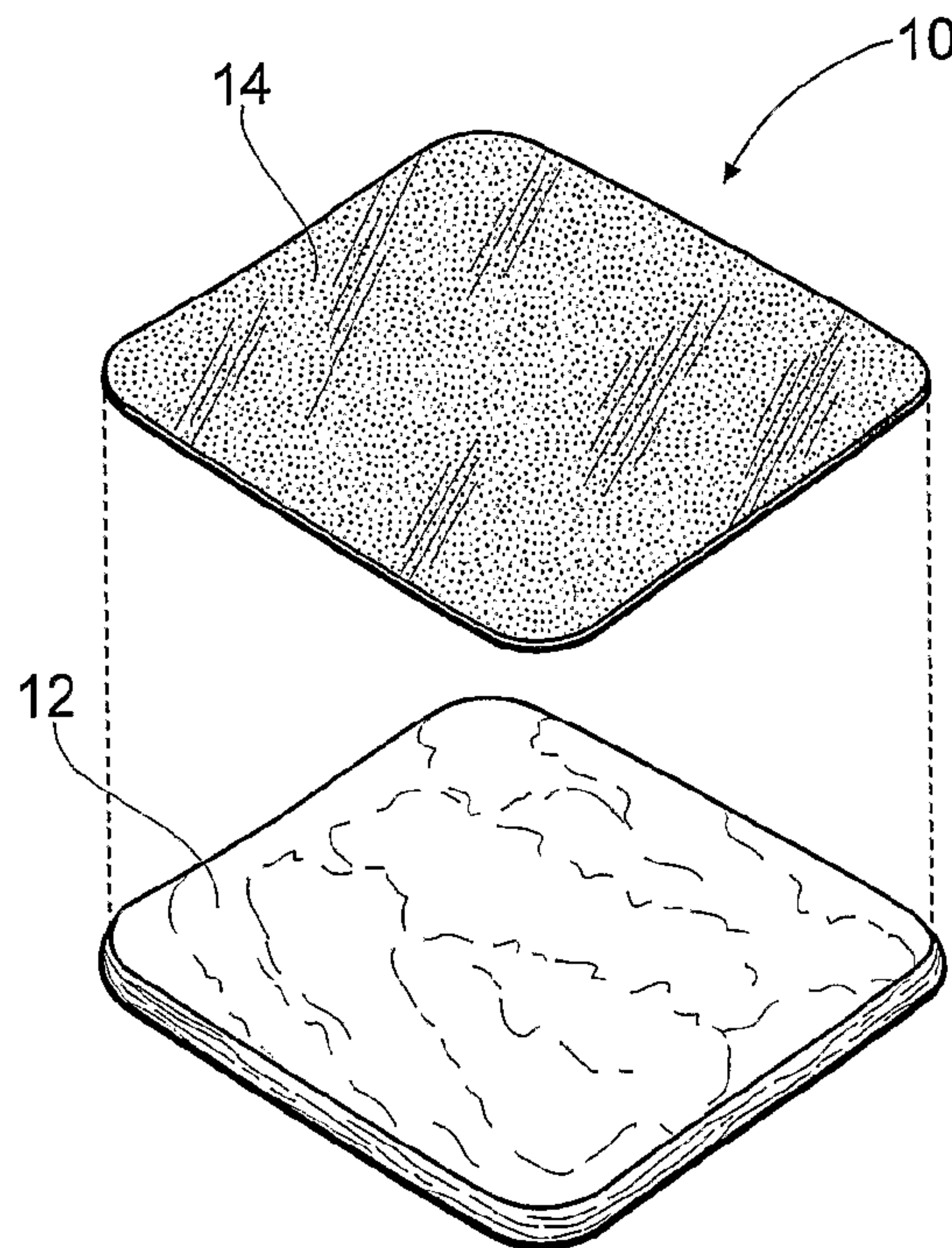




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(71) Demandeur/Applicant:
HEMCON, INC., US
(72) Inventeurs/Inventors:
MCCARTHY, SIMON J., US;
GREGORY, KENTON W., US;
MORGAN, JOHN W., US
(74) Agent: SMART & BIGGAR

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(54) Title: TISSUE DRESSING ASSEMBLIES, SYSTEMS, AND METHODS FORMED FROM HYDROPHILIC POLYMER
SPONGE STRUCTURES SUCH AS CHITOSAN



