposed in a layer form on the outer surface of the balloon (30), and at least part of the elongate bodies (42) is located in the inside of the base layer (41).

FIG. 4

FIG. 1

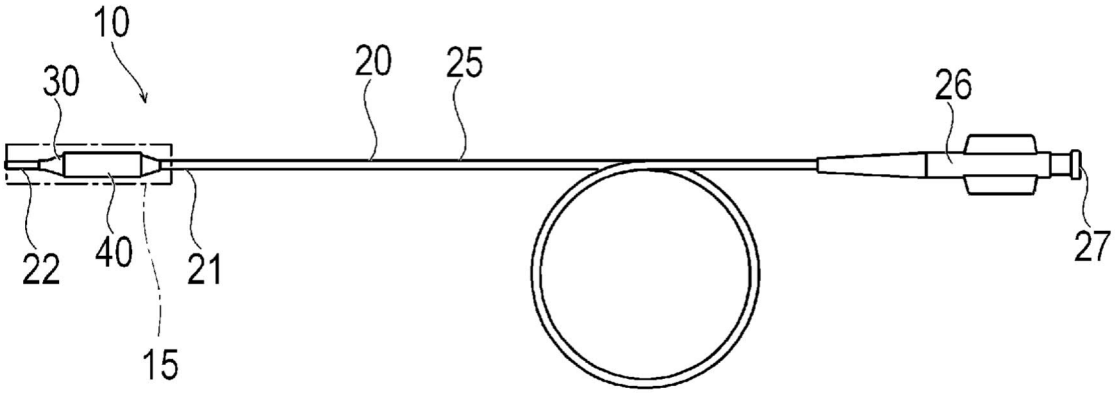


FIG. 2

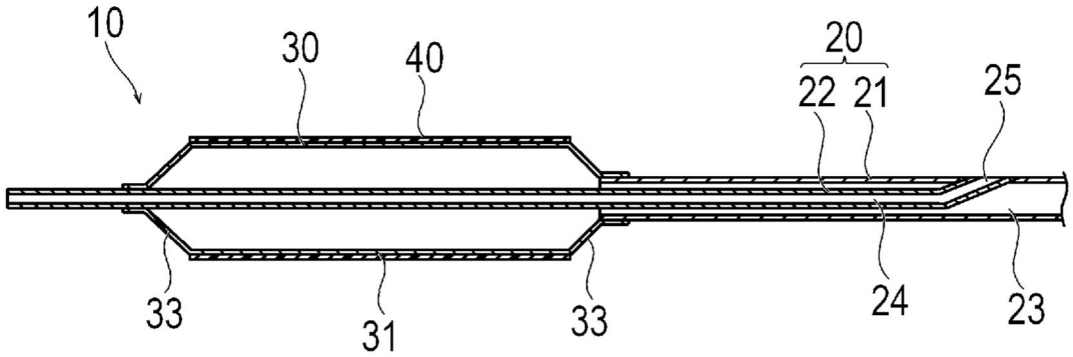


FIG. 3

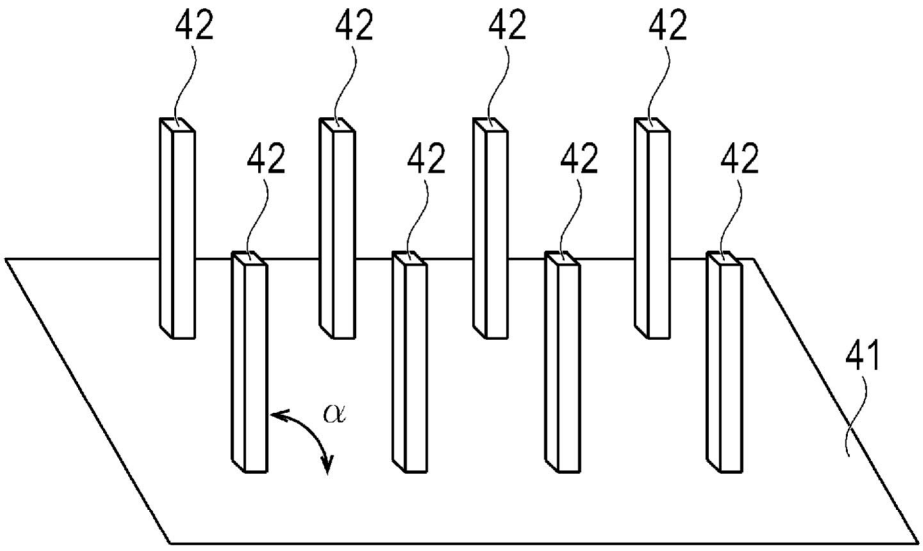


