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Declarations under Rule 4.17:
— *as to the identity of the inventor (Rule 4.17(i)) for all designations*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

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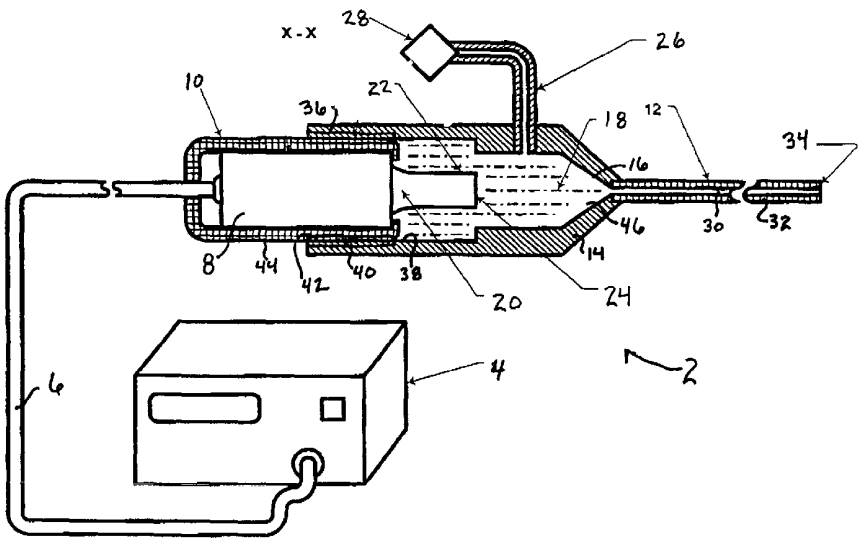
(54) Title: ULTRASONIC CATHETER DRUG DELIVERY METHOD AND DEVICE



(57) Abstract: An ultrasonic catheter drug delivery device comprises an ultrasound transducer to produce ultrasonic waves, which transducer is mechanically attached to a catheter body or chamber. The ultrasonic transducer has a distal tip with a distal radiation surface, and when a therapeutic agent from a fluid source is directed to the catheter body or chamber, the radiation surface creates ultrasonic pressure and delivers liquid and simultaneously ultrasonic energy to a patient's vascularity or a selected body lumen. The method applies therapeutic agent and ultrasonic waves to the vascular area, lung or any body lumen without requiring direct contact between ultrasound transducer and body, dissolves blood clots, and stimulates tissue cells.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ULTRASONIC CATHETER DRUG DELIVERY METHOD AND DEVICE

FIELD OF THE INVENTION

The present invention generally relates to medical devices and methods. More particularly, the present invention relates to apparatus and methods for the ultrasonically enhanced delivery of therapeutic or contrast agents within the vascular and lung areas or other corporeal lumens.

BACKGROUND OF THE INVENTION

Despite the significant progress of medical technology, vascular and lung diseases, as well as arterial thrombosis (blood clots in arteries), remain frequent, costly and serious problems in health care. Current methods of treatment such as drugs, interventional devices, and/or bypass surgery are usually expensive and not always effective, even sometimes causing additional problems. For example, drugs can also dissolve beneficial clots or interventional devices can injure healthy tissue to cause potentially fatal bleeding complications or to form scarring or cellular growth which may itself eventually become a serious obstruction in, for example, a blood vessel (a process known as restenosis).

Ultrasonic energy has been used for enhancing the intravascular delivery of drug, to dissolve clot acoustically, disrupt mechanically and inhibit restenosis. Such energy can be delivered intravascularly using specialized catheters having ultrasonically vibrating surface at or near their distal ends. One type of ultrasonic catheter delivery system uses a wire or other axial transmission element to deliver energy from an ultrasonic energy source, located outside the patient to the internal organs, to desired corporeal lumens. (See, for example, U.S. Patents Nos. 5,002,059, 5,324,255, 5,345,940, and 5,699,805, each of which is incorporated herein by reference.) Such catheters are rigid and cannot be easily inserted through narrow and tortuous vessels and may cause serious damage to vascular walls.

