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(54) **ANTI-ADHESION SPRAYING**

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(57) **ABSTRACT**

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Related U.S. Application Data

(60) Provisional application No. 60/554,009, filed on Mar. 17, 2004.

Dry powders containing bioresorbable hyaluraonic acid (“HA”) are applied directly to a desired location in a patient wound to reduce adhesions, without first forming a hydrated gel. HA includes hyaluronic acid that has been modified, cross-linked or combined with other substances. It is important to control the size of the particles in the powder. The powder is essentially dry and blowable powder. At least 90% of powder particles have a maximum dimension between 30 μ m and 1 mm.

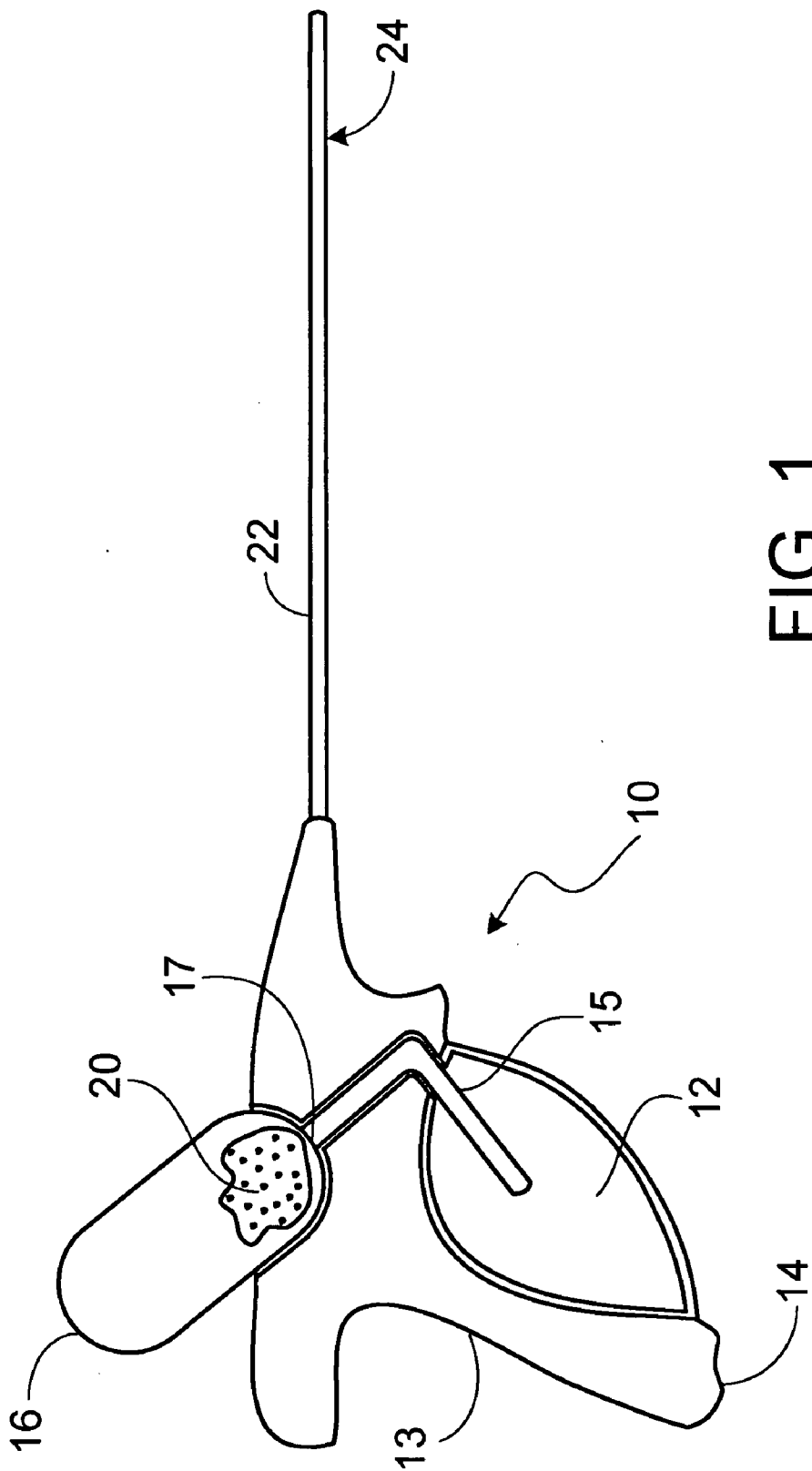


FIG. 1

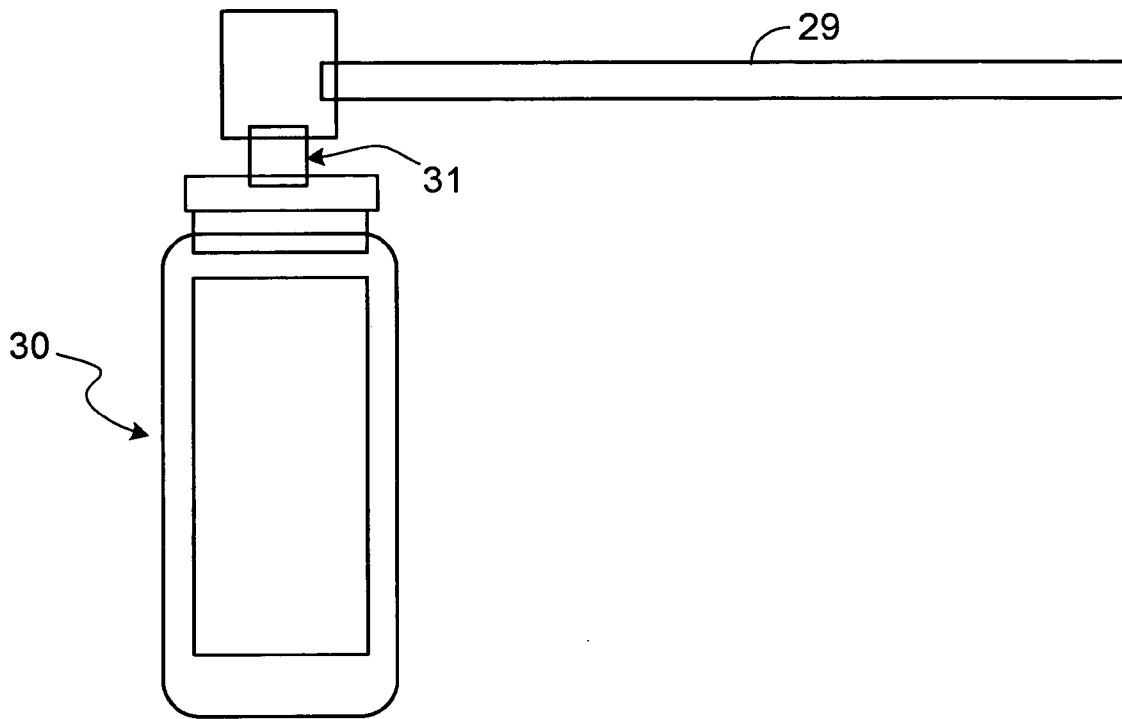


FIG. 2

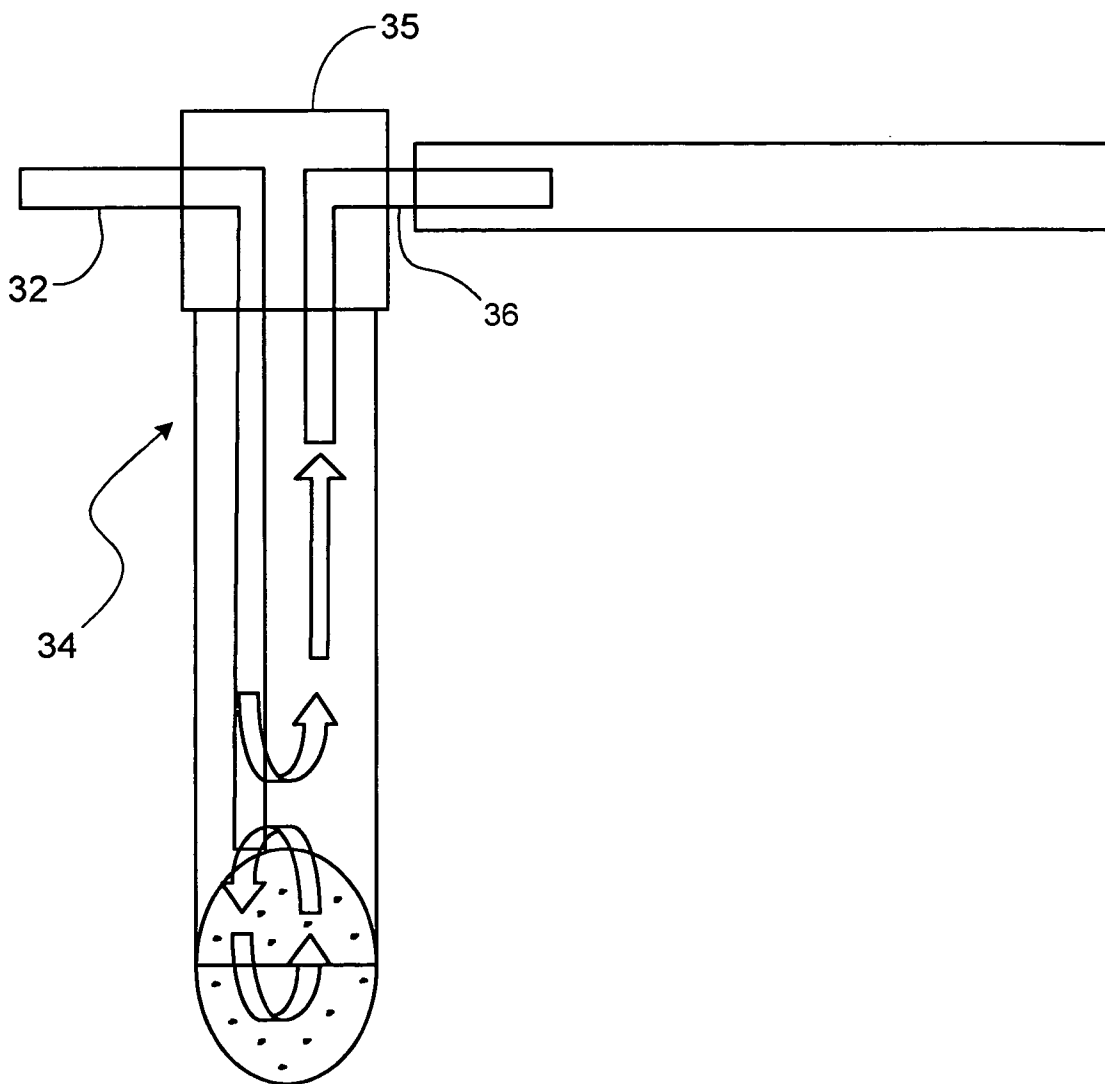


FIG. 3

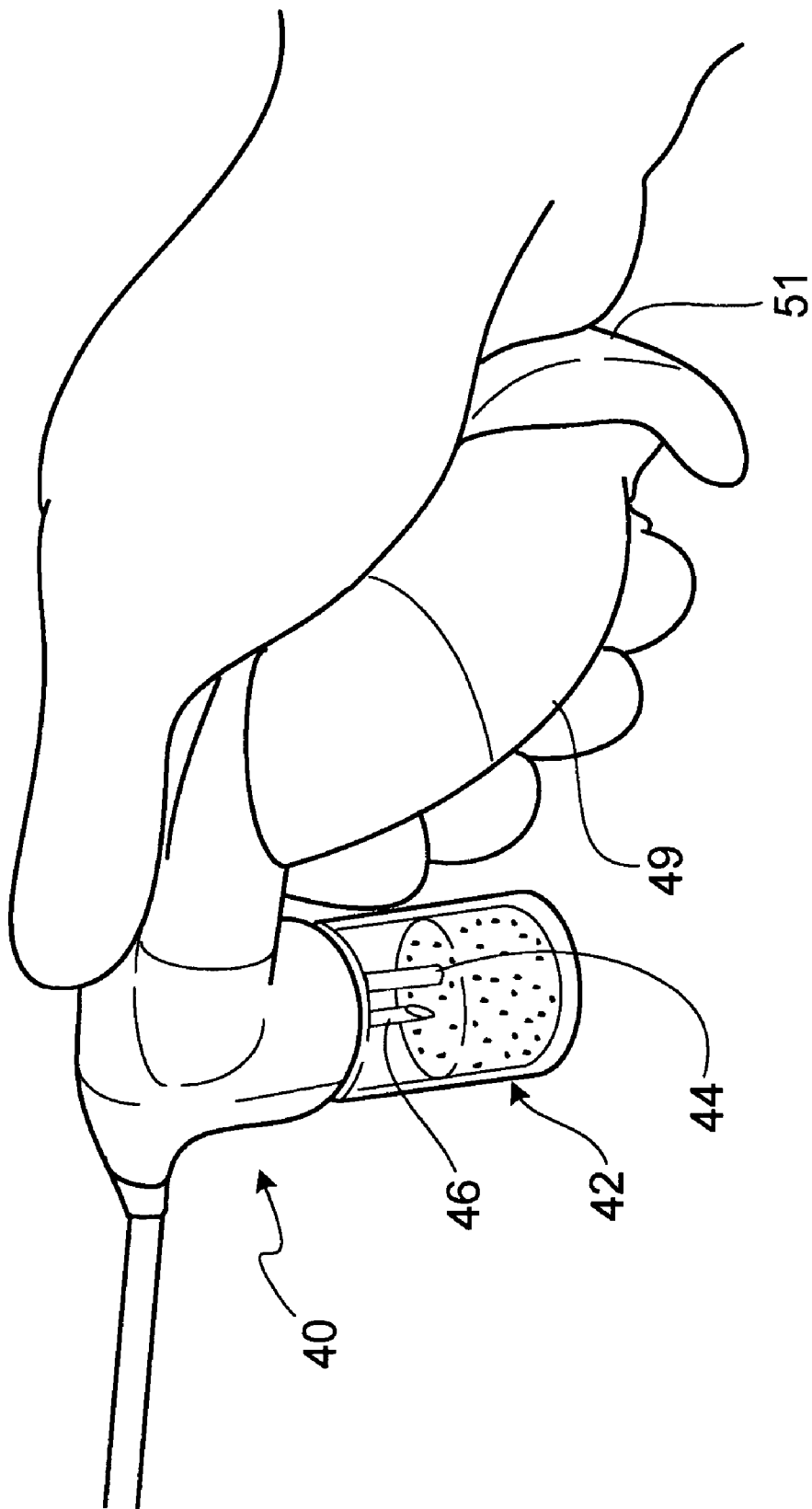


FIG. 4

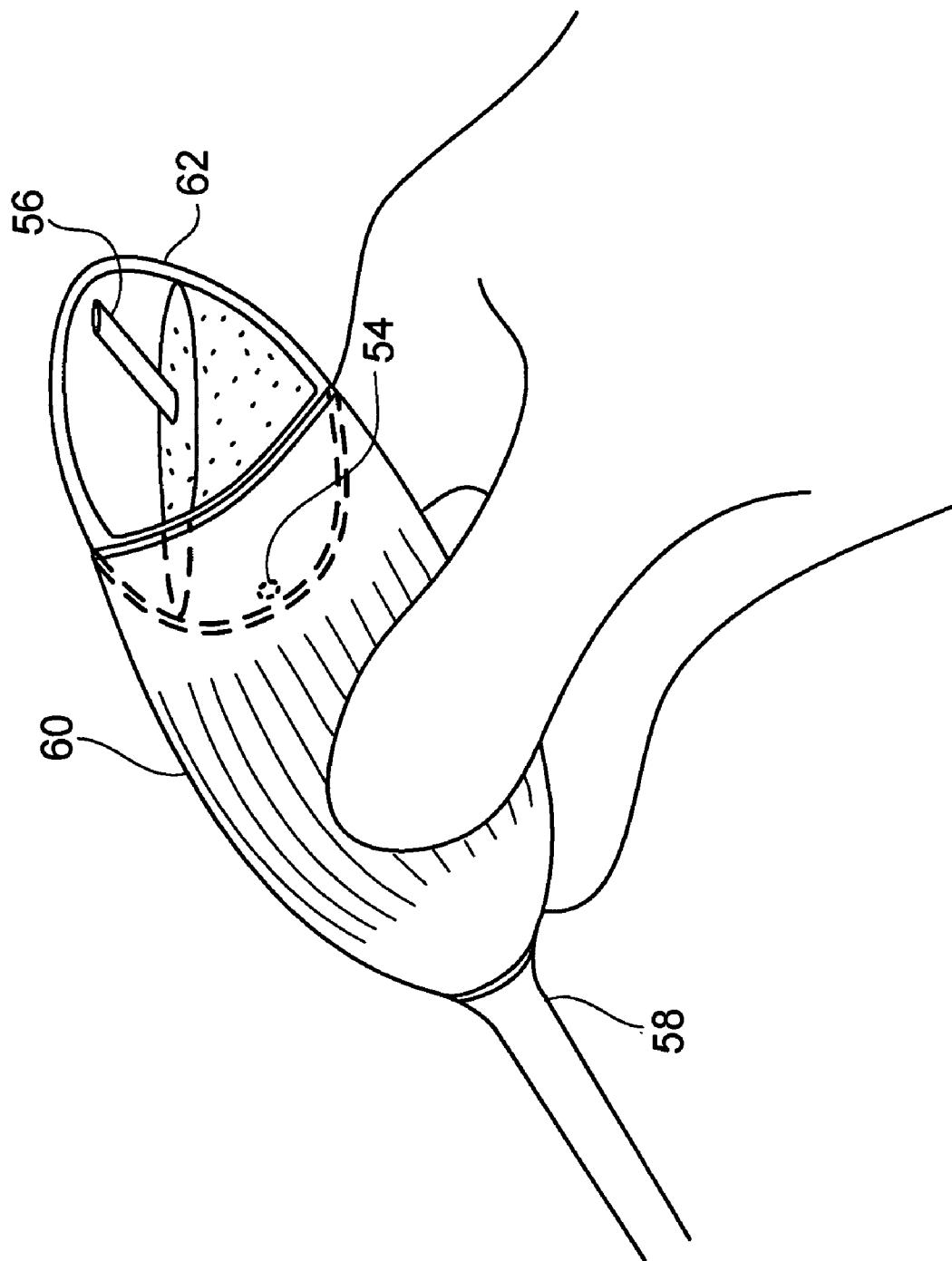


FIG. 5

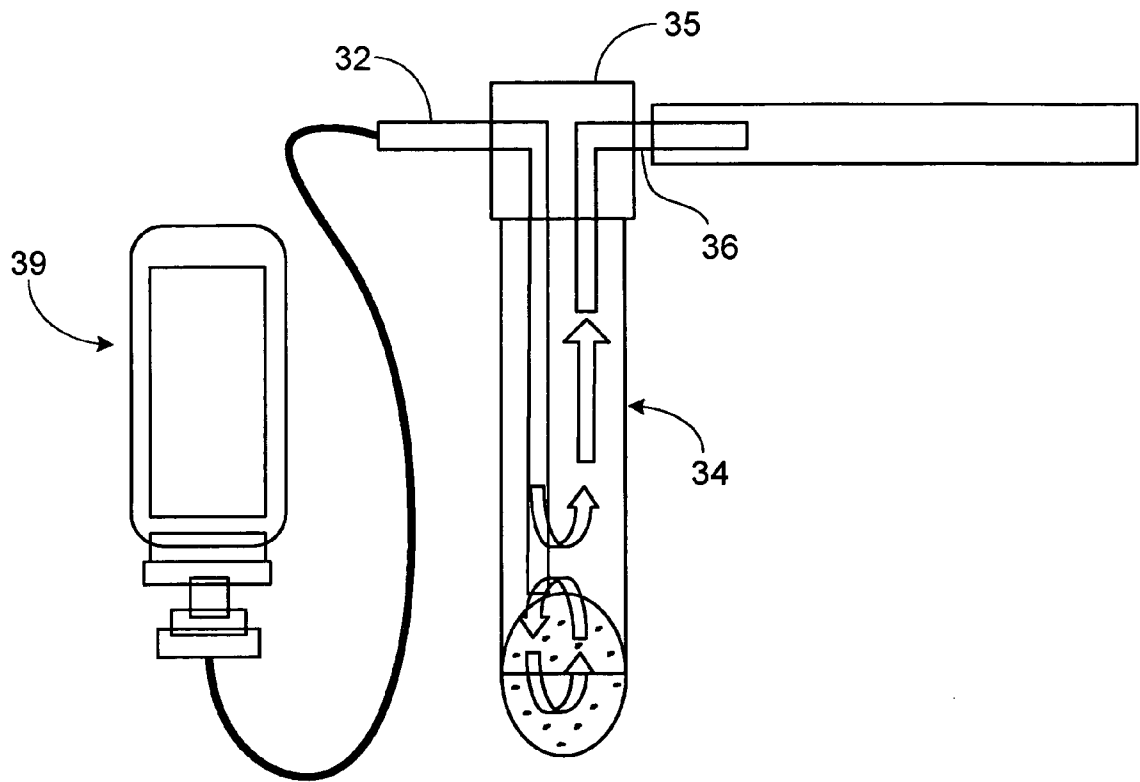


FIG. 6

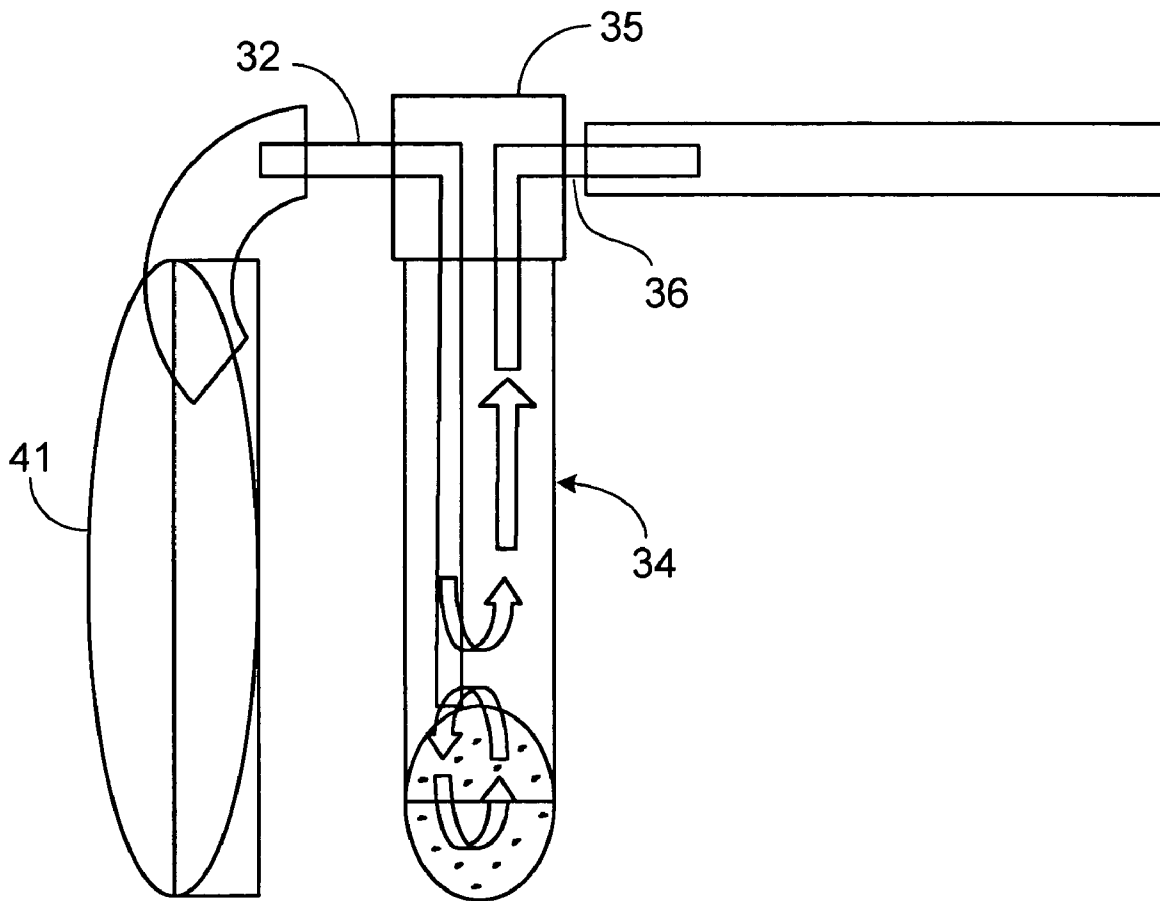


FIG. 7

Sepraspray Process Flow

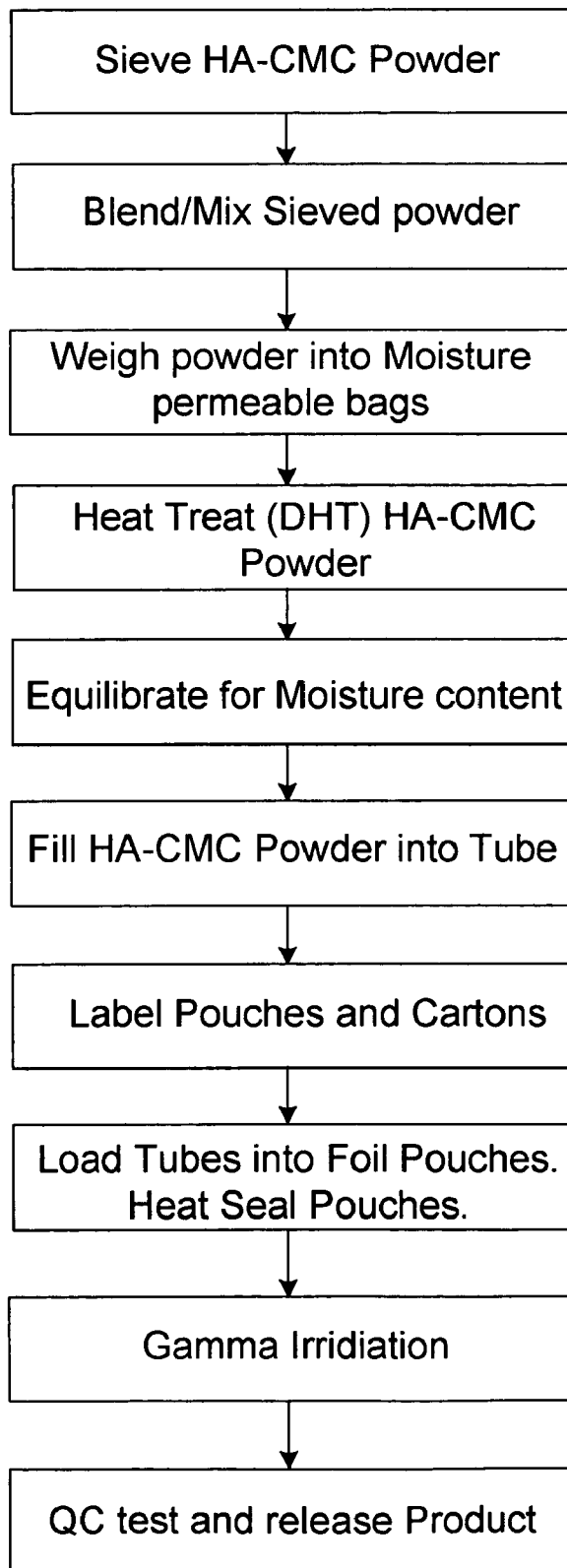


FIG. 8