FIG. 4

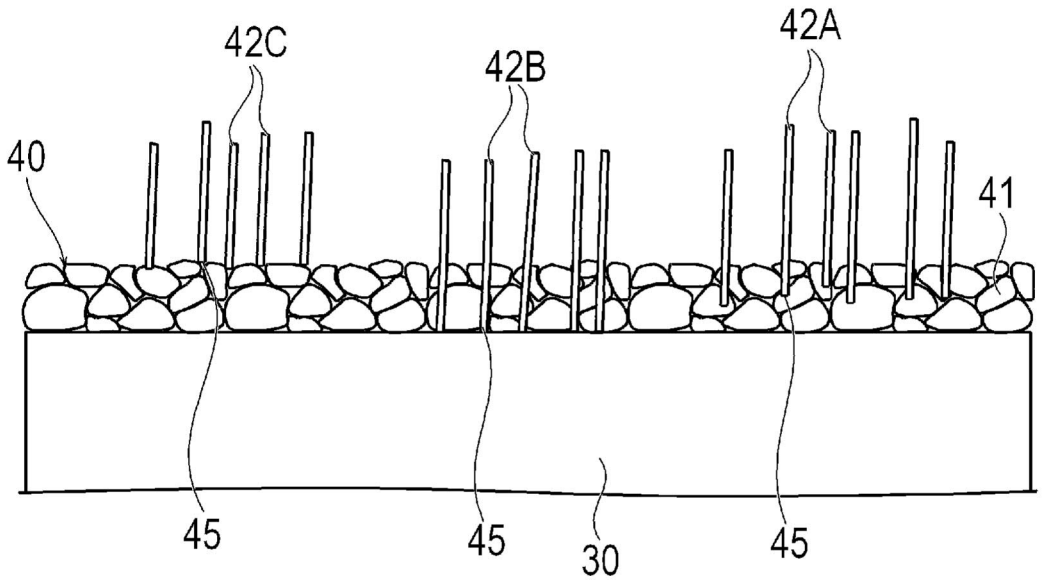


FIG. 5

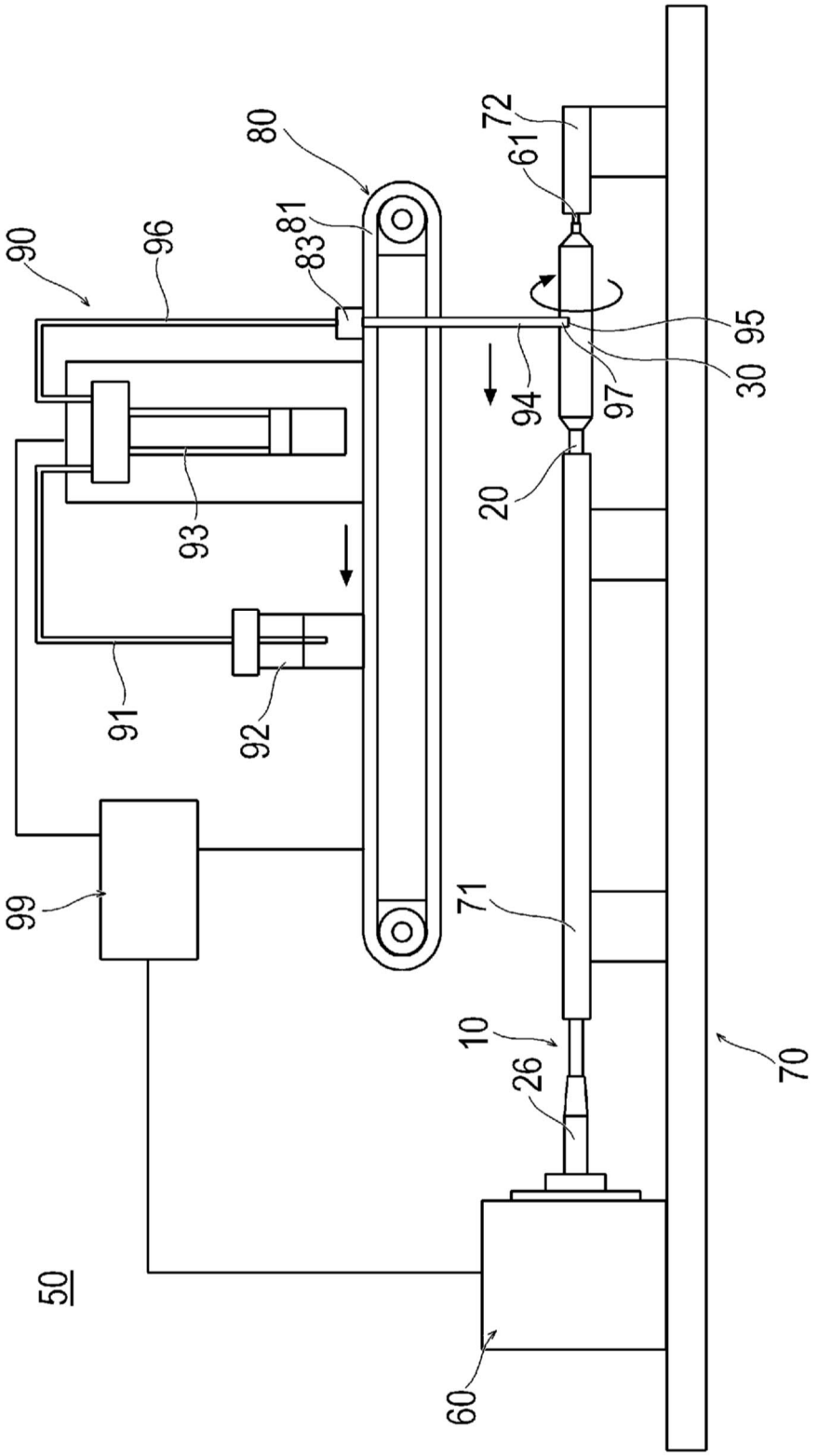


FIG. 6

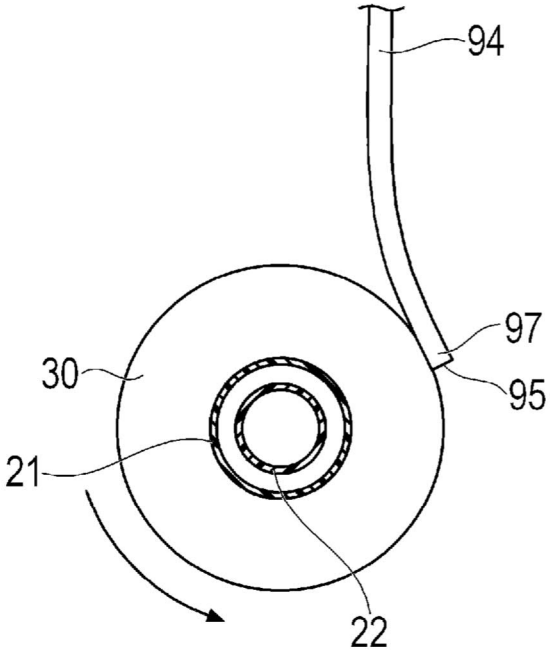


