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<p>(21) International Application Number: PCT/US94/04402 (22) International Filing Date: 21 April 1994 (21.04.94) (30) Priority Data: 08/052,046 22 April 1993 (22.04.93) US (71)(72) Applicant and Inventor: RAMMLER, David, H. [US/US]; Labintelligence, 191 Jefferson Drive, Menlo Park, CA 94025 (US). (74) Agents: ROWLAND, Bertram, I. et al.; Flehr, Hohbach, Test, Albritton & Herbert, Suite 3400, 4 Embarcadero Center, San Francisco, CA 94111-4187 (US).</p>		<p>(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i></p>
<p>(54) Title: SAMPLING BALLOON CATHETER</p>		
<p>(57) Abstract</p> <p>Novel catheter balloons (10) are provided, having shaped surfaces (14, 16), which allow for delivery of drugs to a site in the vessel, provide for agents which allow for determination of blood flow and definition of the vessel walls, and sampling of the materials at the site for diagnosis. In addition, the balloons may be used for angioplasty.</p>		

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SAMPLING BALLOON CATHETERINTRODUCTIONTechnical Field

The field of this invention concerns catheters for use in
5 angioplasty.

Background

Atherosclerosis is a major disease which affects millions of
people. Despite the numerous efforts to reduce cholesterol
intake and improve the food types which are ingested, large
10 proportions of the population still maintain a heavy meat,
heavy fat diet. While diet is believed to be a significant
cause of the build-up of plaques in the vascular system,
nevertheless the mechanism by which plaques build up in
blood vessels is not well understood. The presence of
15 platelets, foamy cells, lipoproteins, as well as other
components, testifies to the complexity of the plaque
formation process.

One of the techniques which is used to diminish the
likelihood of clots at a vessel blockage is angioplasty.
20 Angioplasty involves passing a balloon into the obstructed
vessel and expanding the balloon at the obstruction. This
results in an expansion of the vessel at the site of the
balloon expansion, cracking of the plaque and compaction of
the plaque, so as to open the vessel in this region.

A number of problems are encountered using angioplasty, from inflammation of the expanded site to restenosis. In an unfortunately large proportion of the cases in which angioplasty is used, there is a closing of the vessel at the
5 site of expansion. There is some belief that the balloon expansion activates cells in the region and results in an inflammatory response, which runs counter to the process which is being performed. Furthermore, it is believed that the nature of the lesion may vary widely, so that different
10 treatments may be applicable for a particular lesion as compared to a different lesion. However, there is no way to know what the nature of the components are in the plaque, without surgery and removal of a portion of the vessel or a biopsy at the site of the lesion.

15 Other orifices or vessels require treatments, such as the urethra, anus, etc., where there is an interest in introducing a drug at a predetermined site, sampling physiological tissue at the site, or the like.

There is, therefore, substantial interest in providing
20 techniques which will allow for therapeutic treatment at the site of the plaque during angioplasty and for determining the components of the plaque, particularly where such information may allow for improved therapies for sclerotic lesions as well as treatment of other pathological
25 conditions in other orifices or vessels, where the site can be reached by a catheter.

SUMMARY OF THE INVENTION

Novel balloons for use with catheters are provided, where the balloons are shaped to provide for delivery of
30 medicaments or other agents to a site of a lesion in a vessel and for sampling the plaque or other physiological material present at the site of the balloon expansion. The balloons are shaped to have ridges, where various agents may be included in the troughs between ridges as well as in the

ridges, so that upon expansion of the balloon, the troughs expand and release and/or press the agents against the surface of the vessel. The surface of the balloon at one or more sites may provide for sampling of the lesion components, which will be retained by the balloon upon deflation and be carried with the balloon when removed from the vessel. In addition, the agent may include microbubble forming materials, so that the flow at the site of the balloon treatment can be determined using ultrasonic sound.

10

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective view of a deflated balloon according to this invention;

FIG. 2 is a cross-sectional view of the balloon of FIG. 1 when deflated;

15 FIG. 3 is a cross-sectional view of an inflated balloon according to FIG. 1;

FIG. 4 is a perspective view of an alternative embodiment of a balloon according to this invention;

20 FIG. 5 is a cross-sectional view of the embodiment of FIG. 4;

FIGS. 6, 7 and 8 are respectively cross-sectional views of the deflated and inflated balloon, and a perspective view, of an alternate embodiment of this invention;

25 FIGS. 9, 10 and 11 are respectively cross-sectional views of the deflated and inflated balloon and a perspective view of an alternate embodiment of this invention; and

