(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 February 2009 (12.02.2009)

PCT

(10) International Publication Number
WO 2009/021111 A1

(51) International Patent Classification:
A61M 37/00 (2006.01)

(21) International Application Number:
PCT/US2008/072468

(22) International Filing Date: 7 August 2008 (07.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/954,602 8 August 2007 (08.08.2007) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** FLOW IMPROVEMENTS FOR DELIVERY OF BIOMATERIALS

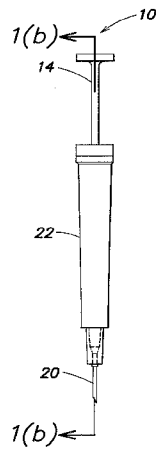

FIG. 1(a)
(Prior Art)

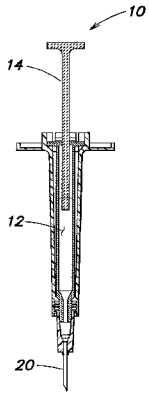

FIG. 1(b)
(Prior Art)

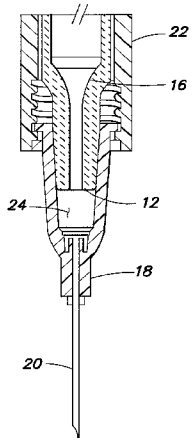

FIG. 1(c)
(Prior Art)

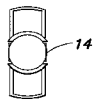

FIG. 1(d)
(Prior Art)

(57) **Abstract:** A delivery system for an aqueous solution of a biomaterial or a mixture of a biomaterial and a biocompatible fluid lubricant includes a syringe and a needle or a needle and catheter combination. A contoured nozzle connects the syringe to the needle and reduces the required plunger force to expel the solution from the needle. An ultrasonic transducer generates acoustic pressure pulses and waves in the solution. The acoustic radiation force of the acoustic field aligns the particles within the solution in the direction of the syringe axis and facilitates expulsion. Also, the acoustic radiation force changes the shape of the biomaterial into oblong shapes, thereby reducing the required expulsion force. Further, the vibratory excitation of the biomaterial by the ultrasonic field facilitates expulsion of the solution. Large pressure pulses may deliver droplets of the solution from the needle opening.

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FLOW IMPROVEMENTS FOR DELIVERY OF BIOMATERIALS

PRIORITY INFORMATION

This patent application claims priority from U.S. patent application serial number 60/954,602 filed August 8, 2007, which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

This invention relates in general to a flow delivery system that delivers a material such as a biomaterial into a body, and in particular to such a system for delivery of an aqueous solution containing solely a biomaterial or a mixture of a biomaterial and a biocompatible fluid lubricant, where such a system involves ultrasonic transducers, acoustic pulse and wave propagation, an acoustic radiation force, a contoured nozzle design for flow resistance reduction, and a control system that utilizes feedback control.

Medical procedures often involve the non-surgical implanting of biomaterials into the body. An example is the injecting of a dermal filler material such as collagen through the use of a syringe and needle system. The biomaterial can be solid and load-bearing and is typically suspended as an aqueous solution of the biomaterial particles. The solution is then injected with a syringe through a needle at the desired site. As an example, for precise placement of materials into the facial dermis, a very fine needle, e.g., 27 gauge (0.0075 inch ID) to 30 gauge (0.0055 inch ID), is preferred. These relatively small ID needles limit the diameter of the suspended particles that may pass through the needle orifice. The diameter of the particle will typically range from 1-20 microns. The size of the deformable asymmetric particles will usually be 500-800 microns in length and less than 20 microns in width. It has been determined that larger

particles are desirable in some situations. However, the larger particles pose a problem when used with the smaller needles required in the facial derma. The larger particles can bridge or agglomerate resulting in clogging of the small orifice needle. Larger particles also result in a greater amount of force needed to translate the syringe plunger. The higher force may cause the surgeon to tremble and slight perturbations of the hand could result in scaring of the patient. Therefore, it is desirable to have applied forces equivalent to a low viscidity Newtonian fluid.

Other applications for implanting a biomaterial into the human body include use of the biomaterial as a bulking or augmenting agent in internal body tissue, such as the tissue that defines various sphincters, for example, in the urinary tract (specifically, in the urinary outflow of the bladder into the urethra) or in the lower esophageal area connecting the esophagus to the stomach. The malfunctioning of these sphincters is usually in the form of improper or incomplete closure of the sphincters, which leads to medical conditions such as urinary incontinence and gastroesophageal reflux disease (GERD) or heartburn, respectively. Treatment of these medical conditions may include injections of a viscous material dispersed in a solution, such as collagen, in the vicinity of the associated sphincter to augment or bulk up and fortify the tissue and thereby assist in the adequate closure of the corresponding sphincter for re-establishment of normal sphincter control. Still other applications for implanting a biomaterial such as collagen into the human body include various other body passages and tissues; for example, for correcting wrinkles not only in the facial derma but in other areas of the body as well.

In these applications it is known to inject the biomaterial, typically suspended in an aqueous solution, into the human body through use of an elongate needle and/or

catheter. This type of flow delivery system may be used as a standalone device or in combination with an appropriate medical instrument, such as a cystoscope, endoscope or gastroscope, which instruments are utilized to view the tissue in the affected area. However, as the length of the elongate needle and/or catheter increases, the amount of force required to properly deliver the suspended mass aqueous solution of biomaterial to the desired body tissue area also increases. With known flow delivery systems, this increased amount of required force can cause problems both with the extrusion of the biomaterial through the flow delivery system and also with the intrusion of the biomaterial into the tissue. Oftentimes poor intrusion into the body tissue is the result of poor extrusion through the flow delivery system.

