[0099] Still referring to FIG. 5B, an epoxy housing 48 is shown, surrounded by an external layer of silicone 50. In the embodiment shown, the ultrasonic radiating elements 36 are potted in the epoxy housing 48. The epoxy may be flush with the outer diameter of silicone 50. The epoxy housing 48 may have an axial length less than the length of the distal region 12. In embodiments including multiple pairs of ultrasonic radiating elements 36, each pair of elements may be confined to a separate epoxy housing 48. In one embodiment, the epoxy housing 48 may have an axial length of between 0.75 and 0.2 inches (19.05mm and 5.08mm). In other embodiments, the epoxy housing 48 may have an axial length of between 0.1 and 0.15 inches (2.54mm and 3.81mm), between 0.11 and 0.12 inches (2.794mm and 3.048mm), or approximately 0.115 inches (2.921mm).

[0100] FIGS. 6A-B show two embodiments of epoxy housings 48 in which an ultrasonic radiating element 36 may be housed. Although the housing depicted is made from epoxy, any suitable material may be used. For instance, the housing may be made from rubber, polyurethane, or any polymer of suitable flexibility and stiffness. In embodiments employing epoxy, the housing may be formed by filling a polyimide sleeve with epoxy followed by curing.

[0101] In some embodiments, epoxy housings 48 may be embedded in the silicone layer with the assistance of chemical adhesives. In other embodiments, the housings 48 may additionally contain structural designs to improve the stability of the housing within the silicone. For instance, the housing 48 shown in FIG. 6A contains a notch 52 which, when fitted with a complementary structure of a silicone layer, may improve the stability of the housing 48 within the silicone layer. Such structural designs may be used in conjunction with or independently of chemical adhesives. FIG. 6B shows another embodiment of an epoxy housing 48. In this embodiment, the raised ridge 54 is designed such that the top surface may lie flush with a silicone layer that surrounds the epoxy housing 48. The presence of ridge 54, when positioned with a complementary silicone layer structure, may help to maintain the position of the housing, and therefore of the ultrasonic radiating element, with respect to the ultrasonic catheter.

[0102] FIGS. 7A-C show an ultrasonic catheter with a modified connector 28 that can be used in combination with the arrangements and embodiments described above. The catheter 10 includes flexible tubular body. Distal to the connector 28 is the proximal port 24, which is in communication with the lumen of the tubular body 16. In the embodiment shown, the proximal port 24 is coaxial with the lumen of the tubular

holes 20 in distal region 12. Additionally, blood or other liquid may flow in the opposite direction, entering the catheter through drainage holes 20, flowing proximally through the lumen, and exiting the catheter 10 through proximal port 24 and into a drainage kit or other disposal means. Ultrasonic energy may also be applied periodically, continuously, sporadically, or otherwise throughout the process as desired. In certain embodiments, external pressure, negative or positive, may be applied in order to facilitate movement of liquids from the proximal port 24 through the lumen and out drainage holes 20, or in the opposite direction. In other embodiments, liquids are permitted to flow through the lumen, unaided by external pressure.

[0108] FIGS. 9A-F illustrate another arrangement for arranging the wires of an ultrasonic catheter. This arrangement can be used with the embodiments and arrangements described above. In this arrangement, a spiral groove extrusion 56 provides structural support to the tubular body 16. In certain embodiments, the groove extrusion 56 may be replaced by a similar structure formed by molding or any other method. The spiral groove design can provide improved kink resistance compared to a solid structure. The spiral groove extrusion 56 may be formed of a variety of different materials. For example, in one arrangement, metallic ribbons can be used because of their strength-to-weight ratios, fibrous materials (both synthetic and natural). In certain embodiments, stainless steel or tungsten alloys may be used to form the spiral groove extrusion 56. In certain embodiments, more malleable metals and alloys, e.g. gold, platinum, palladium, rhodium, etc. may be used. A platinum alloy with a small percentage of tungsten may be preferred due to its radiopacity. A sleeve 58 is arranged to slide over the spiral groove extrusion 56. The material for sleeve 58 may be formed of almost any biocompatible material, such as polyvinyl acetate or any biocompatible plastic or metal alloy. Distal extrusion 60 can house ultrasonic elements as well as drainage holes 20. The distal extrusion 60 can be formed of materials such as those described above with respect to spiral groove extrusion 56. Wires 38 are affixed to the distal extrusion 60 and connected to thermocouple or ultrasound radiating elements. A distal tip 62 is fitted to the end of distal extrusion 60.