FIGS. 12 and 13 are respectively deflated and inflated views of the cross-section of an alternative embodiment of this invention.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

In accordance with the subject invention, balloons are provided in conjunction with balloon dilatation catheters for reaching a lesion in a physiological vessel, particularly of the cardiovascular system. The balloons are shaped so as to be able to carry agents with the balloons, which agents may be released upon inflation of the balloon. Furthermore, a portion of the surface of the balloon can serve to sample the surfaces with which the balloon interacts upon inflation, so as to retain plaque samples with the balloon upon deflation and retraction of the balloon from the vessels of the host. The balloons can be used with any of the conventional angioplasty devices or other devices, used in urology, proctology, etc. which allow for the control of movement of the balloon into the vessels of the host, inflation and deflation of the balloon and retrieval of the balloon from the host.

For the most part, the subject invention finds particular use in angioplasty. The angioplasty apparatus consists of a guiding catheter which is adapted to be inserted into the vessel of a patient. Also included is a guidewire which is adapted to the associated width of the catheter, guiding the catheter under the control of the operator so as to allow the movement of the end of the catheter carrying the balloon to the site for treatment. Finally, the catheter comprises a hollow tube which allows for inflation and deflation of the balloon. Various devices can be used, as described in U.S. Patent Nos. 5,040,548, 4,748,982 and 4,619,274. The particular device may vary depending upon what other functions are desired from the operation.

The characteristics of the balloon may vary. The thickness of the wall from balloon to balloon and within a single balloon may vary widely depending upon the particular shape of the balloon, and what portion of the balloon is to expand and the extent of expansion as compared to other portions,

as well as the function the particular portion of the balloon is to serve. Thus, in many instances, the thickness of the wall will be varied, where thicker walls will be present, where little if any movement of the wall is desired, and thinner walls will be employed where the wall is to move and to expand in accordance with its function. For the most part, the balloons will be tubular having a much larger length than diameter and may be symmetrical or asymmetrical in its cross-section, usually symmetrical.

10 Various materials which are conventionally used for balloons may be employed in accordance with the subject invention, where the materials allow for the desired forming of the balloon. The balloon may be of any convenient polyolefin of varying densities, such as polyethylene, Teflon, silicon, acrylates and mixtures thereof. The uninflated diameter may range from about 0.5 to 1.5 millimeters, and may be inflatable to about 1.5 to 4 millimeters. The balloon will generally be at least about 0.5 centimeters in length and may be 2 centimeters or more in length, depending upon its purpose and an outside diameter of about 0.1 to 0.15 inch. The balloon will be formed so as to provide for the desired conformation upon inflation. The balloon will normally not be inflated to a smooth cylinder, but rather have an uneven surface, involving troughs and peaks, usually extending substantially the full length of the balloon.

In order to achieve the desired shape, the thickness of the balloon may vary, so that the regions related to the trough may be thicker than the regions related to the peaks and, therefore, be substantially less extensible or flexible than the regions which are to be expanded to provide the peaks or ridges or vice versa. In addition, regions of the balloon surface may be roughened, provided with narrow low spines, ridges, protuberances or wrinkles, or roughened areas, where the elevation of the projections may be as small as 0.01 millimeter and as large as about 0.05 millimeter. These elevations may be perpendicular to or parallel to the

long axis of the balloon or have no particular common orientation to the long axis of the balloon.

The balloons may be inflated with any convenient fluid, particularly liquids, which can be delivered and recovered through conventional catheter devices which feed the fluid into the balloon. Upon inflation, the balloon can provide for individual projections or knobs, where the knobs may protrude from the substantially cylindrical surface of the balloon in a symmetrical or asymmetrical or relatively random manner. Alternatively, one may have ridges extending from the cylindrical portion of the balloon, which may also be disposed symmetrically or asymmetrically.

The deflated balloon may be relatively smooth and uniform about its external surface or may already form to a substantially lesser degree the various protuberances which will occur upon inflation. By having the protuberances existing to a minor degree for inflation, the balloon will be easier to inflate and one may be assured that the areas which are to extend outwardly from the surface are more likely to be inflated.

The subject balloons may not only be used for therapeutic purposes, such as angioplasty, but they also may be used to deliver drugs. A portion on substantially all of the surface of the balloon may be coated, in whole or in part, with various therapeutic agents, which may adhere to the surface of the balloon as a result of adsorption, adhesion, use of an adhesive agent, use of protective polymers which will erode with time, so as to release the drug, in accordance with the time frame of the association of the balloon with the site to be treated, and the like. A concavity may be provided at the front of the balloon as a container for a therapeutic agent. A wide variety of drugs can be used, such as anti-inflammatory steroids, anticlotting agents, cell proliferation inhibitors, etc.