ANTI-ADHESION SPRAYING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Under 35 U.S.C. §119(e)(1), this application claims the benefit of prior U.S. provisional application 60/554,009, filed Mar. 17, 2004, which is hereby incorporated by reference in its entirety. This application also incorporates by reference in its entirety a U.S. utility patent application, U.S. Ser. No. 11/_____, filed Mar. 17, 2005 by J. Jeffrey Kablik, Andrew Gentile and A. David Boccuti, entitled POWDER DELIVERY DEVICE.

TECHNICAL FIELD

[0002] This invention relates to preventing adhesions, particularly adhesions that form during healing of surgical wounds.

BACKGROUND

[0003] Undesirable tissue scarring can sometimes connect layers of adjacent bodily tissue, or tissues and internal organs, which should not be connected. Such internal scarring, termed adhesions, may form during the healing that follows surgical procedures, preventing the normal motions of those tissues and organs with respect to their neighboring structures.

[0004] Various adhesion prevention compositions have been proposed, such as hydrated gels of high molecular weight carboxyl-containing biopolymers forming a physical barrier to separate tissues from each other during healing so that adhesions between adjacent structures do not form. Desirably, the barrier is bioresorbable, so that it is gradually eliminated after it is no longer needed.

SUMMARY

[0005] We have discovered that dry powders containing hyaluronic acid ("HA") may be applied directly to a desired location in a patient wound to reduce adhesions. Upon application of the powder, in the presence of body fluids and liquids, the dry powder will hydrate to form gel, which acts as an adhesion barrier. HA includes hyaluronic acid that has been modified, cross-linked or combined with other substances. It is important to control the size of the particles in the powder.

[0006] In general, one aspect of the invention features an essentially dry blowable powder comprising bioresorbable HA. "Dry" means having a water content low enough to permit effective entrainment of the particles in a stream of flowing gas, for example less than 25% water by weight. "Blowable" means having a size, moisture content and shape to permit effective and controllable direction of entrained particles in flowing gas. At least 90% of powder particles have a maximum dimension between 5 μm and 1 mm. In preferred embodiments of this aspect of