(57) **Abrégé/Abstract:**

Tissue dressing assemblies are formed from hydrophilic polymer sponge structures. The tissue dressing assemblies can be used, e.g., (i) stanch, seal, or stabilize a site of tissue injury, tissue trauma, or tissue access; or (ii) form an anti-microbial barrier; or (iii) form an antiviral patch; or (iv) intervene in a bleeding disorder; or (v) release a therapeutic agent; or (vi) treat a mucosal surface; or (vii) combinations thereof. The tissue dressing structures are made compliant, e.g., by (i) micro-fracturing of a substantial portion of the sponge structure by mechanical manipulation prior to use, or (ii) a surface relief pattern formed on a substantial portion of the sponge structure prior to use, or (iii) a pattern of fluid inlet channels formed in a substantial portion of the sponge structure prior to use, or (iv) the impregnation of a sheet material within the sponge structure.

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(71) Applicant (for all designated States except US): **HEM-
CON, INC.** [US/US]; 10575 SW Cascade Avenue, Suite
130, Tigard, OR 97223 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **McCARTHY,
Simon, J.** [AU/US]; 3715 NW Gordon Street, Portland,

OR 97210 (US). **GREGORY, Kenton, W.** [US/US];
3737 S.W. Council Crest Drive, Portland, OR 97201 (US).
MORGAN, John, W. [US/US]; 1957 SW Montgomery
Drive, Portland, OR 97201 (US).

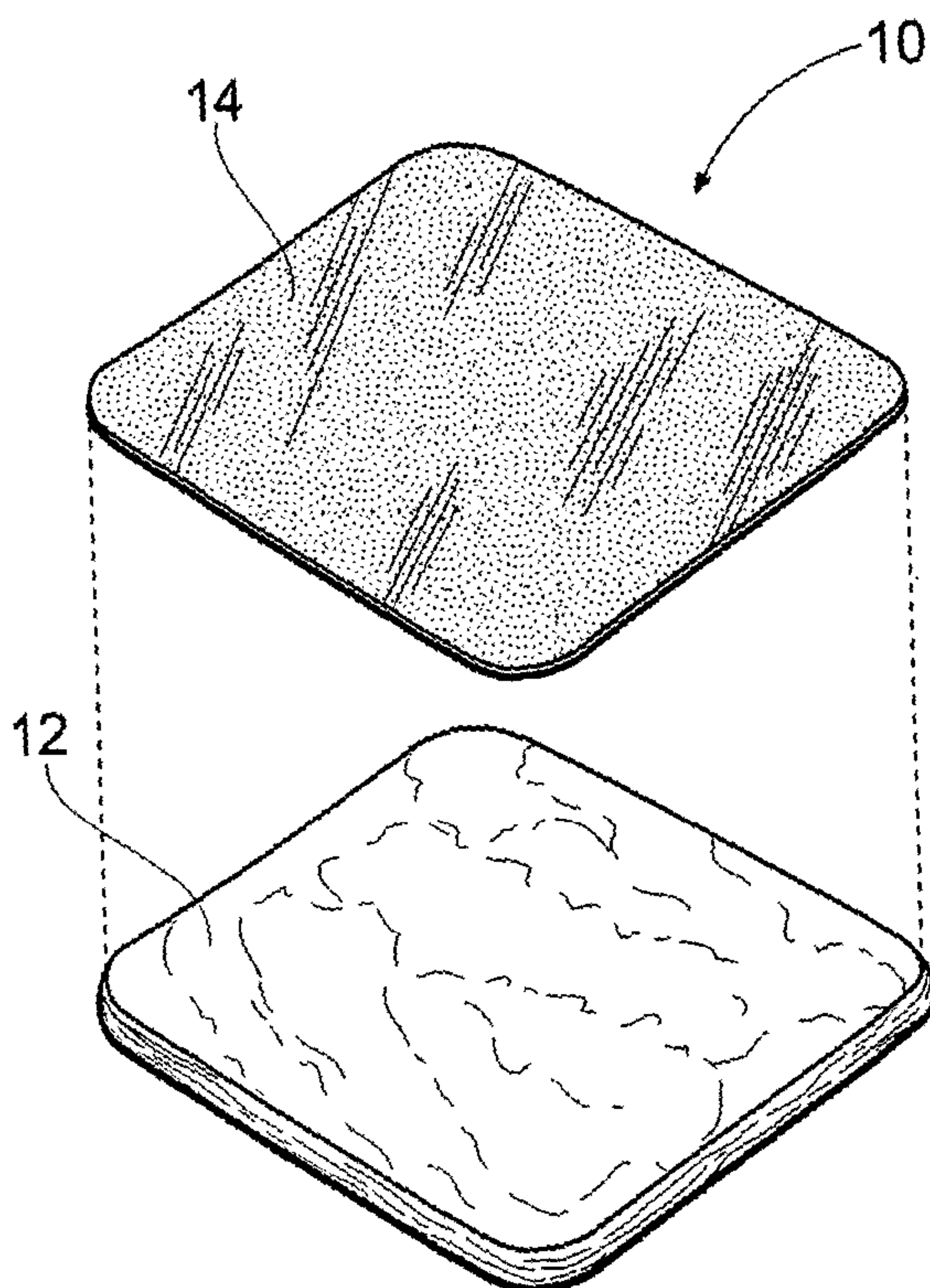
(74) Agents: **RYAN, Daniel, D.** et al.; P.O. Box 26618, Mil-
waukee, WI 53226 (US).