In addition, various physiologically acceptable adhesives may be employed in conjunction with the drugs, where the adhesives will be dissolved or eroded upon inflation of the balloon. Illustrative adhesives include PVC, acrylates, 5 complex carbohydrates, etc. By introducing drugs onto the surface of the balloon, particularly in troughs, when the balloon is deflated, the balloon may be wrinkled, where the drugs will be protected in the wrinkle from release. Upon inflation, and expansion of the protuberances, the drug will 10 then be released and pressed into the vessel wall, as well as exposed to the flow of blood, or other physiological fluid, which will move the drug from the surface into contact with the vessel wall.

Also, the roughened surface and protuberance will be 15 involved with pressing and rubbing against the vessel wall. Where plaques are present, the plaque material which is soft, will be captured on the surface of the balloon by the indentations in the balloon, so that upon deflation, the particulates of plaque or other loose material associated 20 with the vessel wall will be captured in the balloon. In this manner, when the balloon is retracted, the balloon will carry with it samples of the material it has encountered upon inflation. These materials may be analyzed to determine the nature of the plaque, which may then be 25 related to particular indications or diseased states. Thus, the balloon may not only serve to provide therapy, but may also serve to analyze the nature of the injury and compositions associated with the injury.

The channels created upon inflation will allow for movement 30 of blood through the vessel to varying degrees depending on the design of the balloon. If blood or other fluid stoppage is desired, one can form relatively narrow channels or have a fairly smooth outer surface. If flow in the vessel is desired, their channels can be formed which allow for fluid 35 flow while compacting the vessel wall with the protuberances.

Since the balloon will have an uneven surface, plaque present on the vessel wall will not be compacted evenly. One may vary the design, to where the protuberance will have a fairly flat surface at the top and each protuberance will
5 extend a distance from its central axis, so that the protuberances may provide a substantially continuous cylindrical surface pressing against the plaque. In this way, one can only achieve the purposes described above, as well as provide for angioplasty, so as to clear the vessel
10 from blockage.

Instead of or in addition to drugs, the balloon may also serve to provide for various agents which will allow for determining characteristics of interest associated with the vessel. For example, agents may be provided which may be
15 released from the balloon upon inflation which will form microbubbles. Various microbubble agents have been taught in the literature, such as the use of bovine serum albumin, gelatin coated microbubbles, fused saccharide encapsulating pressurized microbubbles, microparticles which trap bubbles,
20 microbubbles within human albumin shells and the like. These particles may be applied to the surface of the balloon, which will be released upon inflation of the balloon, providing microbubbles in the vessel. See, for example, U.S. Patent Nos. 4,466,442 and 4,718,433. The
25 microbubbles may then be used with ultrasonic analysis to determine the rate of flow of blood in the vessel, as well as to provide contrast to detect the walls of the vessel surrounding the microbubbles. Instead of microbubbles, one may provide for fluorescent agents, where the vessel is near
30 the skin wall, or other agents, such as short-lived radionuclides e.g. Tc, which may provide for better definition of the vessel walls.

Where one wishes to also provide for balloon angioplasty, various structures and techniques may be employed. For
35 example, one may inflate the balloon stepwise, so that in a first step, one creates an uneven surface by using an

intermediate pressure to provide for release of drug, but without uniform pressure on the vessel. One can then increase the pressure in the balloon to provide for a fairly uniform circumference, where there is substantially uniform
5 interaction with the vessel surface, so as to compress the plaque and create cracks in the plaque, where a therapeutic drug included on the balloon can be compressed into the crack. The pressure could then be reduced stepwise or in a uniform manner, where plaque particulates would be captured
10 by the hollows or depressions in the balloon.

For further understanding of the subject invention, the drawings will now be considered.

In FIG. 1, one embodiment of the invention is depicted, where the balloon 10 is connected to a liquid supply system
15 by conduit 12. The balloon is generally symmetrical, having roughened ridges 14 symmetrically disposed about the surface of the balloon. The balloon is mildly wrinkled having low ridges 16 and troughs 18 between the ridges 16. A frontal protuberance 20 is present. The balloon has a concavity or
20 small pocket at the front, so that a small finger extends inwardly. This cavity can serve as a container for a therapeutic or other agent. Upon inflation, the finger will move outwardly releasing the drug at the site of interest. In FIG. 2, a cross-section of balloon 10 is shown with
25 ridges 16 and troughs 18. The troughs 18 have a somewhat thicker wall than the protuberances or ridges 16, so that upon inflation, they do not stretch as much and allow for the formation of the ridges 16. On the surface of the ridges, are low elevations or spines 22 which serve for the
30 roughened surface 14. Between the spines 22, there may be included various agents. Alternatively, or in conjunction with the agents present between the spines 22, may be agents coated onto trough 18.