There has been substantial research and experimentation in various chemical compositions to reduce plunger force in a syringe and needle and/or catheter flow delivery system. An area commonly researched is the ability to introduce lubricity between the particles through use of an aqueous suspension of a particulate biocompatible material and a biocompatible fluid lubricant. The biomaterial and lubricant are typically combined in a manner that results in a homogenous mixture. It is believed that the lubricant enhances flow in part by preventing particle to particle contact. See, e.g., U.S. Patent No. 4,803,075. However, a disadvantage of the addition of the lubricant is that it reduces the content of the active component in solution.

FIG. 1, including FIGs. 1(a)-1(d), are various views of a prior art syringe and needle flow delivery system 10. The syringe 12 is made of glass and typically comprises a larger ID section into which the plunger 14 fits. At the nozzle or discharge end of the syringe 12 is a tapered section 16 that significantly reduces the cross section of the

syringe 12 at that location. A plastic housing 18 contains a needle 20, which may also include a catheter as an integral part thereof or as a separate component connected therewith, and is fitted over the glass syringe 12. The glass syringe/plastic housing assembly is held in place by an outer plastic sleeve 22 into which the plastic housing 18 is screwed. The glass syringe 12 is also held in place inside the outer plastic sleeve 22. A significant disadvantage of this prior art embodiment is the lack of a smooth continuous transition from the narrow opening of the glass syringe 12 into the distal end of the needle 20. In this configuration, there is a large plenum 24 located between the exit opening of the glass syringe 12 and the distal opening of the needle 20. This plenum 24 prevents the smooth and continuous operation of the syringe/needle system 10. When the physician pushes the plunger 14 to inject the filler material, the filler material is first squeezed through the narrow constriction at the exit of the glass syringe 12, then the material will expand into the larger plenum 24, and the filler material is squeezed again to enter the needle 20. Measurement of the force necessary to push the filler material through this prior art syringe/needle flow delivery system 10 has demonstrated a significant oscillatory behavior, typically disliked by the physician, along with elevated force levels. This force requirement derives from the existence of the plenum 24 between the needle 20 and the glass syringe 12.

What is needed is an improved flow delivery system for implanting a biomaterial into the human body, where the system has continuously smooth transitions within physical components of the system. What is also needed is such a flow delivery system that utilizes an ultrasonic transducer to assist in the expulsion of the biomaterial out from the system and into the human body.

SUMMARY OF THE INVENTION

Briefly, according to an aspect of the present invention, a flow delivery system includes a syringe and a needle and/or a catheter that delivers an aqueous solution of a material, such as a biomaterial or a mixture of a biomaterial and a biocompatible fluid lubricant, preferably at a constant applied force. The force required to flow the solution is significantly reduced compared to prior art flow delivery systems. In one embodiment, continuous and smooth transitions at various locations in the cross-sectional area of the physical structure of the flow delivery system reduce the flow resistance and thus reduce the force necessary to transport and expel the material through the system. The transitions include those located at the nozzle within the syringe and the transition between the proximal end of the syringe and the distal end of the needle.

In another embodiment, a contoured nozzle connects the main body of the syringe to the distal end of the needle. The contoured nozzle is designed to reduce the steady resistance to the flow of the solution through the syringe. To achieve a steady flow velocity of the solution through the syringe, a smaller force is necessary compared to that in a prior art needle/syringe flow delivery system operating at the same steady velocity. The contoured nozzle may also function as an acoustic horn. Acoustic waves and pulses generated in the solution within the syringe body propagate towards the junction between the needle and the syringe. The contoured nozzle allows for transmission of the acoustic waves or pulses into the needle. The cross-sectional area reduction from the syringe to the needle serves as a mechanical amplifier of the acoustic pressure amplitude. Therefore, the contoured nozzle functioning as an acoustic horn allows for the

transmission and amplification of acoustic waves and pulses into the needle. Without such a design of the acoustic horn, most of the acoustic energy would be reflected back into the syringe body and would not be transmitted into the needle. An example of a preferred contoured nozzle design is that of a cosine function profile.

According to another embodiment of the present invention, an ultrasonic transducer is fitted or disposed around the casing surrounding the syringe body and is used to excite radial acoustic waves in the solution within the syringe. The ultrasonic transducer is tuned to a radial resonance frequency of the syringe cavity. Relatively high amplitude acoustic waves can be achieved in this manner. The acoustic radiation force exerted by the acoustic field on the suspended particles in the solution can be used to align the particles in circle shaped patterns at the stable locations of the acoustic radiation force. The same ultrasonic transducer can be driven in a periodic frequency sweeping pattern that translates the suspended particles towards the center of the syringe. Aligning the particles in the center of the syringe channel will enhance the expulsion of the particles out through the needle. In addition, the same ultrasonic transducer can be driven by a modulated frequency signal that results in shape changes of the suspended particles; for example, into oblong shapes. Through frequency control it is possible to deform the suspended particles into elongated particles, i.e., along the syringe axis, which will be easier to extrude out from the needle. This reduces the force required for extrusion. Still further, the same ultrasonic transducer can be used to send a relatively strong compressive pulse which propagates down the syringe into the needle and ultimately reaches the proximal end of the needle. The strong pulse creates a large velocity of the solution in the vicinity of the needle to generate an outflow of solution from the syringe

into the human body. A subsequent weaker expansion wave may be used to bring the system back to equilibrium, after which a second compressive pulse is used to send a second stream of solution into the human body. This action of the ultrasonic transducer results in a pulsed flow of the solution flowing from the syringe into the human body, without the need of an external applied force. Thus, the mechanical plunger typically utilized in a syringe can be eliminated.

In an alternative embodiment, the ultrasonic transducer is disposed inside the syringe such that it functions as the plunger of the syringe. This allows the plunger to be omitted as no mechanical force from the plunger is required to transport and expel the particle containing solution. The ultrasonic transducer excites axial acoustic waves or pressure pulses in the solution within the syringe and needle. Similar to the previous embodiment, a strong pulse can be generated by the transducer resulting in a pulsed flow of the solution exiting from the needle opening.