A second type of catheter has ultrasonic transducers mounted directly on their distal ends. See, for example; U.S. Patents Nos. 5,362,309, 5,318,014, 5,315,998, 5,269,291,

5,197,946, 6,001069, and 6,024,718, each of which is incorporated herein by reference. Despite enhanced safety and the fact that there is no need to employ a transmission element along the entire length, these catheters suffer from limited ultrasound energy, and the transducer-catheter design is still problematic.

Another type of catheter has an ultrasonic transducer or ultrasound transmission element with a central orifice in the distal end to impart ultrasonic energy into liquid and simultaneously deliver it to a corporeal lumen. See, for example, U.S. Patents Nos. 5,735,811 and 5,197,946, each of which is incorporated herein by reference. Although these catheters are more effective and liquid delivery is more convenient, there are design difficulties and limitation of ultrasound energy from longitudinal waves.

OBJECT OF THE INVENTION

It is an object of the invention to provide an improved method and device for catheter drug delivery.

It is also an object of this invention to provide a method and device for catheter drug delivery using ultrasound energy.

It is another object of the invention to mix different drugs ultrasonically and deliver them to a desired corporeal lumen ultrasonically.

It is a yet another object of the invention to mix drug - liquid solutions with a gas (for example, saline with oxygen) ultrasonically and deliver the mixture to a desired corporeal lumen ultrasonically.

It is a further object of the invention to provide a method and device for delivering drugs to an intravascular area or/and a corporeal lumen, to dissolve blood clots.

It is a yet further object of the invention to treat a blocked and narrowed blood vessel with ultrasound waves.

These and other objects of the invention will become more apparent from the discussion below.

SUMMARY OF THE INVENTION

The present invention relates to apparatus and method for the ultrasonically enhanced delivery of therapeutic or contrast agents within the vascular and lung area or other desired corporeal lumens. Ultrasonic waves are applied to a vascular area, lung or any corporeal lumen without requiring direct contact between ultrasound transducer tip and the patient's body, particularly to dissolve blood clots.

According to the present invention, a catheter system comprises an ultrasound transducer having a distal tip with a radial surface and a distal end surface. The ultrasound transducer is disposed in a chamber at the proximal end of the catheter, and the transducer radiation surface or tip directs ultrasound waves or energy forward into the catheter coaxially via liquid. Longitudinal ultrasound waves induce wave motion in fluid adjacent to the transducer distal end. While particularly intended to enhance the absorption of therapeutic agents delivered to certain body lumens, the catheter system of the present invention is also useful for the delivery of ultrasonic energy to a desired location. The transducer radiation surface or transducer tip, may be cylindrical, flat, concave, convex, irregular or have a different shape-geometry to radiate ultrasound energy into catheter.

The catheter of the present invention may comprise a proximal tubing for delivering therapeutic agent from a reservoir by pump or syringe. The tubing may be located in front of or behind the radiation surface.

In a first embodiment of the invention, an ultrasound transducer and tip are mounted in a proximal portion of a catheter body, located outside of the body of a patient. The remainder of the catheter distal to the proximal portion may be inserted into a blood vessel or attached to a body lumen, to drive a therapeutic agent ultrasonically and/or deliver ultrasonic energy.

In a second embodiment, the distal tip of the transducer does not have an orifice, which is very important to create and deliver ultrasound energy fully to a vessel or body lumen.

In a third embodiment, the catheter system comprises a catheter body, mechanically coupled with an ultrasound transducer through a housing or tip node, which is where the transducer body is outside the catheter. In this way, the catheter body can be provided with two or more tubing inlets (sleeves) for different therapeutic agents, even one or more different gases such as oxygen, and agents to be mixed and delivered ultrasonically.

The catheter system of the invention is particularly advantageous on tissues for which local topical application of a therapeutic agent is desirable but contact with the tissue is to be avoided. Furthermore, ultrasound waves used in the method energize the drug, dissolve the clots and cause the penetration of the drug within the narrow and blocked vessels.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective, partly cross-sectional view of an ultrasonic catheter drug delivery system for use according to the present invention;

FIG. 2 is a lateral view of an ultrasonic catheter system chamber of the invention with two horizontally located sleeves;

FIG. 3 is a frontal view of an ultrasonic catheter system chamber of the invention with three peripherally located sleeves;

FIG. 4 is a lateral, cross-sectional view of a catheter system chamber, mechanically coupled with an ultrasound transducer through the tip; and