As shown in FIG. 3, the trough 18 may have spines 22, which
35 may serve to contain various agents. The outer surface 26

of protuberances 16 will serve to press the spines 22 against the vessel wall, resulting in rubbing against the vessel wall and removing material from the vessel wall. This material will then be confined between the spines and 5 will be captured upon deflation of the balloon, so that upon retraction, the material will be contained between the spines on the surface of the balloon.

In FIG. 3, the protuberances have roughened ridges 14 which will press against the vessel wall and remove small 10 particles from the vessel wall, to be retained on the surface 28. Also, spines which may act as bristles provide roughened a surface 14 which serves to capture and retain the plaque particles. In addition, a catheter can be provided to be capable of rotating the balloon, so that the 15 protuberances will move against the vessel wall, scraping the vessel wall, opening the vessel and removing the plaque and/or other accumulation on the vessel wall. A sound imaging probe (not shown) may be placed at the center of the balloon. These probes are described by and available from 20 Endosonics and Civis Corporation. This imaging tool can be used to determine the site of the balloon and to visualize the internal diameter of the restricted site.

In FIGS. 4 and 5, an alternative embodiment of the subject invention is shown where the balloon 40 has conduit 42 for 25 introducing a fluid into the balloon. In this embodiment, the cylindrical portion of the balloon 44 has protrusion 46, analogous to protrusion 20 of the balloon in FIG. 1. Criss-crossing channels 48 are provided, which upon expansion will be pressed against the vessel wall and will result in 30 material on the vessel wall being deposited in the channels 48. Upon deflation, this material will be captured within the channel so as to be retained upon removal of the balloon from the vessel. A cross-section of balloon 40 is shown in FIG. 5, with channels 48 separated by the wall of the 35 balloon 50.

In FIG. 6, there is shown an alternative embodiment in cross-section, where the balloon 60 has lumen 62 and internal walls 64, which are thicker and will not inflate as much as the ears shaped projections 66. The projections 66 have ears 68 which overlap ears of adjacent projections. Upon inflation, FIG.7, the projections will expand so as to have a substantially cylindrical outer surface, where the ears 68 will be substantially contiguous, one with the other, to form a relatively uniform cylinder while still providing internal channels 70. In this way, one may provide for a substantially uniform compression against the vessel wall, while still providing for delivery of drugs and capture of plaque particles.

In FIG. 8 is shown the deflated balloon 72, having a front 74 which includes the pocket, not shown. The ears shaped projections 66 extend the length of the balloon 72. A tube 76 provides means for connection to a guiding catheter and fluid supply.

FIGS. 9, 10 and 11 provide an alternative balloon 80, when the deflated balloon 80 has a plurality of fingers 82, where the walls are of similar thickness. Drug can be retained between the fingers 82. Upon inflation, as shown in FIG. 10, the outer wall 84 becomes relatively smooth with some depression forming channels 81. Drug on the walls is pressed into the plaque and plaque can be captured between the fingers 82 upon deflation. The deflated balloon has means for connection to a guiding catheter and fluid supply 88. The fingers 82 appear as ridge 90 extending the length of the balloon 80.

In FIGS. 12 and 13, the balloon 100 has curved or floppy fingers 102, which surround lumen 104 and flop over each other, so as to form covered channels 106. While deflated, the balloon results in protected channels which can contain various agents. Upon expansion, the balloon forms an uneven surface 107 with relatively shallow channels 110, which can

serve the same purpose as the channels in the other embodiments and can function in an analogous manner.

In accordance with the subject invention, novel catheter balloons are provided which allow for a number of advantages
5 as compared to presently existing balloons. The balloons provide for the administration of drugs at the site of inflation and collection of sample at the site of inflation. During deflation, the drug is substantially contained in wrinkles or folds of the balloon, so that it can be retained
10 during its movement through the vessels to the site for therapeutic treatment. In addition, sources of microbubbles can be used, so as to permit detection of blood flow and to provide for greater contrast in identifying the vessel wall. Other agents may also be employed to define the vessel wall.
15 By virtue of contact with the vessel wall, samples of material with which the subject balloon is in contact will be retained by the balloon. Upon deflation, the samples will be protected from loss during the travel of the balloon upon retraction. The samples may then be used in a variety
20 of diagnostic techniques, to further understand the diseased site to which the balloon has been introduced.