The ultrasonic transducer can also be used as a sensor. The signal received by the ultrasonic transducer can then be employed in a feedback control system. The feedback control system allows the operation of the syringe in constant force mode which facilitates the operation of the system by a physician such that the physician merely applies a small constant force to deliver the solution. The feedback control system drives the amplitude of the ultrasonic actuator, which assists in the delivery of the solution as needed and on command. A similar control system can be employed to deliver the solution at constant speed.

These and other objects, features and advantages of the present invention will become more apparent in light of the following detailed description of preferred embodiments thereof, as illustrated in the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1, including FIGs. 1(a)-1(d), are various views of an embodiment of a prior art syringe/needle flow delivery system;

FIG. 2 is a cross-sectional view of an embodiment of a flow delivery system of the present invention having a syringe with a contoured nozzle and a needle;

FIG. 3 is detailed cross-sectional view of the contoured nozzle of FIG. 2;

FIG. 4, including FIGs. 4(a)-4(d), are various views of another embodiment of the flow delivery system of the present invention having a contoured nozzle separate from the syringe;

FIG. 5, including FIGs. 5(a)-5(b), are various views of another embodiment of a flow delivery system of the present invention having an ultrasonic transducer disposed around the syringe body;

FIG. 6, including FIGs. 6(a)-6(b), are graphs of exemplary voltage waveforms used in a pulsed flow application of the ultrasonic transducer of FIG. 5;

FIG. 7, including FIGs. 7(a)-7(b), are various views of another embodiment of a flow delivery system of the present invention having an ultrasonic transducer disposed within the syringe body; and

FIG. 8 is a view of the flow delivery system of FIG. 5(b) employing feedback control to maintain constant force.

DETAILED DESCRIPTION OF THE INVENTION

In the figures, like reference numerals refer to like elements. Referring to FIGs. 2 and 3, there illustrated is an embodiment of a flow delivery system 30 which reduces the amount of plunger force required to transport and expel an aqueous solution of solely a biomaterial or a mixture of a biomaterial and a biocompatible fluid lubricant into, e.g., a human body at a desired location, such as, for example, the facial derma or a sphincter; specifically, the sphincter associated with the urinary tract or with the esophageal tract. The biomaterial may comprise collagen or other known materials used as bulking agents to augment or build up the tissue in the desired area to correct for improper sphincter operation or to cure cosmetic defects (e.g., wrinkles). The biocompatible fluid lubricant may comprise a non cross-linked collagen or other known materials that form a homogeneous mixture with the preferred biomaterial. Typically the amount of lubricant required in the mixture with the biomaterial is that which provides for proper intrudability of the biomaterial into the internal body tissue at the desired location and which also provides for proper extrudability of the biomaterial through and out from the flow delivery system.

The system 30 incorporates a syringe (e.g., preferably cylindrical and made from glass) with both a nozzle portion 32 and a geometrically smooth transition portion 34 located where the converging section of the syringe 12 meets the distal end of the needle 20. The syringe/needle flow delivery system 30 of FIGs. 2 and 3 includes a syringe 12, a plunger 14, a plastic housing 18 that contains the needle 20, and an outer plastic casing 22 that holds together the syringe 12 and the needle 20. The needle 20 may also include

a catheter formed as an integral portion of the needle as an extension thereof. Alternatively, the catheter may be connected at an exit end of the needle. Thus, any reference herein to the needle 20 also includes reference to a catheter. In this embodiment, the nozzle 32 and smooth transition portion 34 are both preferably integral portions of the syringe 12. Compared with conventional systems, including that of FIG. 1, the flow delivery system 30 of FIGs. 2 and 3 contains a contoured or streamlined nozzle 32 as part of the syringe 12 which together with the smooth transition portion 34 of the syringe 12, reduces resistance to the flow of the solution from the syringe 12 into the needle 20. This facilitates the flow of the solution through the syringe 12 and out from the needle 20. It also reduces the likelihood that the biomaterial particles in the aqueous solution will clog in the needle 20 or catheter or upstream of the needle in the nozzle 32 or transition portion 34. In addition, the distal end of the needle 20 may reside within the syringe 12, as best illustrated in FIG. 3. As compared to the prior art system 10 of FIG. 1, no plenum 24 exists between the opening in the syringe 12 and the distal end of the needle 20. The combination of the nozzle 32 and the smooth transition portion 34 from the syringe 12 into the needle 20, and the lack of the plenum 34, reduces the necessary plunger force required during operation of the flow delivery system 30 of FIGs. 2 and 3.

FIG. 4 illustrates various views of portions of another embodiment of a syringe and nozzle flow delivery system according to an aspect of the present invention. This embodiment includes a contoured or streamlined nozzle 32 separate from the syringe 12 that, when connected with the syringe 12, allows for a smooth and continuous reduction of the internal cross-sectional diameter (ID) of the syringe 12 from the wider section

fitting the plunger 14 to the smaller section with preferably an identical ID as that of the needle 20. The needle 20 fits flush against the nozzle 32, thereby allowing for a smooth and continuous transition from the syringe 12 to the needle 20.