the invention, the powder further comprises carboxymethyl cellulose (CMC), and the HA or CMC or both may be modified to reduce solubility or to enhance anti-adhesive properties of said powder or both. The modification can be such that the powder comprises the reaction product of HA or CMC, or both, with a carbodiimide or a divinylsulfone. Preferably, at least 90% of the powder particles have a maximum dimen-

sion between 70 μm and 600 μm , particularly when the powder is to be applied by spraying.

[0007] In another aspect of the invention, a powder comprising bioresorbable HA, CMC, or both is applied into a location in a wound where adhesion reduction is desired, in a concentration sufficient to reduce adhesions as the wound heals. Preferably, at least 90% of powder particles have a maximum dimension between 5 μm and 1 mm.

[0008] In preferred embodiments of this aspect of the invention, the powder is applied in a mass per area that is greater than 2 mg/cm². Typically the wound is a surgical wound. For example the powder may be applied through an open incision directly to a location within a surgical field where adhesions may be a problem. It may be applied by a sprayer or from a shaker that has a powder reservoir and orifices sized to release powder when the shaker is agitated. The invention may also be used to prevent adhesions during healing of a surgical wound produced by a laparoscopic procedure on a patient. In that case, the powder is applied to the wound via a conduit (trocar cannula) communicating from a first location outside the patient's body to a second location within the patient's body. The invention thus provides an improved way to coat a dry mesh tissue prosthesis with an adhesion barrier via a laparoscopic device. Once the mesh is in place in the wound, the powder is then applied to a surface of the mesh via the exit conduit.

[0009] More generally, the above method can be used to coat a tissue prosthesis (e.g. a mesh) that has already been positioned in the wound. For example, adhesions that may form around the edge of the prosthesis are controlled by coating the edges of the prosthesis in situ. Tacks or stitches in the prosthesis may also be coated to reduce adhesions at those locations. Alternatively, the prosthesis may be positioned in the wound without any barrier layer, and then covered with powder. Preferably the prosthesis is saturated with an aqueous solution before the powder is applied.