FIG. 5 is a lateral, cross-sectional view of an ultrasonic catheter drug delivery system for delivering therapeutic agent to the catheter body or chamber through a central orifice of the ultrasonic tip.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a method and device, which provides treatment of luminal conditions, particularly for the treatment of coronary and peripheral arterial disease and thrombosis, where the purpose is to dissolve or disrupt the clot, plague or other stenotic

lesions which cause the disease, and for dilation of narrowed vessels. The method and device of the present invention also useful to enhance the administration of therapeutic agents primarily responsible for the disruption of the clots or other stenotic material. The ultrasonic energy agitates and promotes the penetration of the drug into the stenotic material. Due to delivery of therapeutic agent and ultrasound energy through the agent, this method and device of the present invention are further useful for treatment of other body lumens, such as the urethra, ureter, fallopian tubes, or urological disorders related with prostate gland (BPH – Benigh Proctatic Hyperplasia), and can be used for impotency (erectile dysfunction) treatment by ultrasonically stimulating sexual organs, urinary tract, and the like.

The present invention can be used for targeted and localized drug delivery for treatment of lung, vasculature, vasopasm and tumor treatment. In addition, this invention is very useful for the treatment of closed wounds as a fistulas, canals, etc., by destroying bacteria cells and stimulating healthy tissue cells.

The invention can perhaps be better appreciated by referring to the drawings. FIG. 1 is a perspective view of ultrasound catheter drug delivery system 2, comprising an ultrasound generator 4, a connector 6 operatively connecting ultrasound generator 4 with a transducer 8, a housing 10 surrounding transducer 8, and a catheter 12 having a proximal portion 14 with a chamber 16 containing a therapeutic agent 18. Transducer 8 has a tip 20 with a radial surface 22 and a distal radiation surface 24. Chamber 16 is in fluid communication through tubing 26 with a fluid source 28, and directly with at least one lumen 30 of the distal portion 32 of catheter 12 that extends to catheter distal end 34. Fluid source 28 can be, for example, a reservoir with a pressure pump or syringe.

The proximal section 36 of catheter proximal portion 14 sealingly engages housing 10. Preferably the inner surface 38 of proximal section 36 has threads 40 that engage reciprocal threads 42 on the outer surface 44 of housing 10. This arrangement will allow the operator to vary the distance between distal radiation surface 24 and the distal end 46 of chamber 16 to regulate ultrasonic pressure and energy level. While radial surface 22 can be smooth or substantially smooth, it is preferred that this surface is not smooth, for example,

with rings, threads, barbs, or the like, which will create more ultrasonic pressure in catheter 12.

In the embodiment of the invention shown in Fig. 1, ultrasonic energy at a pre-selected frequency is sent through the catheter 10 with fluid such as a therapeutic agent as a transmission member. Ultrasound energy will pass through therapeutic agent 18 to catheter distal end 34. Catheter 12 may be formed from a conventional rigid or flexible material, dependent upon the application. It would be appropriate for catheter 12 to be flexible if the catheter is to be inserted into tortuous vascularity or if catheter distal end 34 is to be attached to a vessel, fistula, or the like.

A second embodiment of the invention is shown in Fig. 2, where transducer 50 is fixedly, optionally removably, attached to the proximal section 52 of the proximal portion 54 of a catheter 56. Transducer 50 has a tip 58 with a radial surface 60 and a distal radiation surface 62. Catheter proximal portion 54 has a chamber 64 with a therapeutic agent 66 that is in fluid communication with each of two fluid sources 68,70 through lumens 72,74, respectively. Fluid sources 68,70 may provide two or more fluids, e.g., liquid or gas, such as saline or oxygen, to be ultrasonically mixed and delivered through lumen 76 to catheter distal end 78.

Fig. 3 is a semi-cross-sectional view of the proximal end of a catheter according to the invention wherein three fluid sources 80 are each in fluid communication through a lumen 82 with chamber 84 of catheter proximal section 86. The distal radiation surface 88 of a transducer (not shown) is positioned within chamber 84.