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(57) Abstract: Tissue dressing assemblies are formed from hydrophilic polymer sponge structures. The tissue dressing assemblies can be used, e.g., (i) stanch, seal, or stabilize a site of tissue injury, tissue trauma, or tissue access; or (ii) form an anti-microbial barrier; or (iii) form an antiviral patch; or (iv) intervene in a bleeding disorder; or (v) release a therapeutic agent; or (vi) treat a mucosal surface; or (vii) combinations thereof. The tissue dressing structures are made compliant, e.g., by (i) micro-fracturing of a substantial portion of the sponge structure by mechanical manipulation prior to use, or (ii) a surface relief pattern formed on a substantial portion of the sponge structure prior to use, or (iii) a pattern of fluid inlet channels formed in a substantial portion of the sponge structure prior to use, or (iv) the impregnation of a sheet material within the sponge structure.

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TISSUE DRESSING ASSEMBLIES, SYSTEMS, AND METHODS
FORMED FROM HYDROPHILIC POLYMER SPONGE STRUCTURES
SUCH AS CHITOSAN

Related Applications

5 This application is a continuation-in-part of U.S.
Patent Application No. 10/743,052, filed on December 23,
2004, entitled "Wound Dressing and Method of Controlling
Severe Life-Threatening Bleeding," which is a
continuation-in-part of U.S. Patent Application No.
10 10/480,827, filed on December 15, 2003, entitled "Wound
Dressing and Method of Controlling Severe Life-
Threatening Bleeding," which was a national stage filing
under 37 C.F.R. § 371 of International Application No.
PCT/U502/18757, filed on June 14, 2002, which claims the
15 benefit of provisional patent application Serial No.
60/298,773 filed June 14, 2001, which are each
incorporated herein by reference.

Field of the Invention

20 The invention is generally directed to tissue
dressings applied on a site of tissue injury, or tissue
trauma, or tissue access to ameliorate bleeding, fluid
seepage or weeping, or other forms of fluid loss, as well
as provide a protective covering over the site.

Background of the Invention

25 The application of continuous pressure with gauze

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bandage remains a primary intervention technique used to stem blood flow, especially flow from severely bleeding wounds. However, this procedure neither effectively nor safely stanches severe blood flow. This has been, and
5 continues to be, a major survival problem in the case of severe life- threatening bleeding from a wound.

Hemostatic bandages such as collagen wound dressings or dry fibrin thrombin wound dressings or chitosan and chitosan dressings are available, such dressings are not
10 sufficiently resistant to dissolution in high blood flow. They also do not possess enough adhesive properties to serve any practical purpose in the stanching of severe blood flow. These currently available surgical hemostatic bandages are also delicate and thus prone to failure
15 should they be damaged by bending or loading with pressure. They are also susceptible to dissolution in hemorrhagic bleeding. Such dissolution and collapse of these bandages may be catastrophic, because it can produce a loss of adhesion to the wound and allow
20 bleeding to continue unabated.

There remains a need for improved hemostatic dressings with robustness and longevity to resist dissolution during use.