[0010] According to one aspect of the invention, the powder is entrained in airflow passing through a chamber containing the powder. The resulting airflow with entrained powder is directed to the location. The airflow may be provided by a hand powered air pump or a squeeze bulb or by a source of pressurized gas in a hospital operating room. The entrained powder may be provided to the location via a tubular conduit positioned to carry the powder from the reservoir to the location in the wound. The conduit may include an airflow modifier, such as a swirl inducer positioned in the conduit to impart a radial component to the airflow.

[0011] It is preferable to irrigate the wound location prior to applying the powder to provide liquid for hydrating the powder into a gel.

[0012] Another aspect of the invention features apparatus for delivering powder (such as the above described powder) to a wound. The apparatus includes a powder reservoir connected to an incoming airflow conduit and an exiting airflow conduit. The conduits are connected to the reservoir to entrain powder in airflow that enters through the incoming conduit and exits through the exiting airflow conduit. Airflow may be provided by a hand powered air pump or a squeeze bulb connected to the incoming airflow conduit, and the pump or squeeze bulb may be positioned within a

handgrip to permit the user to hold the apparatus in one hand and, while holding it, to squeeze the pump or bulb and deliver powder from the exiting airflow conduit. Alternatively, the incoming airflow conduit includes a connector for attachment to a hospital operating room gas supply. The exit conduit may include a swirl inducer adding a radial component to airflow velocity. The apparatus may also include a valve positioned upstream of the reservoir to prevent backflow from the reservoir. The reservoir may be removable, so that after use, the spent reservoir can be replaced with a reservoir comprising a new powder charge. Preferably at least the exit conduit is hydrophobic to prevent fluid accumulation, e.g., it is coated with a hydrophobic material or made of a hydrophobic material such as hydrophobic plastic.

[0013] In one embodiment the powder is HA or CMC, or both.

[0014] Still another aspect of the invention features a method of making the powder described above by providing a solid material comprising HA, milling solid material comprising HA, and sieving solid material comprising HA to select material characterized in that at least 90% of powder particles have a maximum dimension between 5 μm and 1 mm.

[0015] The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

[0016] FIG. 1 is a side view of one embodiment of a hand-held pistol-grip sprayer for delivering anti-adhesion powder.

[0017] FIG. 2 is a side view of a second embodiment of a sprayer for delivering anti-adhesion powder, using a pressurized canister with a spray valve.

[0018] FIG. 3 is a diagrammatic view, partially in section, showing entrainment of powder particles.

[0019] FIG. 4 is a view of another embodiment of a hand-held pistol-grip sprayer.

[0020] FIG. 5 is a view of another embodiment of a bulb sprayer.

[0021] FIG. 6 is a diagrammatic view, partially in section, of a sprayer using a source of pressurized gas.

[0022] FIG. 7 is a diagrammatic view, partially in section, of another embodiment of a bulb sprayer.

[0023] FIG. 8 is a process flow diagram for a method of making powder.

[0024] Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0025] Powder Formulation

[0026] The invention features hyaluronic acid ("HA")-containing powders, as well as their manufacture and uses. We first describe the material itself and then we describe powder formation.

[0027] HA is a naturally occurring mucopolysaccharide found, for example, in synovial fluid, in vitreous humor, in blood vessel walls and umbilical cord, and in other connective tissues. The polysaccharide consists of alternating N-acetyl-D-glucosamine and D-glucuronic acid residues joined by alternating β -1-3 glucuronidic and β -1-4 glucosaminidic bonds, so that the repeating unit is $-(1\rightarrow4)\beta$ -D-GlcA- $(\rightarrow3)\beta$ -D-GlcNAc-. In water, non-modified hyaluronic acid dissolves to form a highly viscous fluid. The molecular weight of hyaluronic acid isolated from natural sources generally falls within the range of 5×10^4 up to 1×10^7 Daltons.

[0028] We use the term HA to include hyaluronic acid as described above and any of its hyaluronate salts, including, for example, sodium hyaluronate (the sodium salt), potassium hyaluronate, magnesium hyaluronate, and calcium hyaluronate. We also mean to include HA in chemically modified ("derivatized") form. Specifically, we prefer the HA/CMC material used in Genzyme's Septrafilm® and Sepramesh® products. General disclosures of suitable materials can be found in U.S. Pat. Nos. 6,235,726, 6,030,958 and 5,760,200, each of which is hereby incorporated by reference. "HA" means a substance containing hyaluronic acid, including hyaluronic acid that has been modified, cross-linked or combined with other substances.

[0029] Further background regarding derivatized HA, Danishefsky et al., 1971, Carbohydrate Res., Vol. 16, pages 199-205, describes modifying a mucopolysaccharide by converting the carboxyl groups of the mucopolysaccharide into substituted amides by reacting the mucopolysaccharide with an amino acid ester in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride ("EDC") in aqueous solution. They reacted glycine methyl ester with a variety of polysaccharides, including HA. The resulting products are water-soluble; that is, they rapidly disperse in water or in an aqueous environment such as is encountered between body tissues.

[0030] Proposals for rendering HA compositions less water-soluble include cross-linking the HA. R. V. Sparer et al., 1983, Chapter 6, pages 107-119, in T. J. Roseman et al., Controlled Release Delivery Systems, Marcel Dekker, Inc., New York, describe modifying HA by attaching cysteine residues to the HA via amide bonds and then cross-linking the cysteine-modified HA by forming disulfide bonds between the attached cysteine residues. The cysteine-modified HA was itself water-soluble and became water insoluble only upon cross-linking by oxidation to the disulfide form.

[0031] De Belder et al., PCT Publication No. WO 86/00912, describe a slowly-degradable gel, for preventing tissue adhesions following surgery, prepared by cross-linking a carboxyl-containing polysaccharide with a bi- or polyfunctional epoxide. Other reactive bi- or polyfunctional reagents that have been proposed for preparing cross-linked gels of HA having reduced water solubility include: 1,2,3,4-diepoxybutane in alkaline medium at 50° C. (T. C. Laurent et al., 1964, Acta Chem. Scand., vol. 18, page 274); divinyl sulfone in alkaline medium (E. A. Balasz et al., U.S. Pat. No. 4,582,865, (1986); and a variety of other reagents including formaldehyde, dimethylolurea, dimethylethylene urea, ethylene oxide, a polyaziridine, and a polyisocyanate (E. A. Balasz et al., U.K. Patent Appl. No. 84 20 560 (1984). T. Malson et al., 1986, PCT Publication No. WO 86/00079,

describe preparing cross-linked gels of HA for use as a vitreous humor substitute by reacting HA with a bi- or polyfunctional cross-linking reagent such as a di- or polyfunctional epoxide. T. Malson et al., 1986, EPO 0 193 510, describe preparing a shaped article by vacuum-drying or compressing a cross-linked HA gel.