In Fig. 4, a connector 110 operatively connects an ultrasound generator (not shown) with a transducer 112, which has a tip 114 with a radial surface 116 and a distal end surface 118. A catheter 120 has a proximal portion 122 with a chamber 124 containing a therapeutic agent 126. Chamber 124 is in fluid communication through tubing 130 with a fluid source 132, and directly with at least one lumen 134 of the distal portion 136 of catheter 120 that extends to catheter distal end 140. Fluid source 132 can be, for example, a reservoir with a pressure pump or syringe.

The proximal section 142 of catheter proximal portion 122 sealingly engages radial surface 116. Chamber 124 must be attached to ultrasonic transducer distal tip 114 at the mechanical resonant node, such as node 144. If chamber 124 is not connected to the resonant node (either a little before or a little after the mechanical node), the intensity of the ultrasound energy at distal end 140 will be attenuated, i.e., damped, and ultrasound waves and/or energy will be transferred to the walls of chamber 126, possibly damaging the chamber 126 structure assembly, which may cause leakage.

In the embodiment of the invention set forth in Fig. 5, a connector 150 operatively connects an ultrasound generator (not shown) with a transducer 152, which has a distal tip 154 with a radial surface 156 and a distal end surface 158. A catheter 160 has a proximal portion 162 with a chamber 164 containing a therapeutic agent 166.

Transducer distal tip 154 has a central orifice 170. Chamber 164 is in fluid communication with at least one fluid source 172 through central orifice 170, which can be smooth, waved, ringed, slotted, grooved, or threaded, and infusion lumen 174 within tubing 176. Two or more fluid sources 172 and infusion lumens 174 can mix and deliver different therapeutic agents. Chamber 164 is also in fluid communication with lumen 180 in the distal portion 182 of catheter 160 that extends to distal end 184. The non-smooth surface of orifice 170, such as rings or threads, increases the pressure of liquid in chamber 164.

Chamber 164 should be attached to ultrasonic transducer distal tip 158 at a mechanical resonant node, such as node 190. Similarly, each lumen 174 should intersect central orifice 170 at a resonant node, such as node 192.

The catheter systems herein are comprised of conventional materials. The transducer and catheter chamber are preferably comprised of suitable metallic or even polymeric substances. Most preferably the transducer distal tip is comprised of a metal such as titanium or nitinol.

As is mentioned throughout, the invention here can deliver one or more liquid or gaseous substances to a catheter distal end. Such substances include, but are not limited to, therapeutic agents such as antibiotics or antiseptics, saline, oil, water, oxygen, anticoagulants

such as heparin or cumadine, or even liquid medical polymers, or mixtures of two or more thereof.

It is provided that the distal radiation surface is driven with a constant, modulated or pulsed frequency. It is also provided that the distal radiation surface is driven with a sinusoidal, rectangular, trapezoidal or triangular wave form. It is further provided that the transducer is capable of being operated at a frequency from 10 kHz to 10,000 MHz.

The preceding specific embodiments are illustrative of the practice of the invention. It is to be understood, however, that other expedients known to those skilled in the art or disclosed herein, may be employed without departing from the spirit of the invention or the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A catheter system for ultrasound drug delivery, comprising:

a catheter having a proximal portion comprising a chamber and a distal end, wherein at least one lumen extends longitudinally from said chamber to said distal end,

at least one fluid source in fluid communication with said chamber, and

an ultrasound transducer having a distal end, said transducer distal end extending coaxially into said catheter chamber,

wherein said transducer generates ultrasound waves that induce wave motion in fluid in said chamber to deliver liquid and/or ultrasound energy to the catheter distal end.

2. The catheter system of Claim 1, wherein the transducer distal tip is positioned coaxially within the chamber.

3. The catheter system of Claim 1, wherein wave motion is induced in fluid adjacent to the transducer distal end.

4. The catheter system of Claim 1, wherein liquid and ultrasound energy are delivery simultaneously to the catheter distal end.

5. The catheter system of Claim 1, wherein there are two fluid sources.

6. The catheter system of Claim 1, wherein the transducer distal tip has a central orifice in fluid communication with at least one fluid source and said chamber.

7. The catheter system of Claim 6, wherein the surface of the orifice is non-smooth.

8. The catheter system of Claim 7, wherein the orifice surface is ringed, slotted, waved, grooved, or threaded.

9. The catheter system of Claim 6, wherein there are at least two fluid sources and fluids from the fluid sources are admixed in the orifice.