Summary of the Invention

25 The invention provides tissue dressing assemblies, systems and methods formed from hydrophilic polymer sponge structures. The tissue dressing assemblies can be used, e.g., (i) to stanch, seal, or stabilize a site of tissue injury, tissue trauma, or tissue access; or (ii)
30 to form an anti-microbial barrier; or (iii) to form an antiviral patch; or (iv) to intervene in a bleeding disorder; or (v) to release a therapeutic agent; or (vi) to treat a mucosal surface; or (vii) combinations thereof.

35 According to one aspect of the invention, the

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hydrophilic polymer sponge structure includes at least one of (i) micro-fracturing of a substantial portion of the structure by mechanical manipulation prior to use, or (ii) a surface relief pattern formed on a substantial portion of the structure prior to use, or (iii) a pattern of fluid inlet channels formed in a substantial portion of the structure prior to use.

According to another aspect of the invention, the tissue dressing assembly comprises at least one woven or non-woven or permeable membranous sheet present within the hydrophilic sponge structure.

According to another aspect of the invention, the tissue dressing assembly comprises an absorbent component secured to the hydrophilic sponge structure.

The incorporation of one or more of these aspects imparts compliance, flexibility, and longevity to sponge structure.

In one embodiment, the hydrophilic polymer sponge structure includes a chitosan biomaterial.

In one embodiment, the hydrophilic polymer sponge structure is desirably densified by compression to a density of between 0.6 to 0.1 g/cm³.

Other features and advantages of the invention shall be apparent based upon the accompanying description, drawings, and claims.

Description of the Drawings

Fig. 1 is a perspective assembled view of a tissue dressing pad assembly that is capable of adhering to body tissue in the presence of blood, fluid, or moisture.

Fig. 2 is a perspective exploded view of the tissue dressing pad assembly shown in Fig. 1.

Fig. 3 is a perspective view of the tissue dressing pad assembly shown in Fig. 1 packaged in a sealed pouch for terminal irradiation and storage.

Figs. 4 and 5 are perspective views of the sealed

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pouch shown in Fig. 3 being torn open to expose the tissue dressing pad assembly for use.

5 Figs. 6 and 7 are perspective views of the tissue dressing pad assembly being held and manipulated by folding or bending prior to application to conform to the topology of a targeted tissue site.

Figs. 8 to 10A/B are perspective views of the tissue dressing pad assembly being applied to a targeted tissue site to stanch bleeding.

10 Fig. 11 is a perspective view of two tissue dressing pad assemblies being applied in an overlapping fashion to a targeted tissue site to stanch bleeding.

15 Figs. 12 and 13 are perspective views of pieces of a tissue dressing pad assembly being cut and fitted to a targeted tissue site to stanch bleeding.

Figs. 14 and 15 are perspective views of the tissue dressing pad assembly being held and manipulated by molding into a concave or cup shape to conform to a targeted tissue site.

20 Fig. 16 is a diagrammatic view of the steps of a process for creating the tissue dressing pad assembly shown in Fig. 1.

25 Fig. 17 is a partially diagrammatic view of a test fixture used to quantify acute adhesive and cohesive sealing properties of the tissue dressing pad assembly, shown in Fig. 1, in a simulated arterial wound environment.

30 Figs. 18A to 18C are partially diagrammatic views showing the use of the test fixture in Fig. 17 being used to conduct a burst pressure test on a test sample of a tissue dressing pad assembly.

35 Fig. 19 is a graph showing the difference in burst pressures, determined by use of the test fixture shown in Fig. 17, among hydrophilic polymer sponge structures manufactured at different freezing temperatures.

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Figs. 20, 21A/B, and 22A/B are perspective views of an embodiment of the steps for conditioning a hydrophilic polymer sponge structure to create micro-fractures, which provide improved flexibility and compliance.

5 Figs. 23A and 23B are views of an embodiment of the steps for conditioning a hydrophilic polymer sponge structure by forming deep relief patterns, which provide improved flexibility and compliance.

10 Figs. 24A to 24F are plane views of relief patterns that can be applied to condition a hydrophilic polymer sponge structure following the steps shown in Figs. 23A and 23B.

15 Figs. 25A and 25B are graphs demonstrating the improvement in flexibility and compliance that the treatment steps shown in Figs. 23A and 23B can provide.

Figs. 26A and 26B are views of an embodiment of the steps for conditioning a hydrophilic polymer sponge structure by forming vertical channels (perforations), which provide improved flexibility and compliance.

20 Fig. 27 is a plane view of vertical (perforated) channels that can be applied to condition a hydrophilic polymer sponge structure following the steps shown in Figs. 26A and 26B.