[0109] FIG. 9C shows a cross-sectional view of the tubular body 16 taken along line N-N of FIG. 9B. Outer diameter 64 may be approximately 0.2 inches (5.08mm). In other embodiments, the outer diameter 64 may be approximately 0.213 inches (5.4102mm). The inner diameter 66 may be approximately 0.1 inches (2.54mm). In other embodiments, the inner diameter

may be approximately 0.106 inches (2.6924mm). As will be apparent, the dimensions of the inner and outer diameters will be selected according to the application intended based on, e.g., the diameter of the access path through the skull, the treatment site, the volume of therapeutic agent delivered, and anticipated volume of blood to be drained.

[0110] In the embodiment shown, the distal extrusion 60 may contain a window 68 in which an ultrasound radiating element may be affixed. In other embodiments, multiple ultrasonic radiating elements, each with a corresponding window 68, may be employed. As discussed above, the number, orientation, and relation of the ultrasonic radiating elements 36 may vary widely.

[0111] FIG. 9E shows a cross-sectional view of distal extrusion 60 taken along line M-M of FIG. 9D. The drainage holes 20 are, in the embodiment shown, longitudinal gaps in the external surface of the distal extrusion 60. As can be seen in FIG. 9E, the distal extrusion 60 contains four drainage holes 20, each positioned approximately 90 degrees apart circumferentially. In other embodiments, two or three longitudinal drainage holes may be employed. In exemplary embodiments, five or more longitudinal drainage holes may be used.

[0112] FIGS. 10A-D show another embodiment of an ultrasonic catheter. As with FIGS. 9A-F, a spiral groove extrusion 56 provides the structural support to the flexible tubular body 16. Sleeve 58 is dimensioned to fit over the spiral extrusion 56. In the embodiment shown, the distal extrusion 60 has been excluded. Instead, the spiral extrusion 56 includes at its distal end drainage holes 20. Additionally, sleeve 58 also contains holes 70 designed to align with the drainage holes 20 of the spiral groove extrusion 56. In some embodiments, the spiral extrusion 56 and sleeve 58 may be joined before drainage holes 20 are drilled through both layers. Wires 38 are connected to ultrasound radiating elements 36. In the embodiment shown, the ultrasound radiating elements 36 and wires 38 are arranged to lie between the spiral extrusion 56 and the sleeve 58. As discussed above, the wires may be arranged in various other configurations. In certain embodiments, the wires may be arranged to lie within the spiral groove.

[0113] FIG. 10C shows a cross-sectional view of the proximal region of the ultrasonic catheter taken along line P-P of FIG. 10B. The outer diameter 64 of the flexible tubular body 16 may be approximately 0.2 inches (5.08mm). In certain embodiments, the outer diameter 64 may be approximately 0.197 inches (5.0038mm). The inner diameter 66 of the

flexible tubular body 16 may be approximately 0.01 inches (0.254mm). In certain embodiments, the inner diameter 66 may be approximately 0.098 inches (2.4892mm). As described above, the dimensions of the inner and outer diameters may vary based on the intended application.

[0114] As can be seen in FIG. 10D, in certain embodiments the spiral groove may become straight at the distal region 12 of the catheter. In this arrangement, the straightened region permits drainage holes 20 to be drilled in an arrangement of rows. Additionally, ultrasonic radiating elements 36 and wires 38 may be arranged to lie within the straight portion of the groove.