FIG. 5 illustrates another embodiment of a flow delivery system 30. This embodiment is similar to that of FIGs. 2 and 3, except that an ultrasonic transducer 40 is fitted around the outer casing 22 of the glass syringe 12. The ultrasonic transducer 40, when driven by appropriate electrical signals from a controller (e.g., FIG. 8), excites acoustic waves through the wall of the syringe 12 into the solution containing the biomaterial or mixture of a biomaterial and lubricant located inside the syringe 12. The ultrasonic transducer 40 may be tuned to a radial resonance frequency of the syringe cavity. Relatively high amplitude acoustic waves can be achieved in this manner. The acoustic radiation force exerted by the acoustic field on the suspended particles in the solution can be used to align the particles in circle shaped patterns at the stable locations of the acoustic radiation force. The ultrasonic field generated by the transducer 40 facilitates the extrusion of the biomaterial solution through the syringe 12 and out from the needle 20 and, where included, the catheter. This occurs through the combined effects of: (a) vibratory excitation of the suspended particles in the solution; (b) concentration and translation of the particles toward the syringe axis; and (c) shaping the particles into oblong shapes. Periodic frequency sweeping of an ultrasonic standing wave field can also be used to translate the concentrated particles, for example towards the center of the syringe 12. Also, a modulated ultrasonic excitation of the transducer 40 results in deforming the suspended particles in the solution into oblong shapes aligned with the axis of the syringe 12. The streamlined nozzle 32 employed either as an integral

part of, or separate from the syringe 12 acts as an ultrasonic acoustic horn and amplifies the pressure of the wave. The ultrasonic transducer 40 may comprise a piezoelectric transducer. Typical materials that may be used for the piezoelectric transducer include PZT-4 and PZT-8, but other materials may be used. Also, other types of actuators and/or transducers may be used. Typical frequencies of operation may be in the range of 500,000 cycles per second up to several million cycles per second.

A different usage of the embodiment of the flow delivery system 30 of FIG. 5 is that of an ultrasonic pump of the biomaterial or mixture of biomaterial and lubricant contained within the solution in the syringe 12. By applying one of the voltage waveforms illustrated in FIG. 6 to the transducer 40, a relatively strong compressive pulse is generated in the biomaterial. This pulse propagates through the nozzle 32 and into the needle 20. At the end of the needle 20 the compressive pulse accelerates the biomaterial located at the proximal end of the needle 20. When the velocity of the material reaches a certain threshold, the material starts flowing, and a small amount of biomaterial is delivered from the needle 20. The strong compressive pulse is followed by a weaker expansion wave which allows the system 30 to reach equilibrium, and the plunger 14 drops by a small amount to compensate for the solution that has escaped the syringe 12 and the needle 20. The system 30 is then ready for the next compressive pulse and subsequent delivery of the next amount of solution. Usage of the embodiment in this manner results in a pulsed flow system. Another application of this embodiment is as an assisting device to the physician, i.e., it allows the physician to operate the syringe and needle flow delivery system 30 with a smaller externally applied force. The compressive

pulse provides acceleration to the material in the needle and assists the physician in delivering the material.

FIG. 7 illustrates yet another embodiment of the present invention. In this embodiment, the ultrasonic transducer 40 is embedded inside the body of the syringe 12, and functions much like a plunger 14. Through the action of the ultrasonic wave field a reduction in the necessary external force to extrude the biomaterial out from the needle or needle and catheter is achieved. Similar actions are taking place as in the previous embodiments; that is, ultrasonic radiation force, concentration and translation of particles, and vibratory excitation of particles.

It is also possible to use the embodiment of FIG. 7 as a pulsed flow system, when excited by the voltage waveforms of FIG. 6. In this case, the velocity of the biomaterial solution in the proximal end of the needle 20 is sufficient to flow from the needle 20 into the delivery medium. As such, it may be possible to eliminate the use of the plunger 14 or any other type of mechanical force to transport and expel the solution. A second potential use of this system 30 is as an assisting device to the physician which allows the physician to operate the device with reduced external force.

Referring to FIG. 8, the flow delivery system 30 of the present invention may include a controller 50 connected with the piezoelectric transducers 40. Here, the piezoelectric transducer 40 is used during part of the operating cycle as a driver (transmitter) and during another part of the operating cycle as a sensor (receiver). The signal obtained during the sensing mode is sent to the micro-chip controller 50, where a control algorithm varies the voltage sent to the transducer 40 through an amplifier 52 during the driving cycle to maintain a constant force operation of the system 30. In this

way, the physician has to employ a reduced and constant force to inject the biomaterial into the delivery medium. Whenever an increased resistance is sensed by the transducer 40 during the expulsion process, the controller sends an increased voltage signal to the transducer 40 that compensates for the increase in friction force, and thereby allowing the physician to operate the device with the same constant force as he was originally using. A similar type controller 50 may be utilized in an open- or closed-loop system to provide the various driving voltages illustrated in FIG. 6 or may provide the various frequency signals discussed hereinabove in the embodiments of FIGs. 5 and 7 to the ultrasonic transducer 40 to achieve the desired acoustic waves propagating in the flow delivery system 30 of the present invention.

Although the present invention has been illustrated and described with respect to several preferred embodiments thereof, various changes, omissions and additions to the form and detail thereof, may be made therein, without departing from the spirit and scope of the invention.

What is claimed is:

1. A system for delivery of a solution, comprising:

a syringe having a contoured portion at one end with a continuously reducing diameter along at least a portion of a length of the syringe, where the diameter of the syringe in the contoured portion of the syringe is reduced as compared to the diameter of the syringe in other than the contoured portion of the syringe; and

a needle connected to the end of the syringe with the continuously reducing diameter, where the connection between the needle and the end of the syringe forms a smooth and continuous transition;

where the contoured portion of the syringe comprises a streamlined nozzle that reduces resistance to flow of the solution and thus an amount of force required to move the solution through the syringe and needle and facilitates a continuous and smooth transport of the solution from the syringe into the needle.

2. The system of claim 1, further comprising a plunger that provides a mechanical force to propel the solution through the syringe.