All publications and patent applications cited in this specification are herein incorporated by reference as if
25 each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of
30 clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A catheter balloon comprising:
means for inflation of said balloon;
an uneven surface comprising depressed and elevated
5 regions upon inflation extending substantially the full
length of said balloon, said surface being roughened at
least in part to retain a solid drug, particulate plaque, or
other physiological material.
2. A catheter balloon according to Claim 1, wherein said
10 balloon comprises alternating regions parallel to the long
axis of said balloon catheter resulting in troughs and
ridges upon inflation.
3. A catheter balloon according to Claim 2, wherein said
trough regions have thicker walls than said ridge regions.
- 15 4. A catheter balloon according to Claim 2, wherein said
ridge regions partially extend above the surface of said
trough regions and have a slack surface while deflated.
5. A catheter balloon according to Claim 1, wherein a
portion of at least said ridges has a roughened surface.
- 20 6. A catheter balloon according to Claim 1, wherein at
least a portion of said balloon is in contact with a drug.
7. A catheter balloon according to Claim 1, having a
plurality of protuberances upon inflation.
8. A catheter balloon comprising:
25 an uneven surface comprising trough and ridge regions
upon inflation extending substantially the full length of
said balloon, substantially parallel to the long axis of
said balloon, said surface being roughened at least in part
to be capable of retaining a solid drug, particulate plaque
30 or other physiological material,

said balloon having an inflated diameter to length ratio in the range of about 1:2-20; and
means for inflation of said balloon.

9. A catheter balloon according to Claim 8, wherein at
5 least one of said ridges has a roughened surface.

10. A method for treating and/or diagnosing a lesion, said
method comprising;
introducing into a cardiovascular vessel a catheter
balloon comprising:
10 means for inflation of said balloon; and
an uneven surface comprising depressed and elevated
regions upon inflation extending substantially the full
length of said balloon, said surface being roughened at
least in part to retain a solid drug, microbubble producing
15 agent, particulate plaque or other physiological material;
inflating said balloon at a site suspected of
comprising a lesion, whereby any lesion present at said site
is at least partially compressed and any drug or microbubble
agent on said balloon is released, and plaque particles or
20 other physiological material are restrained in said
depressed regions;
deflating said catheter balloon enclosing said plaque
particles or other physiological material; and
retracting said catheter balloon from said site
25 retaining said plaque particles or other physiological
material.

11. A method according to Claim 10, wherein a drug is
present on said balloon surface.

12. A method according to Claim 10, wherein a microbubble
30 agent is present on said balloon surface and including the
additional steps of applying sound to said site to detect
the flow of blood at said site or define the surface of said
lesion.

13. A method according to Claim 10, wherein said catheter balloon is inflated stepwise, wherein sufficient pressure is applied to said balloon to compress said lesion substantially uniformly.

5 14. A method according to Claim 10, wherein said catheter balloon is rotated after inflation to compress said lesion.