[0115] FIG. 11A-I show an ultrasonic catheter assembly according to one embodiment, in which a coaxial ultrasonic core is introduced into a separate external drain.

[0116] FIGs. 11A-C illustrate one embodiment of a drain 96. The distal portion 98 of the drain 96 includes drainage holes 100. In a preferred embodiment, the drainage holes 100 may span approximately 3cm along the distal portion 98. In other embodiments, the drainage holes 100 may span shorter or longer distances, as desired. The drain 96 comprises an elongate tubular body 102, and may include distance markers 104. Distance markers 104 may be, for instance, colored stripes that surround the drain. In other embodiments, the distance markers 104 may be notches, grooves, radiopaque material, or any other material or structure that allows the regions to be visualized. The distance markers 104 may be spaced apart at regular intervals, for instance, every 2cm, 5cm, or other distance. In other embodiments they may be spaced in gradually increasing intervals, gradually decreasing intervals, irregularly, or in any other manner. In some embodiments, the distance between each marker will be written onto external surface of the drain. The presence of distance markers 104 may advantageously facilitate careful placement of the drain at a treatment site. In modified embodiments, a suture wing may be positioned at about 6 inches (15.24cm) along the length of the catheter. Allowing a physician to visually observe the distance that the drain is advanced may improve control and placement precision.

[0117] The drain 96 includes a central lumen 106 which allows for the free flow of liquids from the drainage holes 100 towards the proximal portion 108 of the drain. As will be discussed in more detail below, in certain embodiments, any number of therapeutic compounds may be passed through the lumen 106 and out the drainage holes 100, where they then enter a treatment site. The diameter of the lumen may be

ultrasound energy can be randomized or varied according to complex non-linear algorithms in order to enhance the efficacy of the ultrasound treatment.

[0148] Drug delivery can be controlled by monitoring, for example, byproducts of the metabolized drug. For example, in the treatment of blood clots with lytic compounds, lysis byproducts such as D-dimer in the effluent evacuated from the blood clot can be monitored. A high and/or increasing concentration of D-dimer in the effluent can indicate that lysis of the blood clot is proceeding adequately, and therefore drug delivery can be maintained, reduced or stopped. A low or decreasing concentration of D-dimer in the effluent can indicate that lysis of the blood clot is inadequate or slowing or that the clot is nearly dissolved, and therefore drug delivery can be increased if the clot is not nearly dissolved, and reduced or stopped if lysis is almost complete. Alternatively, the concentration of the drug can be monitored to determine whether more drug should be delivered and whether treatment is complete. In some embodiments involving treatment of blood clots, as lysis of the blood clot proceeds, lytic is freed from the lysed clot, thereby increasing the concentration of lytic in the effluent. Therefore, increased lytic concentration can correlate to lysis completion. One way of determining the concentration of lytic and/or D-dimer in the effluent is to measure the color of the effluent that is evacuated from the blood clot. The redder the effluent, the greater the concentration of lytic and/or D-dimer in the effluent.

[0149] In some embodiments, neuroprotective drugs or agents that assist in the functional recovery and/or the reduction of cell and tissue damage in the brain can also be delivered to the brain and blood clot with the methods and apparatus described above. These neuroprotective drugs or agents can be delivered before, with, or after the delivery of the thrombolytic drugs. Delivery of these drugs using the methods and apparatus described above is particularly useful where the drug delivery through the blood brain barrier is enhanced with ultrasound treatment, or where ultrasound enhances cell penetration by the drug, or where the drug is sonodynamic.