3. A system for delivery of a solution, comprising:

a syringe having a body of a diameter and having opposing first and second ends;

a needle having a diameter that is less than the diameter of the syringe; and

a nozzle connected with one of the first and second ends of the syringe, where the nozzle has opposing first and second ends, the first end of the nozzle connected with the second end of the syringe, the second end of the nozzle connected with an end of the needle, where the nozzle has a diameter that reduces in size from the first end of the

nozzle to the second end of the nozzle, where the nozzle reduces resistance to flow of the solution and thus an amount of force required to move the solution through the syringe and needle and facilitates a continuous and smooth transport of the solution from the syringe into the needle.

4. The system of claim 3, further comprising a plunger that provides a mechanical force to propel the solution through the syringe.

5. The system of claim 3, where the nozzle comprises an acoustic horn that amplifies any acoustic waves and/or pulses located in the solution moving through the syringe and thereby facilitates the movement of the acoustic waves and/or pulses in the solution through the nozzle and into the through the needle.

6. The system of claim 5, where the nozzle comprises a cosine function profile.

7. A system for delivery of a solution containing particles of a biomaterial, comprising:

a syringe;

a needle, where the needle is connected to the syringe by one of an end of the syringe at a contoured reducing diameter portion of the syringe and a separate nozzle that is of a contoured reducing diameter and that is connected between the syringe and the needle; and

an ultrasonic transducer connected with the syringe, where the ultrasonic transducer provides radial acoustic waves in the solution within the syringe, where the radial acoustic waves exert a force on the biomaterial particles in the solution within the syringe to thereby effect a change in a characteristic of the biomaterial particles in the solution which facilitates the movement of the particles through and out from the needle.

8. The system of claim 7, where a casing surrounds at least a portion of the syringe, and where the ultrasonic transducer is disposed on an outer surface of the casing.

9. The system of claim 7, where a casing surrounds at least a portion of the syringe, and where the ultrasonic transducer is disposed between a body of the syringe and an inner surface of the casing.

10. The system of claim 7, further comprising a plunger that provides a mechanical force to propel the solution through the syringe.

11. The system of claim 7, where the change in a characteristic of the biomaterial particles in the solution is an alignment of the particles in circle shaped patterns at stable locations of the force exerted by the radial acoustic waves.

12. The system of claim 7, where the ultrasonic transducer is tuned to a radial resonance frequency of a cavity of the syringe.

13. The system of claim 7, where the ultrasonic transducer is driven in a periodic frequency sweeping pattern that translates the biomaterial particles in the solution towards a center of the syringe.

14. The system of claim 7, where the ultrasonic transducer is driven by a modulated frequency that changes the shape of the biomaterial particles in the solution.

15. The system of claim 14, where the changed shape of the biomaterial particles is an oblong shape.

16. The system of claim 7, where the change in a characteristic of the biomaterial particles in the solution is a change in the shape of the particles to an elongated shape that facilitates the passage of the biomaterial particles out from the needle.

17. The system of claim 7, where the ultrasonic transducer is driven to provide a compressive pulse that propagates within the solution in the syringe to thereby increase the velocity of the solution within the syringe and towards the needle.

18. The system of claim 17, where following the ultrasonic transducer being driven to provide a compressive pulse, the ultrasonic transducer is driven with a relatively weaker expansion wave after which the ultrasonic transducer is driven to provide another compressive pulse, thereby resulting in a pulsed flow of the solution flowing from the syringe to the needle.

19. The system of claim 7, where the ultrasonic transducer also provides a sensed signal indicative of a resistance to the flow of the solution within the syringe, where the system further comprises a controller responsive to the sensed signal to provide a signal to the ultrasonic transducer to adjust an amplitude of the acoustic waves provided by the ultrasonic transducer when necessary to achieve a desired amount of the force exerted on the biomaterial particles in the solution.

20. The system of claim 19, where the desired amount of the force is a constant force.

21. The system of claim 7, where the needle includes a catheter formed integral with the needle as an extension thereof or where the catheter is connected at an exit end of the needle, where the solution passes through the needle and the catheter and out from an end of the catheter, and where the radial acoustic waves exert a force on the biomaterial particles in the solution within the syringe to thereby effect a change in a characteristic of the biomaterial particles in the solution which facilitates the movement of the particles through and out from the catheter.

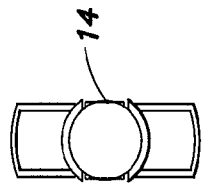

FIG. 1(d)
(Prior Art)

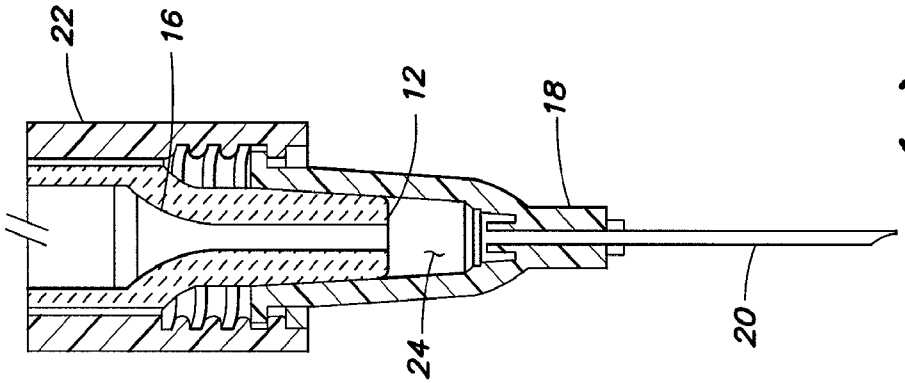

FIG. 1(c)
(Prior Art)

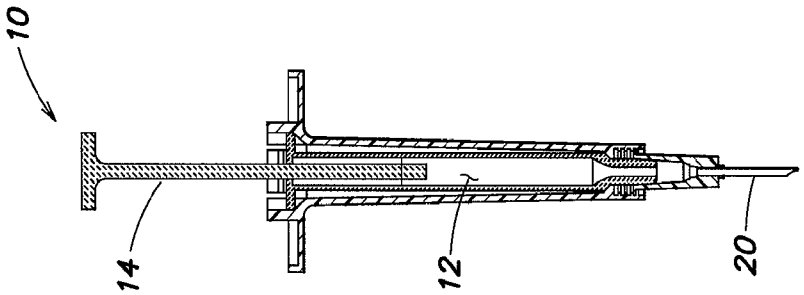

FIG. 1(b)
(Prior Art)