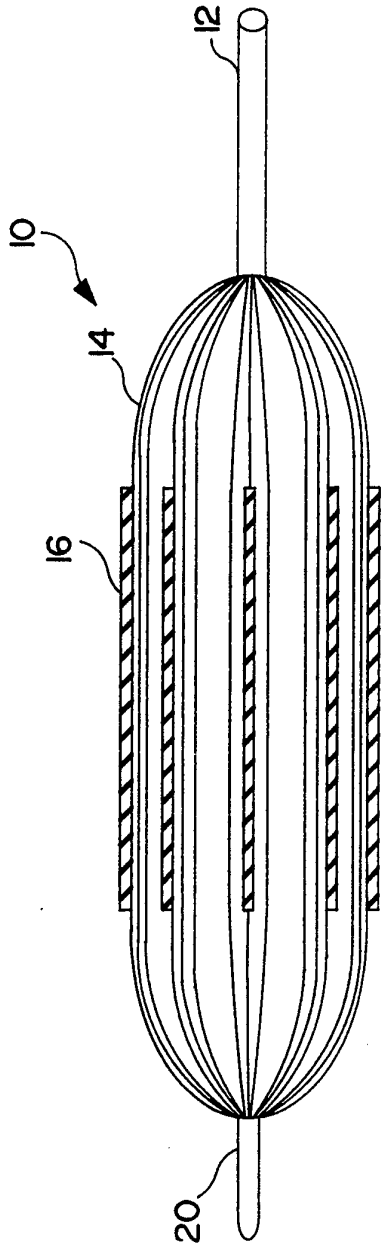


FIG. 1

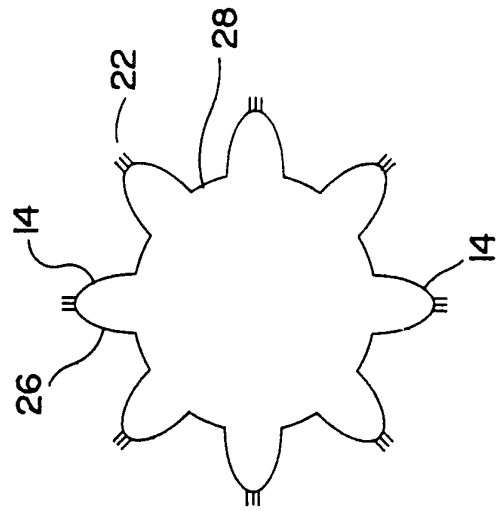


FIG. 3

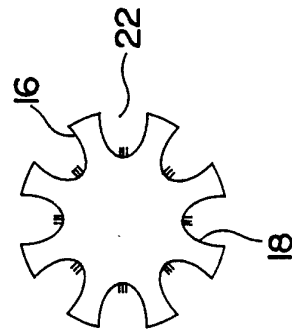


FIG. 2

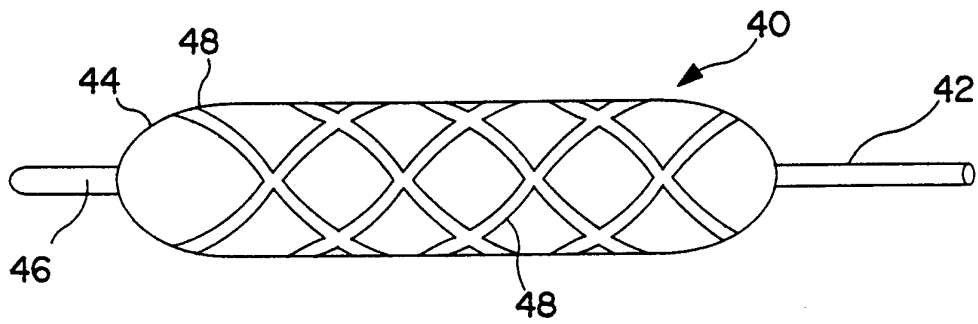


FIG. 4

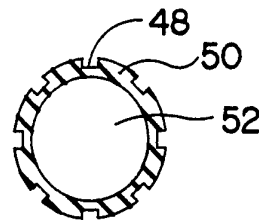


FIG. 5

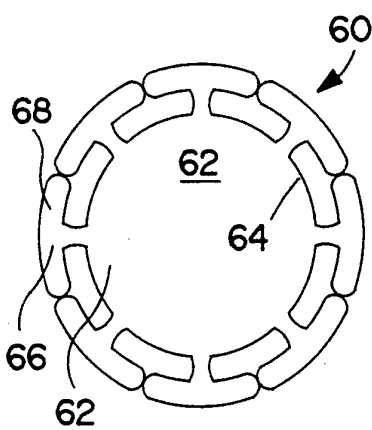


FIG. 6

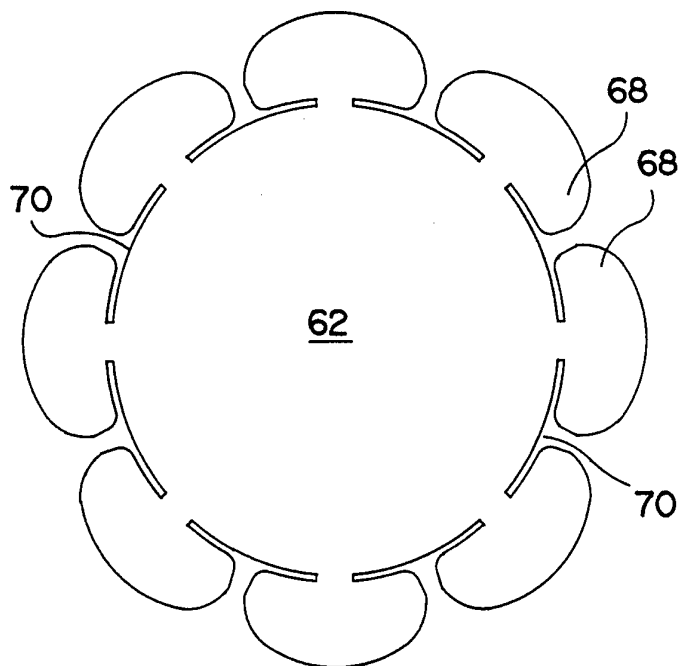


FIG. 7

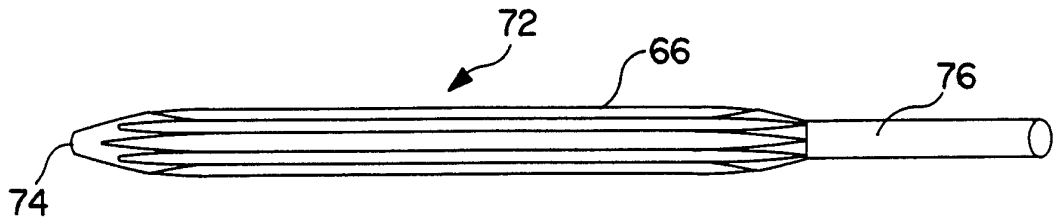


FIG. 8

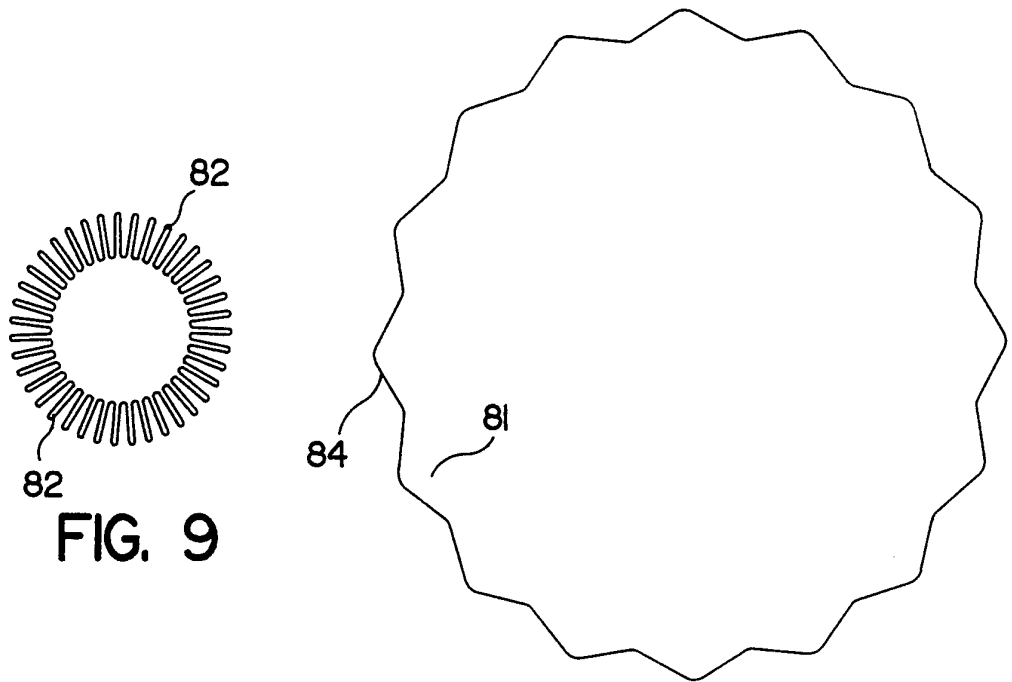


FIG. 9

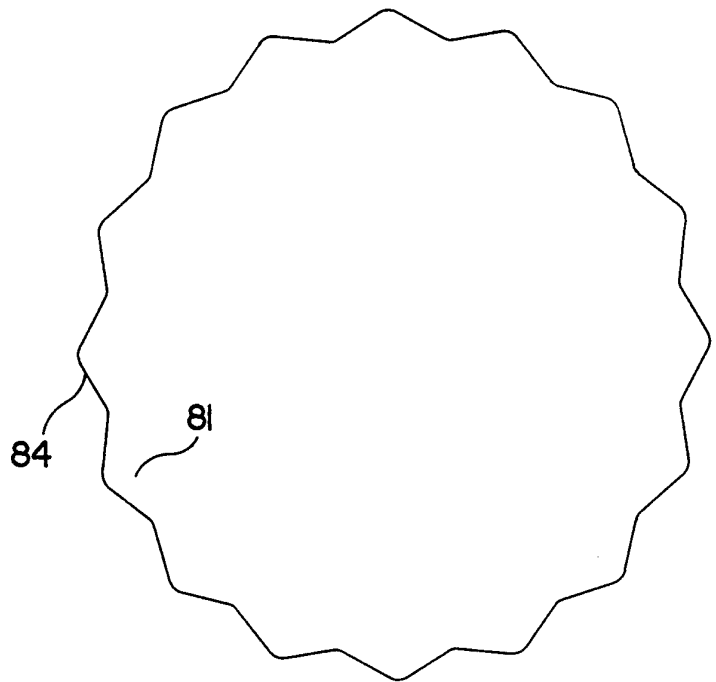


FIG. 10



FIG. 11

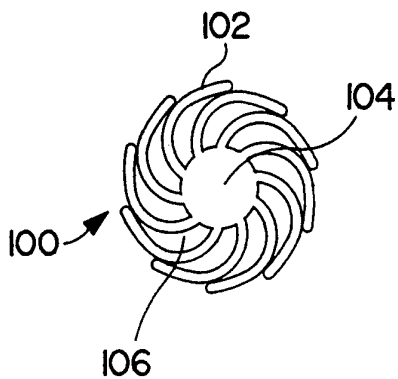


FIG. 12

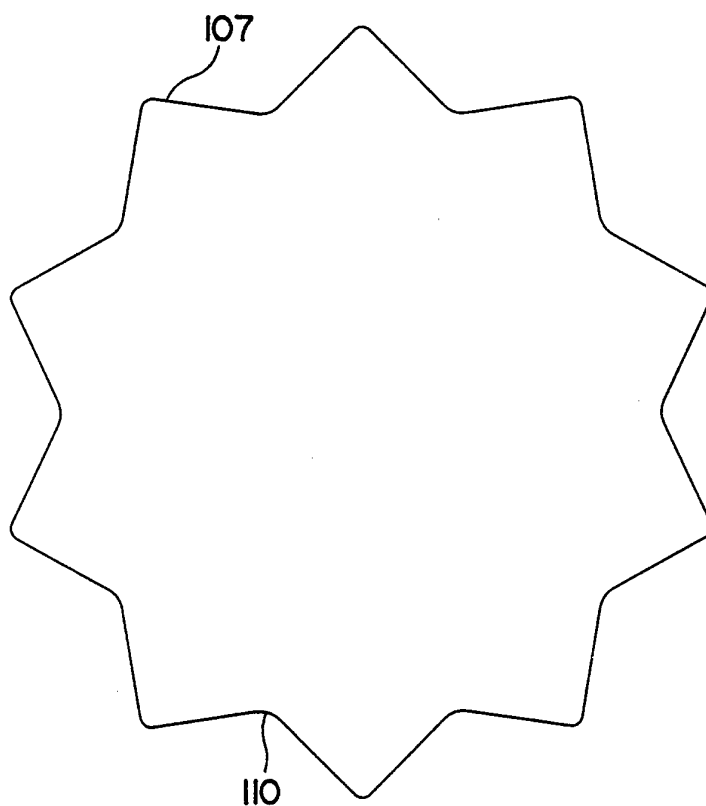


FIG. 13

INTERNATIONAL SEARCH REPORT

Int. national application No.
PCT/US94/04402

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61M 29/00; A61B 10/00