[0150] Another embodiment of an ultrasonic catheter is shown in FIGS. 16A-E. Similar to the embodiments described above with respect to FIGS. 2A-D, the catheter includes wires 38 embedded within the wall of the tubular body 16. The wires 38 are connected to and may control ultrasonic radiating elements 36 located within the distal region 12 of the catheter 10. The wires extend from the proximal end of the tubular body 16. In certain embodiments, the wires extend more than six inches (15.24cm) from the proximal

WHAT IS CLAIMED IS:

1. A method of delivering compounds to a target region, comprising the steps of:

advancing an ultrasound catheter to the target region, the ultrasound catheter comprising two or more ultrasound radiating elements and a first passage , wherein the two or more ultrasound radiating elements are spaced apart longitudinally along the ultrasound catheter;

introducing a first therapeutic compound to the target location via the first passage; and

sequentially activating the two or more ultrasound radiating elements such that the first therapeutic compound is directed to a first target area.

2. The method of Claim 1, wherein the step of sequentially activating the two or more ultrasound radiating elements comprises alternately activating adjacent ultrasound radiating elements such that at least a portion of the fluid proximate a proximal-most ultrasound radiating element flows distal the activated ultrasound radiating elements.

3. The method of Claims 1 or 2, wherein the step of sequentially activating the two or more ultrasound radiating elements comprises alternately activating adjacent ultrasound radiating elements such that at least a portion of the fluid proximate a distal-most radiating element flows proximal the activated ultrasound radiating elements.

4. The method according to any of Claims 1 to 3, wherein the step of sequentially activating the two or more ultrasound radiating elements comprises simultaneously activating two or more ultrasound radiating elements such that at least a portion of the fluid remains between the activated ultrasound radiating elements.

5. The method according to any of Claims 1 to 4, wherein step of introducing a first therapeutic compound into the target region comprises activating a first pump in fluid communication with the first passage.

6. The method according to any of Claims 1 to 5, further comprising synchronizing the activation of the two or more ultrasound radiating elements with the activation of the first pump such that the first therapeutic compound is directed to the first target area

7. The method according to any of Claims 1 to 6, wherein the ultrasound catheter further comprises a second passage.

~~8. The method of Claim 7, further comprising draining fluid from the cavity through the second passage.~~

~~9. The method according to Claim 7, further comprising introducing a second therapeutic compound into the cavity via the second passage and sequentially activating the two or more ultrasound radiating elements such that the second therapeutic compound is directed to a second target area.~~

~~10. The method according to any of Claims 1 to 9, further comprising increasing the permeability of the target region using at least one of the first and second ultrasound radiating elements.~~

CLAIMS

~~11~~1. An apparatus for delivering drugs to a target region, the apparatus comprising:

an ultrasound catheter comprising:

a tubular body comprising a first lumen;

two or more ultrasound radiating elements spaced apart longitudinally along the tubular body; and

a first passage in fluid communication with the lumen; and

a processing unit, the processing unit configured to selectively activate ultrasound radiating elements to control the flow of a fluid surrounding the ultrasound catheter.

~~12~~2. The apparatus of Claim ~~11~~1, further comprising a pump in fluid communication with the lumen, the pump configured to pump a first therapeutic compound through the lumen and out of the first passage.

~~13~~3. The apparatus of Claim ~~11~~1 or ~~12~~2, further comprising a second passage in fluid communication with a second lumen.

~~14~~4. The apparatus of Claim ~~13~~3, further comprising a second pump in fluid communication with the second lumen.

~~15~~5. The apparatus of Claim ~~11~~1, wherein the processing unit is configured to alternately activate adjacent ultrasound radiating elements such that at least a portion of the fluid proximate a proximal-most ultrasound radiating element flows distal the activated ultrasound radiating elements.

~~16~~6. The apparatus of Claim ~~11~~1, wherein the processing unit is configured to alternately activate adjacent ultrasound radiating elements such that at least a portion of

the fluid proximate a distal-most radiating element flows proximal the activated ultrasound radiating elements.

~~17~~7. The apparatus of Claim ~~11~~1, wherein the processing unit is configured to simultaneously activate two or more ultrasound radiating elements such that at least a portion of the fluid remains between the activated ultrasound radiating elements.