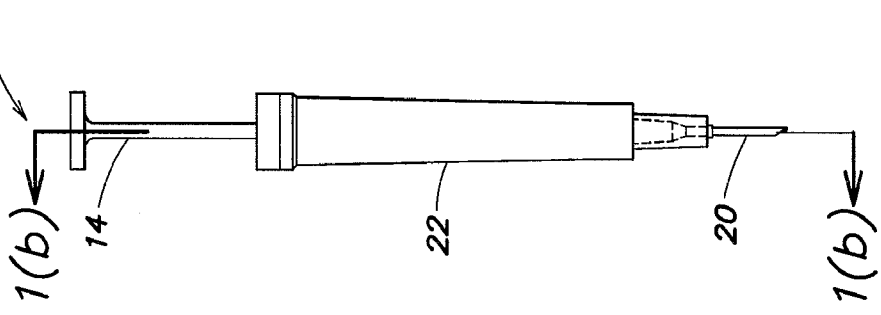

FIG. 1(a)
(Prior Art)

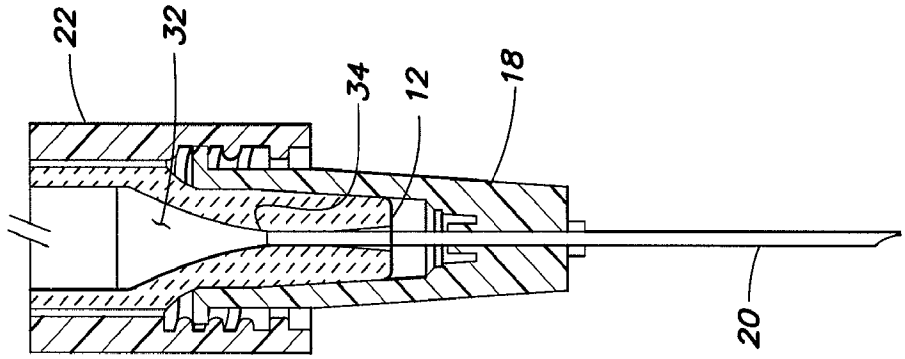

FIG. 3

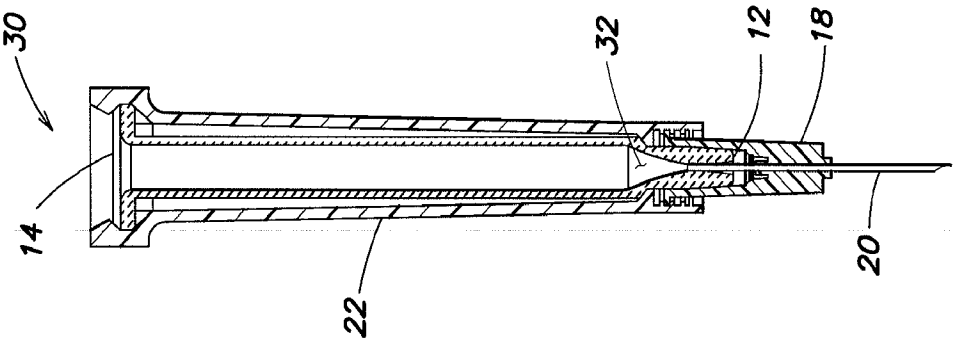

FIG. 2

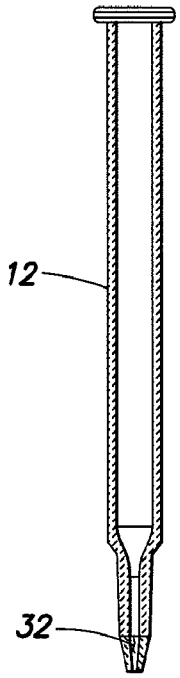

FIG. 4(a)

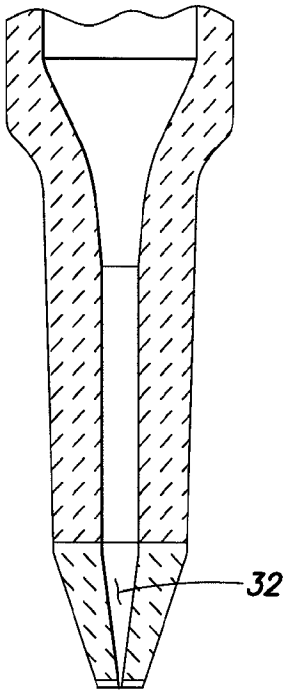

FIG. 4(b)

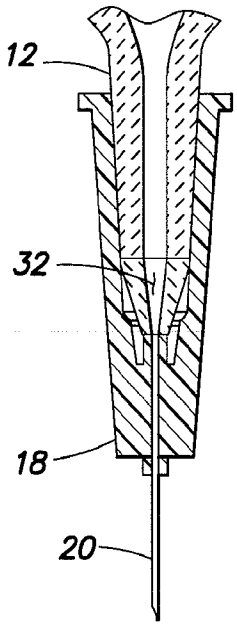

FIG. 4(c)