10. The catheter system of Claim 1, wherein the transducer is capable of operating at a frequency of from about 10 kHz to 10^3 MHz.

11. The catheter system of Claim 1, wherein the transducer distal tip comprises a radial surface and a distal radiation surface.

12. The catheter system of Claim 11, wherein the radial surface is not smooth.

13. The catheter system of Claim 12, wherein the radial surface is ringed, slotted, waved, grooved, or threaded.

14. The catheter system of Claim 11, wherein the distal radiation surface is flat, conical, oval, circular, semi-spherical, square, or rectangular.

15. The catheter system of Claim 1, wherein the fluid is a therapeutic agent.

16. The catheter system of Claim 1, wherein the ultrasound transducer is connected to the proximal portion of the catheter.

17. The catheter system of Claim 1, wherein the distal end of the ultrasound transducer is connected to the proximal portion of the catheter.

18. The catheter system of Claim 1, wherein the ultrasound transducer or distal tip can be moved backward or forward toward the catheter body to change ultrasound pressure and/or delivered ultrasound energy level.

19. A method for ultrasonically treating an interior area of the body, the method comprising the steps of:

providing a catheter having at least one lumen;

providing a transducer having a distal radiation surface configured and dimensioned for coupling with a proximal end of the catheter and for emitting ultrasonic energy therein;

introducing at least a liquid within the proximal end of the catheter; and

delivering the emitted ultrasonic energy to the interior area of the body through the at least one lumen and the liquid for treating the interior area of the body with ultrasonic energy.

20. The method according to Claim 19, wherein the transducer operates at a frequency from 10 kHz to 10,000 MHz.

21. The method according to Claim 19, wherein the liquid includes one or more components selected from the group consisting of antibiotics, antiseptics, saline, oils, anticoagulants, and water.

22. The method according to Claim 19, wherein the step of delivering the emitted ultrasonic energy to the interior area of the body causes a therapeutic effect to occur within the body, and wherein the therapeutic effect is selected from the group consisting of increasing blood flow by decreasing the amount of stenosis within a body lumen, stimulating cell growth, alleviating urological disorders, and treating impotency.

23. The method according to Claim 19, wherein the transducer is driven by at least one of a constant, pulsed, and modulated frequency, and wherein the driving wave form of the transducer is selected from the group consisting of sinusoidal, rectangular, trapezoidal and triangular wave forms.

24. The method according to Claim 19, further comprising the step of translating the distal radiation surface within the proximal end of the catheter for

regulating at least one characteristic of the emitted ultrasonic energy.

25. The method according to Claim 19, further comprising the step of introducing a gas within the proximal end of the catheter for intermixing with the liquid and being delivered to the interior area of the body.

26. The method according to Claim 19, wherein the liquid is introduced within the proximal end of the catheter from a corresponding fluid source, and wherein the corresponding fluid source is a reservoir or a syringe.

27. The method according to Claim 19, further comprising the step of sealingly engaging the distal radiation surface within the proximal end of the catheter.

28. A catheter system for ultrasonically treating an interior area of the body, the system comprising:

a catheter having at least one lumen;

a transducer having a distal radiation surface configured and dimensioned for coupling with a proximal end of the catheter and for emitting ultrasonic energy therein; and

means for introducing at least a liquid within the proximal end of the catheter, wherein the emitted ultrasonic energy is delivered to the interior area of the body through the at least one lumen and the liquid for treating the interior area of the body with ultrasonic energy.

29. The catheter system according to Claim 28, wherein the transducer operates at a frequency from 10 kHz to 10,000 MHz.

30. The catheter system according to Claim 28, further comprising means for translating the distal radiation surface within the proximal end of the catheter for regulating at least one characteristic of the emitted ultrasonic energy.

31. The catheter system according to Claim 28, further comprising means for introducing a gas within the proximal end of the catheter for intermixing with the liquid and being delivered to the interior area of the body.

32. The catheter system according to Claim 28, further comprising means for sealingly engaging the distal radiation surface within the proximal end of the catheter.