FIG. 7

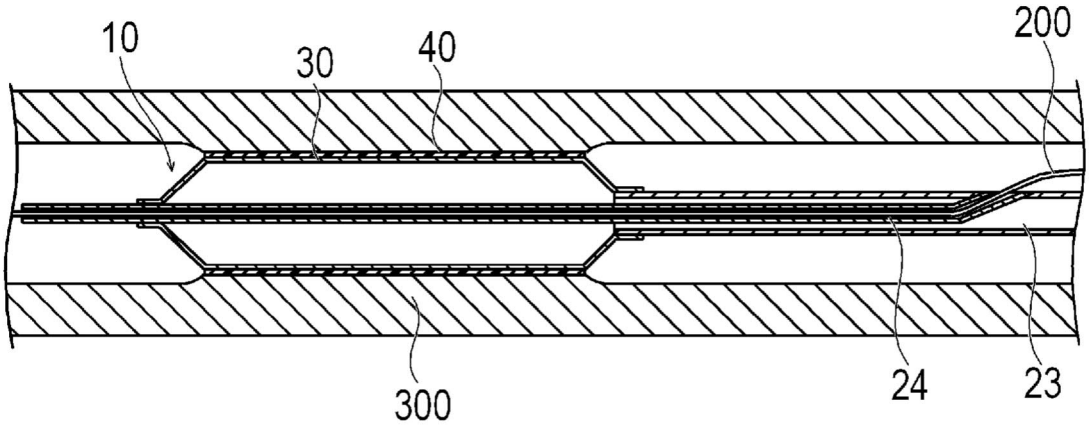


FIG. 8

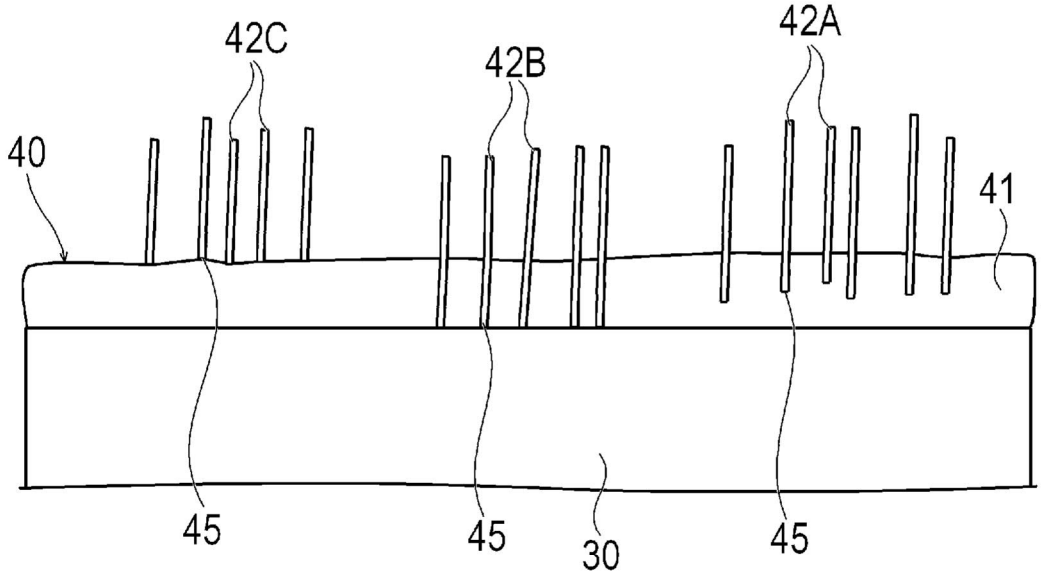


FIG. 9

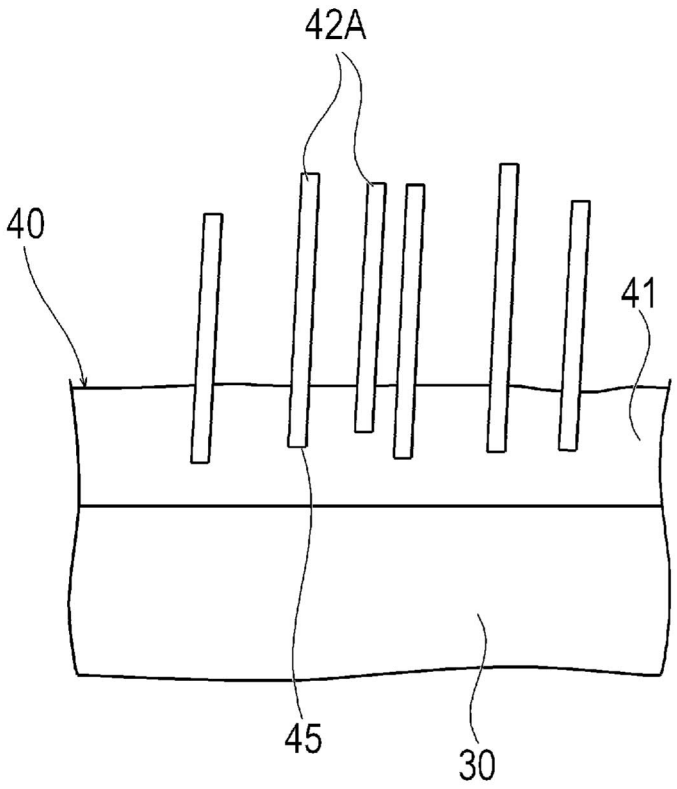


FIG. 10