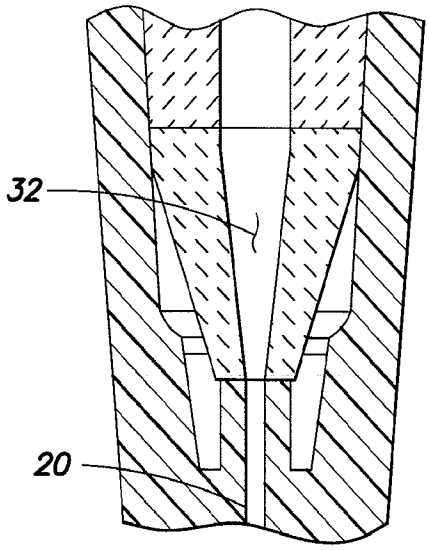

FIG. 4(d)

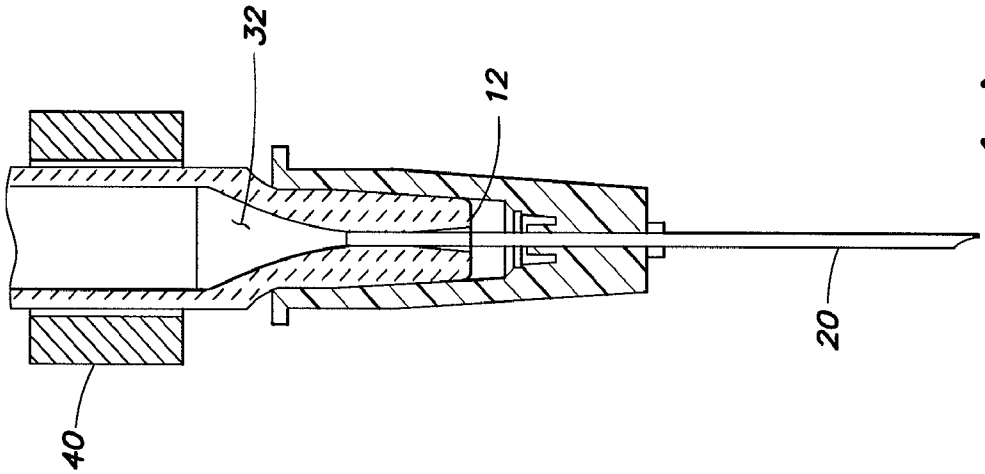

FIG. 5(b)

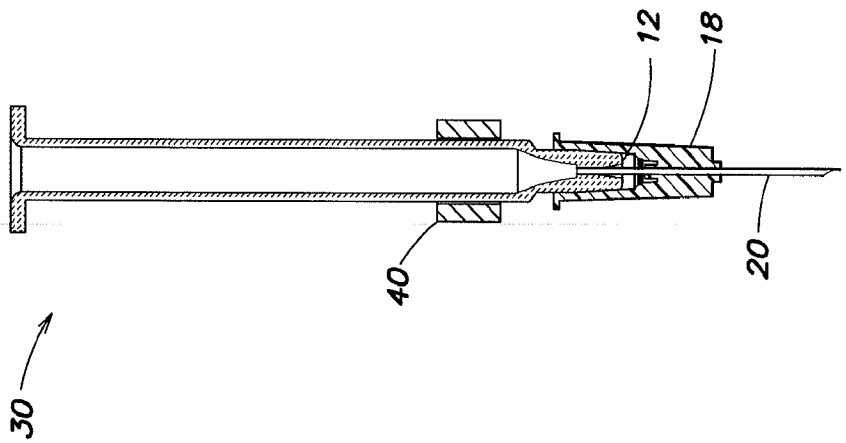

FIG. 5(a)

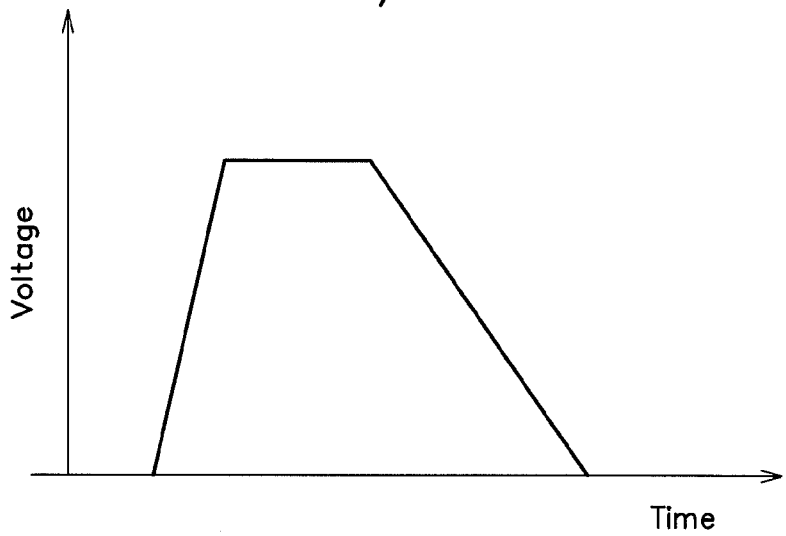

FIG. 6(a)

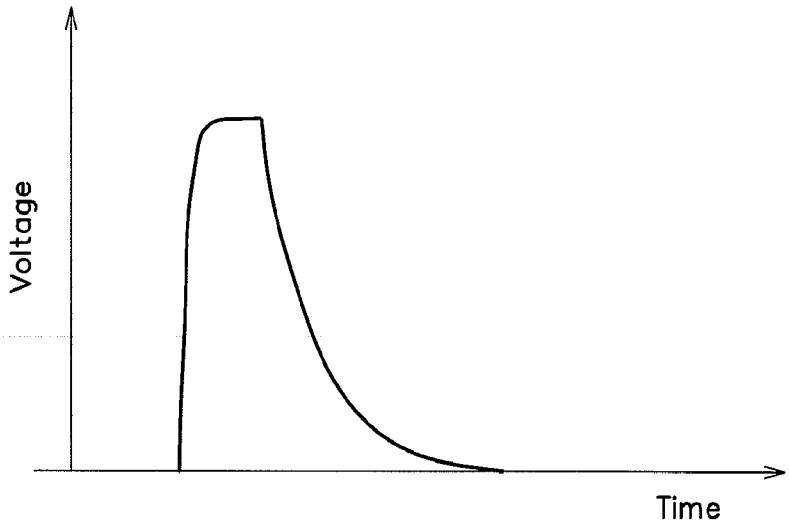

FIG. 6(b)