[0032] The above references generally disclose how to obtain the material in particulate form suitable for hydration to produce a gel. Generally, to produce powders suitable for use according to the present invention, the raw material obtained from chemical processing is precipitated as described in various references cited above, dried, and milled using standard milling techniques to eliminate clumps and reduce particle size.

[0033] Particle size control is achieved by sieving the milled particles. The powder is placed in a series of sieves with varying size screen openings. The sieves are then agitated by hand or machine until the powder is either captured on a screen or allowed to pass through. Varying ranges of particle sizes can be collected. The particle size distribution can be measured by weighing all of the sieved portions or by particle sizing equipment such as laser diffraction particle sizers.

[0034] A distribution of the maximum dimension of powder particles can be obtained by sieving or particle sizing equipment such as laser diffraction particle sizers.

[0035] We generally prefer a range of particles sizes between 70 μm and 600 μm , although we have tested particles outside that range and they may work in some circumstances, particularly when applied directly from a shaker or a relatively short spray tube to an open operating field. If the particles are too small, say below 60 μm , they have a tendency to make a "cloud", rather than to be entrained in a controllable airflow that can be effectively sprayed.

[0036] The cloud diffuses rather than flows and is difficult to control its position in the wound, e.g. the abdomen. If on the other hand the particles are too large, they will not be effectively entrained in the airflow. We prefer to keep the maximum particle dimension below 1 mm and preferably below 600 μm for spraying. Desirably most particles are between about 35 μm and 425 μm in size. One specific particle size distribution that can be used as a reference is: fewer than about 15% of the particles with $>425 \mu\text{m}$; about 30% having a particle size less than about 425 μm ; and about 10% having a particle size less than 38 μm . For applications that involve spraying the particles through a relatively narrow conduit, e.g., in a laparoscopic application, clogging can be an issue. This is particularly true if the conduit contains airflow control structures such as swirl inducers. For these applications, tighter manufacturing controls can be imposed. It is also desirable to avoid particles that are so large that they form granules (e.g., a dimension over 1 mm) that do not readily form a uniform coating on the wound location.

[0037] By way of example, and not as a limitation, the procedure of FIG. 8 may be used to produce, package and sterilize the powder. The HA-CMC powder is sieved to retain powder between sieves sized at 425 microns and approximately 100 microns. For example, sieved 200 g aliquots are mixed on a mechanical shaker until 458 g of

total sieved HA-CMC is obtained. The powder is agitated using mechanical shaking device. The powder from the desired particle size range is collected and mixed together to provide a more uniform powder with respect to the powder's physical properties. This mixing step may be performed directly after sieving as indicated or it may be moved to just before the filling operation. Once mixed, the powder is dispensed into moisture permeable bags (e.g., polyethylene) which retain the powder but allow the powder to release moisture during the subsequent (DHT) step. This De-Hydrothermal Treatment (DHT) step is designed to heat the powder for a minimum of six hours at $100^{\circ} \text{C} \pm 5^{\circ} \text{C}$. After the DHT step, the powder is equilibrated in an area controlled for temperature and humidity. The length of this equilibration step is chosen to provide a steady state condition with respect to moisture resulting in a minimal ($<1\%$) weight change during the filling operations. For example, equilibration with ambient humidity (e.g., 40% relative humidity) continues for 32 hours. The HA-CMC powder is dispensed into a vial to be used to fill a device described elsewhere herein, e.g., having a nominal fill size of 0.5, 1.0 and 2.0 grams. Additional powder is added to compensate for the water content of the powder, filling tolerances and the inability to dispense all of the powder. The vials are then packaged in containers that provide a moisture barrier and a sterile barrier, and the materials, which in turn is packaged for bulk sterilization. The product is gamma irradiated at 25-40 kilograys, and appropriate quality control is performed.

[0038] Methods and Apparatus For Applying the Powder

[0039] The most straightforward method of applying the powder is from a shaker having orifices sized to release it. This method is suitable where a relatively open operating field is available to the surgeon. It can be used for coating the underlying viscera prior to implanting a mesh prosthesis in such a wound.

[0040] Alternatively, the powder may be entrained in an airflow directed to the wound location where adhesion prevention is desired. FIGS. 1-7 show various spray apparatus that can be used for this purpose. In FIG. 1, a handgrip sprayer 10 includes a squeeze bulb 12 positioned in the grip 13. The squeeze bulb has an inlet valve 14 and a conduit 15 connected to a powder reservoir 16. A backflow prevention valve 17, e.g., a flapper valve, prevents suction of powder into the squeeze bulb. Powder 20 sits in the bottom of reservoir 16. As squeeze bulb 12 is squeezed, air flows into reservoir 16 through conduit 15 via valve 17. The air flows through the powder, entraining it in the airflow that exits via conduit 22. The beginning of conduit 22 within reservoir 16 is positioned at the top of the reservoir, spaced away from the powder and the end of conduit 15. A spiral diffuser 24 positioned in conduit 22 imparts a radial component to the airflow, so that the airflow and the entrained powder spread out as they leave conduit 22 at the wound site.

[0041] Alternative delivery methods are shown in FIGS. 2-7. FIG. 2 shows a standard aerosol canister 30 that includes a source of pressurized gas (e.g. a CO_2 canister) and an internal reservoir (not shown) containing the powder to entrain the airflow from the canister. Pressure is released by activating valve 31, which releases powder entrained in a flow of pressurized gas through exit conduit 29.

[0042] FIG. 3 shows an alternative powder reservoir configuration in which the incoming airflow is provided via a

conduit 32 that enters the top of the reservoir 34 through a hole in a stopper/cap 35 and extends to the bottom. Airflow with entrained powder exits via a second conduit 36 at the top of the reservoir. Airflow may be provided to such a reservoir by a pressurized gas canister 39 as in FIG. 6 or by a squeeze bulb 41 as in FIG. 7.