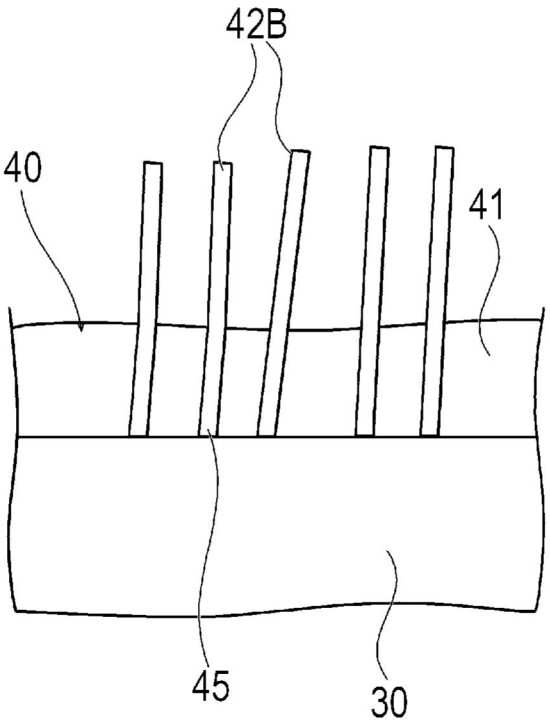


FIG. 11

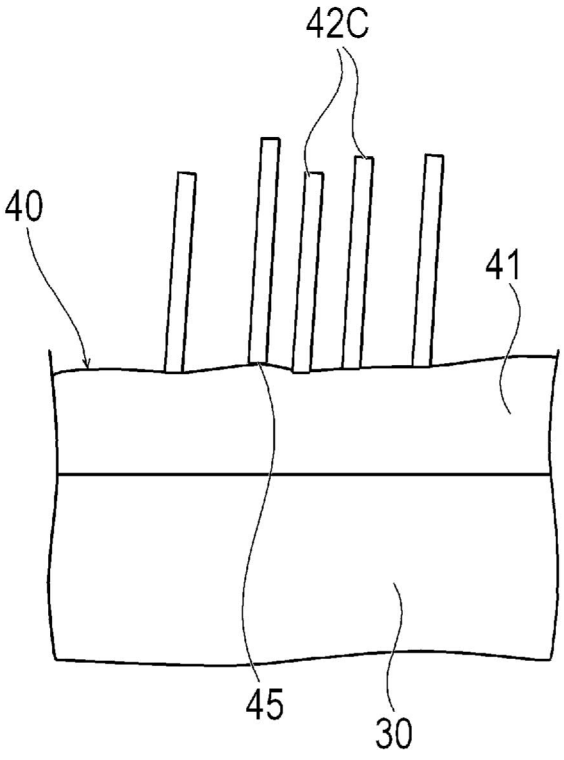


FIG. 12

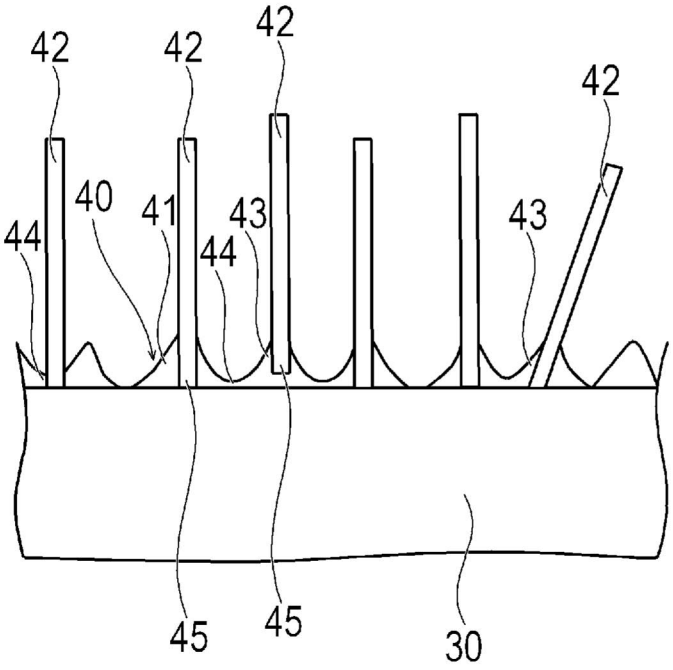


FIG. 13