US CL : 604/96; 128/756

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/749, 756, 757, 759, 760, 768; 604/1, 2, 96-103, 265, 280, 281; 606/191-195

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

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---, P Y	US, A, 5,250,070, (PARODI), 05 October 1993. See figures and disclosure.	1-5, 7-10, 13, 14 ----- 6, 11, 12
X --- Y	US, A, 5,108,414, (ENDERLE ET AL.), 28 April 1992. See Fig. 2.	1-5, 7-10, 13, 14 ----- 6, 11, 12
X	US, A, 3,664,328, (MOYLE, R., ET AL.), 23 May 1972. See entire disclosure.	1, 7
X	US, A, 2,701,559, (COOPER), 08 February 1955. See entire document.	1, 7

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

<p>* Special categories of cited documents:</p> <p>*A* document defining the general state of the art which is not considered to be part of particular relevance</p> <p>*E* earlier document published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search	Date of mailing of the international search report
01 JUNE 1994	JUN 27 1994

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/04402

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,192,290, (HILAL), 09 March 1993. See entire document	1, 7
X ---- Y	US, A, 5,196,024, (BARATH), 23 March 1993. See Figs. 6 and 7.	1-5, 7-11, 13, 14 ----- 6, 11, 12
Y	US, A, 5,102,402, (DROR ET AL.), 07 April 1992. See micro-capsules.	6, 11-12
Y	US, A, 5,049,131, (DEUSS), 17 September 1991. See disclosure of medicaments.	6, 11, 12