[0043] FIG. 4 shows an alternative squeeze bulb 49/hand-grip 51 device 40 having the reservoir 42 positioned so that it can be inserted and removed without inverting the device. Incoming air conduit 44 extends into the powder that is entrained in the airflow as the airflow exits through conduit 46.

[0044] FIG. 5 shows an integral squeeze bulb 60/powder reservoir 62, in which the airflow-entrained powder is forced through the squeeze bulb to the delivery conduit. Powder reservoir 50 is removably inserted in a recess in the back of squeeze bulb 52. Squeezing bulb 52 forces air through orifice 54 and the powder is entrained in airflow exiting through conduit 56 that communicates with the delivery conduit 58.

[0045] Advantageously, the surgeon needs only one hand to hold the grip and squeeze the bulb.

[0046] The coating of the sprayed powder should have a density greater than 2 mg/cm². Preferably the coating density should be at least 2.5 mg/cm² or even greater, e.g., 5 mg/cm². If the coating is too thick it may obscure the operating field and cause other complications. If the coating is too thin it may be less effective.

[0047] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. For example, a commercial spraying device is sold by Richard Wolf GmbH, Postfach 1164 75434 Knittlingen Germany. Accordingly, other embodiments are within the scope of the following claims.

[0048] Applicants note that some unclaimed aspects of the spray devices disclosed herein may have been contributed by other individuals, such as the inventors of the above-referenced application entitled Powder Delivery Device.

What is claimed is:

1. An essentially dry blowable powder comprising bioresorbable HA, said powder being characterized in that at least 90% of powder particles have a maximum dimension between 5 μ m and 1 mm.

2. The powder of claim 1 in which said powder further comprises CMC.

3. The powder of claim 1 or claim 2 in which said HA or CMC or both is modified to reduce solubility or to enhance anti-adhesive properties of said powder or both.

4. The powder of claim 3 in which said powder comprises the reaction product of HA or CMC, or both, with a carbodiimide.

5. The powder of claim 3 in which said powder comprises the reaction product of HA with a divinylsulfone or a diepoxide.

6. The powder of claim 1 in which said powder is characterized in that at least 90% of the powder particles have a maximum dimension between 70 μ m and 600 μ m.

7. A method of reducing undesirable adhesions during wound healing, comprising applying the powder of claim 1

into a location in a wound where adhesion reduction is desired, said powder being applied to be present in a mass per area sufficient to reduce adhesions as the wound heals.

8. A method of reducing undesirable adhesions in a wound comprising applying a dry, blowable powder into a location in said wound where adhesion reduction is desired, said powder being applied to be present in a mass per area sufficient to reduce said adhesions, said powder comprising bioresorbable HA, CMC, or both.

9. The method of claim 7 or claim 8 in which said mass/area is greater than 2 mg/cm².

10. The method of claim 7 or claim 8 in which said wound is a surgical wound.

11. The method of claim 7 or claim 8 in which said powder is applied directly to an open wound.

12. The method of claim 11 in which said powder is applied to said wound from a shaker comprising a powder reservoir and orifices sized to release powder when the shaker is agitated.

13. The method of claim 10 in which said surgical wound is produced by a laparoscopic procedure on a patient, and said powder is applied to said wound via a conduit communicating from a first location outside the patient's body to a second location within the patient's body for delivery to said location in said wound.

14. The method of claim 13 further comprising,

a. delivering a mesh material to said wound via a laparoscopic device; and

b. then applying said powder to a surface of said mesh via said exit conduit.

15. The method of claim 7 or claim 8 in which said location is on a surface of a tissue prosthesis.

16. The method of claim 7 or claim 8 in which said location includes the edges of said prosthesis.

17. The method of claim 7 or claim 8 comprising

a. providing airflow through a chamber containing said powder to entrain said powder in said airflow; and

b. directing the airflow with entrained powder to said location.

18. The method of claim 17 in which said airflow is provided by a hand powered air pump or a squeeze bulb.

19. The method of claim 18 in which said airflow is provided by a source of pressurized gas in a hospital operating room.

20. The method of claim 7 or claim 8 in which said powder is provided via a tubular conduit positioned to carry said powder from said reservoir to said location in said wound.

21. The method of claim 20 in which said conduit includes an airflow modifier.

22. The method of claim 21 in which said airflow modifier comprises a swirl inducer positioned in said conduit to impart a radial component to said airflow.

23. The method of claim 7 or claim 8 comprising irrigating the location prior to applying the powder.

24. The method of claim 15 comprising saturating said prosthesis with an aqueous solution prior to introducing the powder.

25. Apparatus for delivering powder to a wound, said apparatus comprising a powder reservoir connected to an incoming airflow conduit and an exiting airflow conduit, said conduits being connected to said reservoir to entrain

powder in airflow that enters through said incoming conduit and exits through said exiting airflow conduit, said reservoir comprising the powder of claim 1.

26. The apparatus of claim 25 in which said incoming airflow conduit is connected to a squeeze bulb.

27. The apparatus of claim 26 comprising a handgrip, said squeeze bulb being positioned within said grip so as to permit the user to hold the apparatus in one hand and, while holding it, to squeeze the bulb and deliver powder from the exiting airflow conduit.

28. The apparatus of claim 25 in which said incoming airflow conduit includes a connector for attachment to a hospital operating room gas supply.

29. The apparatus of claim 25 in which the exit conduit comprises a swirl inducer adding a radial component to airflow velocity.

30. The apparatus of claim 25 in which the reservoir is removable, so that after use, the spent reservoir can be replaced with a reservoir comprising a new powder charge.

31. The apparatus of claim 25 in which at least the exit conduit is hydrophobic.

32. The apparatus of claim 31 in which the exit conduit is coated with a hydrophobic material.

33. The apparatus of claim 31 in which the exit conduit is made of a hydrophobic material.

34. The apparatus of claim 32 or claim 33 in which the hydrophobic material is a hydrophobic plastic.

35. Apparatus comprising a dry, blowable powder to be introduced into a location in said wound where adhesion reduction is desired, said powder comprising HA or CMC, said apparatus further comprising a reservoir to contain said powder and exit orifices to apply the powder to said location.

36. A method of making the powder of claim 1 comprising, in any sequence, providing a solid material comprising HA, milling solid material comprising HA, and sieving solid material comprising HA to select material characterized in that at least 90% of powder particles have a maximum dimension between 5 μm and 1 mm.

* * * * *