FIGURE 1

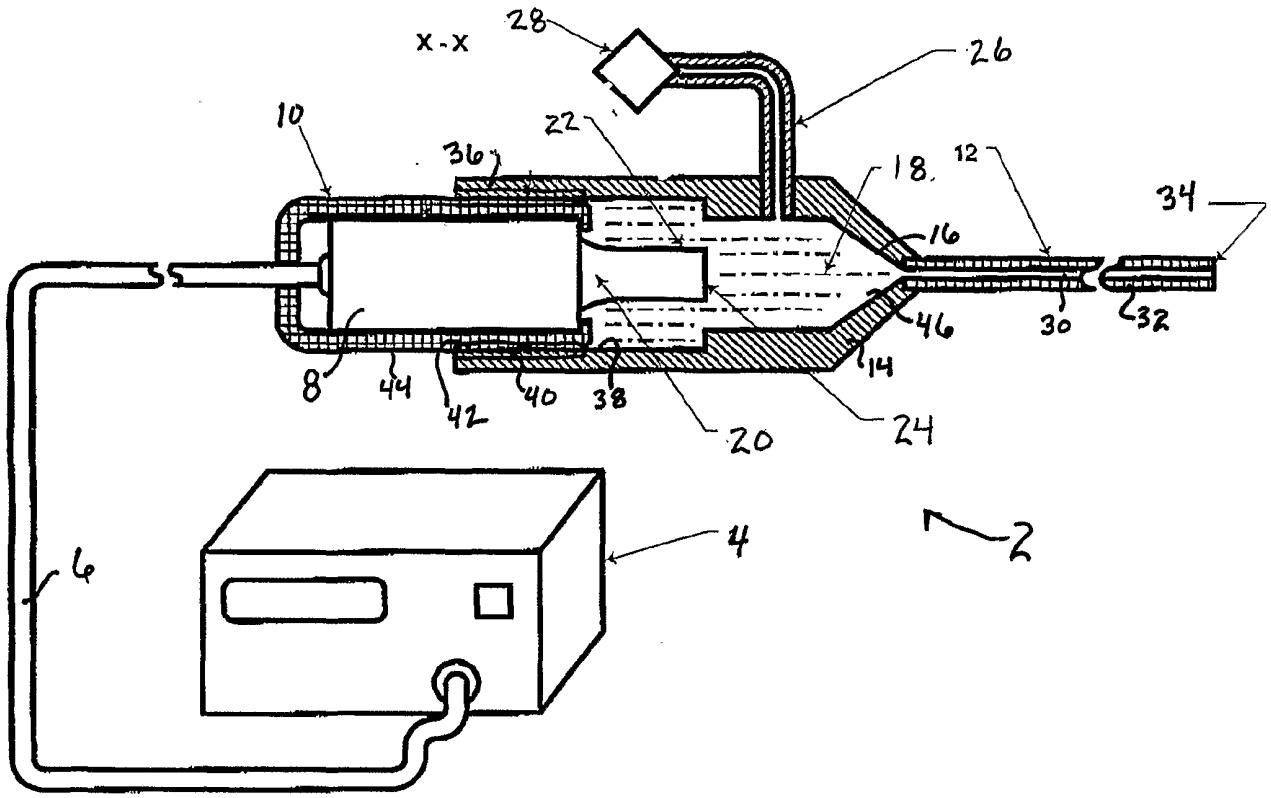


FIGURE 2

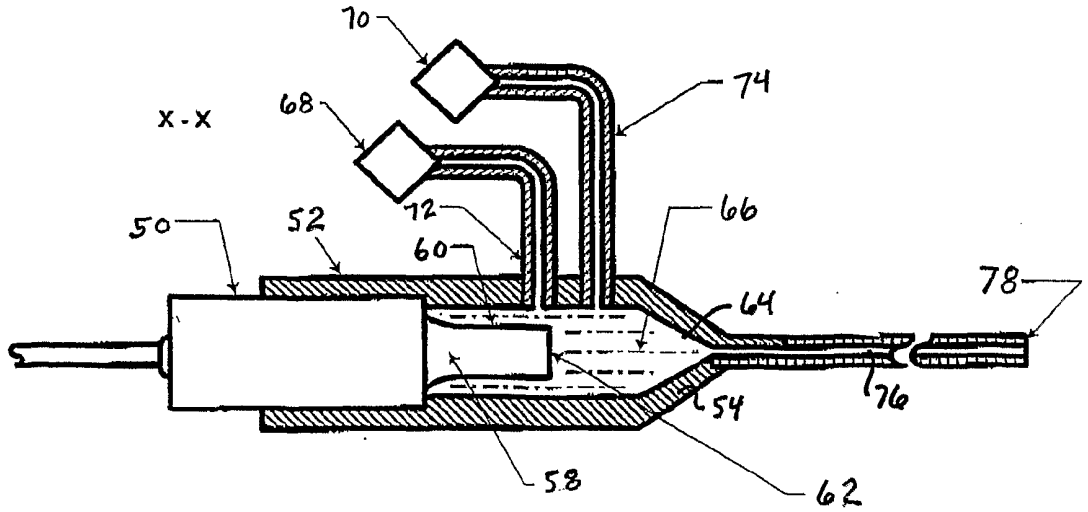


FIGURE 3

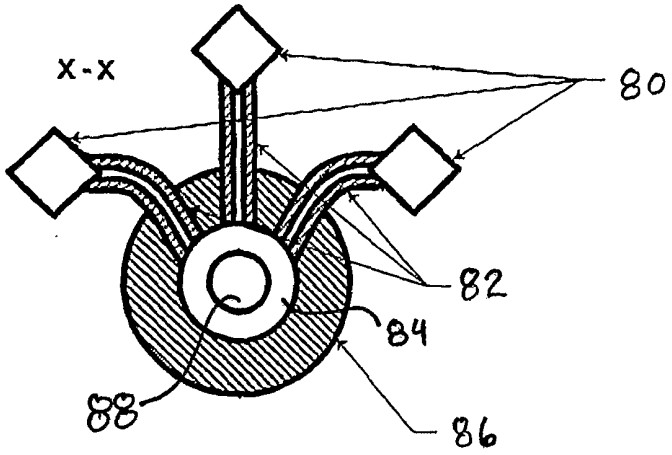


FIGURE 4

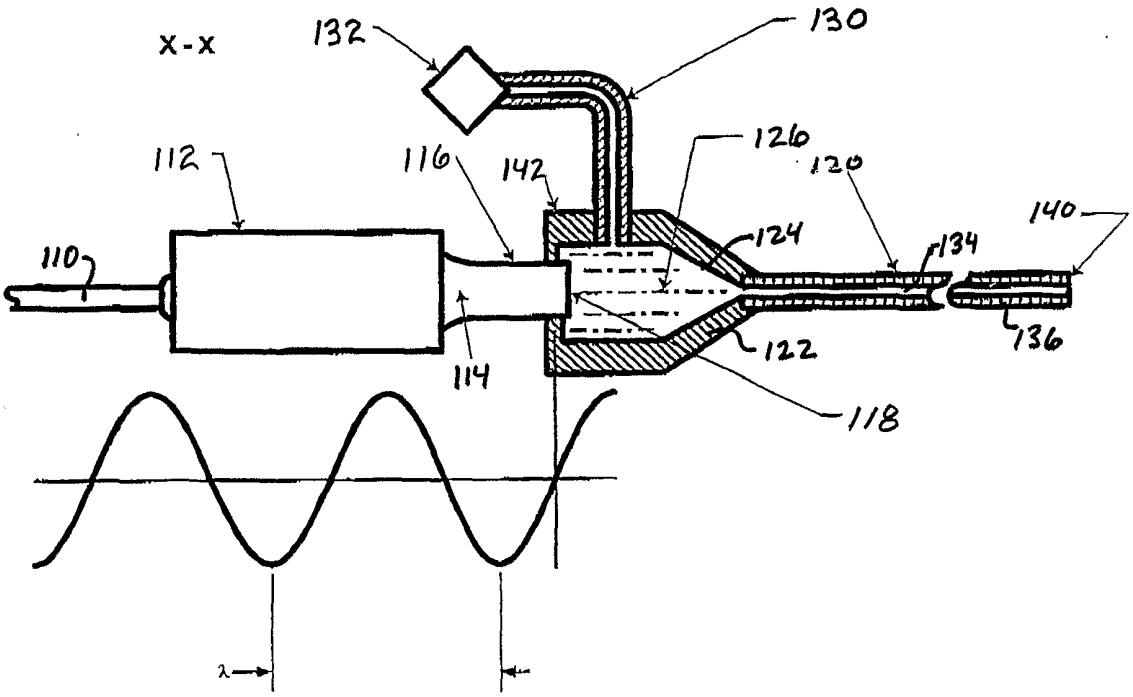
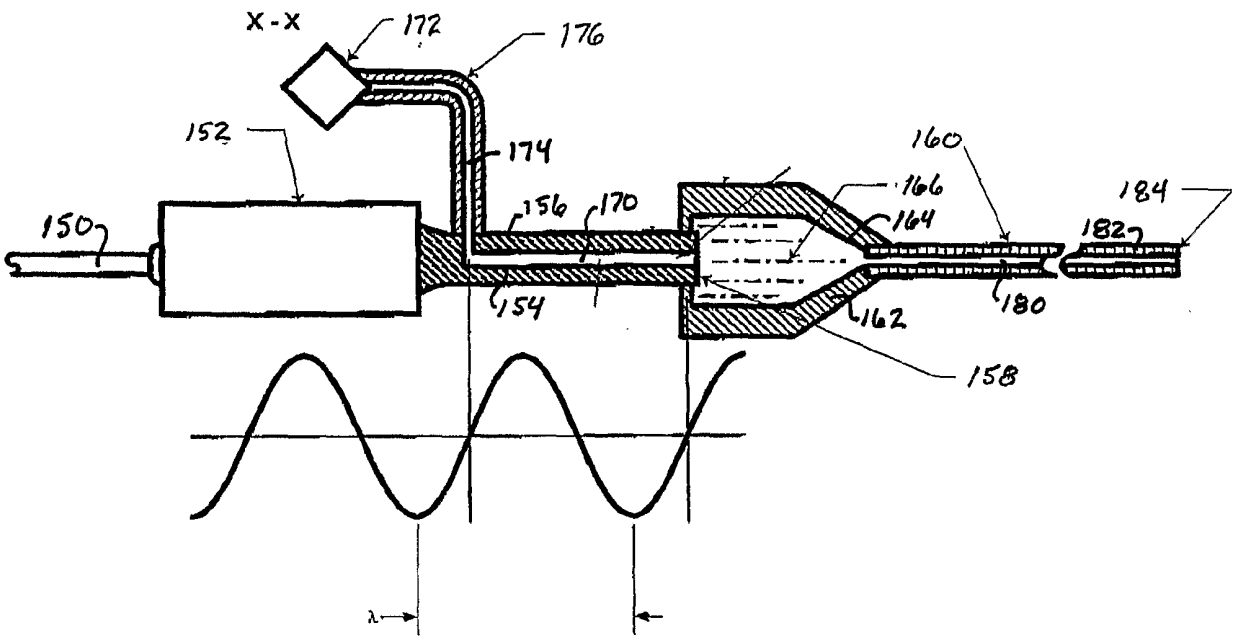


FIGURE 5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INTERNATIONAL SEARCH REPORT

Int[illegible]tional Application No
PCT/US 02/08503

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M37/00

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)
IPC 7 A61M A61B

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 38 12 841 A (SCHUBERT WERNER) 2 November 1989 (1989-11-02) the whole document	1-5, 15-18,28
A	WO 00 06032 A (PHARMASONICS INC) 10 February 2000 (2000-02-10) page 11, line 13 - line 25; figures	1,10,15, 28-30
A	WO 00 00095 A (EKOS CORP) 6 January 2000 (2000-01-06) claim 1; figures	1,28
A	US 5 735 811 A (BRISKEN AXEL F) 7 April 1998 (1998-04-07) cited in the application abstract; figures	1,28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2002	06/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kousouretas, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/08503

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 362 309 A (CARTER ROBERT E) 8 November 1994 (1994-11-08) cited in the application abstract; figures	1,28
A	US 5 197 946 A (TACHIBANA SHUNRO) 30 March 1993 (1993-03-30) cited in the application abstract; figures	1,28

INTERNATIONAL SEARCH REPORT

ɪrnational application No.
PCT/US 02/08503

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-27
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/08503

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