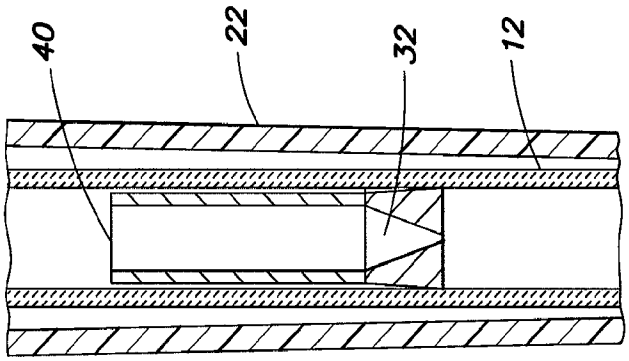

FIG. (b)

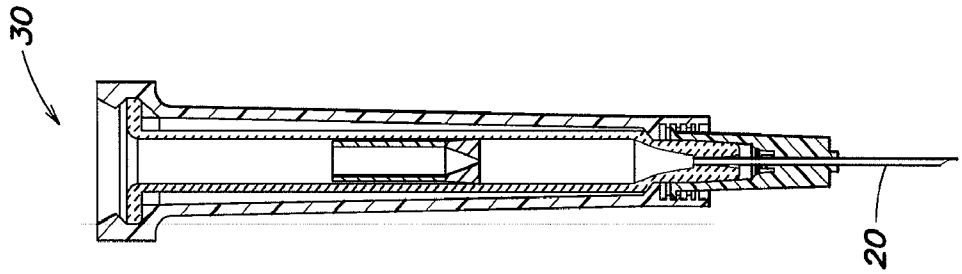

FIG. 7(a)

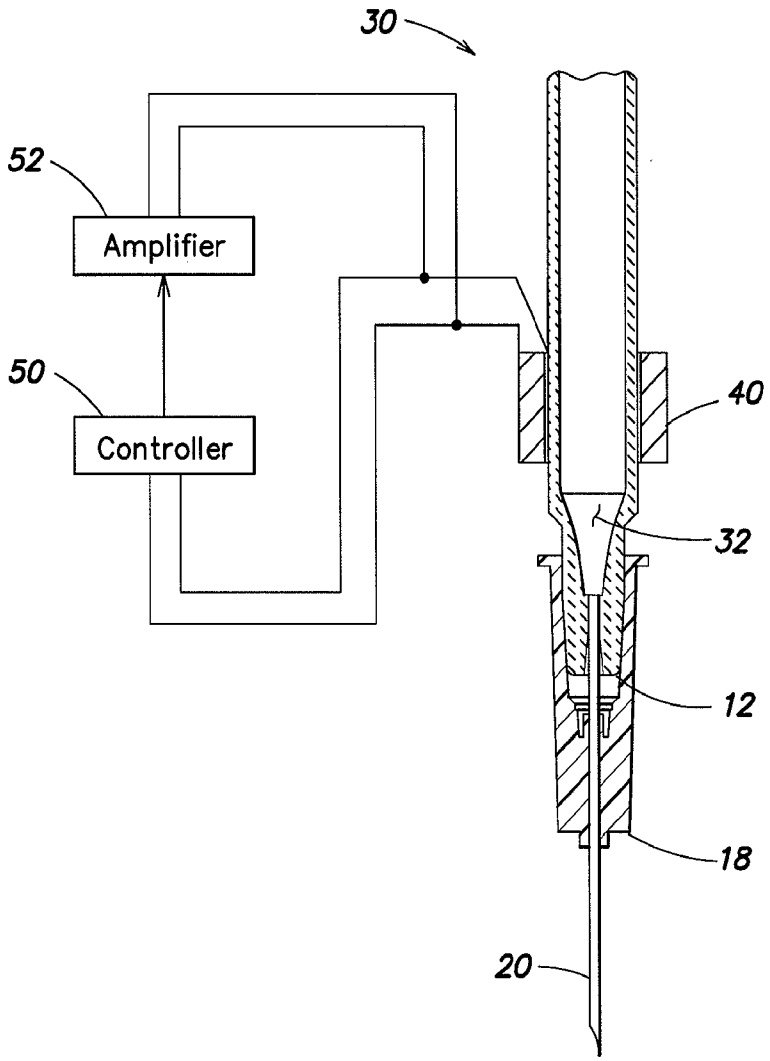

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/072468

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M37/00 (2008.04)
USPC - 604/131
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(8) - A61M37/00 (2008.04)
USPC - 604/131

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 practicable, search terms used)
PatBase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 5,131,394 (GEHLBACH) 21 July 1992 (21.07.1992) entire document.	1-4 — 5-21
Y	US 2003/0229304 A1 (BABAEV) 11 December 2003 (11.12.2003) entire document.	5, 6, 21
Y	US 2006/0000284 A1 (SHERMAN et al) 05 January 2006 (05.01.2006) entire document.	7-21
Y	US 2005/0075620 A1 (IGER) 07 April 2005 (07.04.2005) entire document.	17, 18
Y	US 2003/0221561 A1 (MILO) 04 December 2003 (04.12.2003) entire document.	8, 13
Y	US 2004/0173541 A1 (KURIHARA et al) 09 September 2004 (09.09.2004) entire document.	19, 20
Y	US 2002/0000681 A1 (GUPTA et al) 03 January 2002 (03.01.2002) entire document.	11, 14-16

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"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
22 October 2008	12 NOV 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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