25 Fig. 28 is a graph demonstrating the improvement in flexibility and compliance that the treatment steps shown in Figs. 26A and 26B can provide.

Fig. 29 is a perspective assembled view of a tissue dressing sheet assembly that is capable of adhering to body tissue in the presence of blood, fluid, or moisture.

30 Fig. 30 is a perspective exploded view of the tissue dressing sheet assembly shown in Fig. 29.

Fig. 31A is a perspective assembled view of tissue dressing sheet assemblies arranged in sheet form.

35 Fig. 31B is a perspective assembled view of tissue dressing sheet assemblies arranged in roll form.

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Fig. 32 is a perspective view of the stuffing of a tissue dressing sheet assembly in roll form into a targeted tissue region to stanch bleeding.

Fig. 33 is a diagrammatic view of the steps of a process for creating the tissue dressing sheet assembly shown in Fig. 29.

Fig. 34 is a perspective view of the tissue dressing pad assembly shown in Fig. 29 packaged in a sealed pouch for terminal irradiation and storage.

Fig. 35 is a graph demonstrating the flexibility and compliance of a tissue dressing sheet assembly, as shown in Fig. 29, compared to an untreated tissue dressing pad assembly shown in Fig. 1.

Fig. 36A is a graph showing the simulated wound sealing characteristics of a tissue dressing sheet assembly, as shown in Fig. 29 prior to gamma-irradiation.

Fig. 36B is a graph showing the simulated wound sealing characteristics of a tissue dressing sheet assembly, as shown in Fig. 29 before and after gamma-irradiation.

Fig. 37 is a perspective assembled view of a composite tissue dressing assembly that is capable of adhering to body tissue in the presence of blood, fluid, or moisture.

Fig. 38 is a perspective exploded view of the composite tissue dressing assembly shown in Fig. 37.

Fig. 39 is a side section view of the composite tissue dressing assembly shown in Fig. 37.

Fig. 40 is a perspective view of a composite tissue dressing assembly of the type shown in Fig. 37 that has been shaped and configured to form a gasket assembly to adhere about and seal an access site for an indwelling catheter.

Fig. 41 is a side section view of the gasket assembly shown in Fig. 40.

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Fig. 42 is a perspective view of a tissue dressing pad assembly of the type shown in Fig. 1 that has been shaped and configured to form a gasket assembly to adhere about and seal an access site for an indwelling catheter.

5 Fig. 43 is a perspective view of a tissue dressing sheet assembly of the type shown in Fig. 29 that has been shaped and configured to form a gasket assembly to adhere about and seal an access site for an indwelling catheter.

Detailed Description

10 To facilitate an understanding of this disclosure, the following listing summarizes the topical areas covered, arranged in the order in which they appear:

List of Topical Areas Described

- I. The Tissue Dressing Pad Assembly
 - 15 A. Overview
 - 1. The Tissue Dressing Matrix
 - 2. The Backing
 - 3. The Pouch
 - B. Use of the Tissue Dressing Pad Assembly
 - 20 Example 1
 - C. Manufacture of the Tissue Dressing Pad Assembly
 - 1. Preparation of a Chitosan Solution
 - 2. Degassing the Aqueous Chitosan Solution
 - 25 3. Freezing the Aqueous Chitosan Solution
 - 4. Freeze Drying the Chitosan/Ice Matrix
 - 5. Densification of the Chitosan Matrix
 - 7. Securing the Backing
 - 8. Placement in the Pouch
 - 30 9. Terminal Sterilization
 - D. Evaluating the Adhesive/Cohesive Sealing Properties of a Hydrophilic Polymer Sponge Structure
 - 1. The Arterial Wound Sealing Test
 - 35 Fixture

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2. Discernment of an Aging Phenomenon
Example 2
3. Discernment of Adhesive/Cohesive
Properties Among Different Hydrophilic
Polymer Sponge Structure Configurations
- 5 E. Altering the Compliance Properties of a
Hydrophilic Polymer Sponge Structure
 1. Controlled Micro-Fracturing
Example 3
 - 10 2. Controlled Macro-Texturing
Example 4
 3. Controlled Formation of Vertical
Channels
Example 5
- 15 II. Tissue Dressing Sheet Assembly
 - A. Overview
 - B. Use of Tissue Dressing Sheet Assembly
 - C. Manufacture of the Tissue Dressing Sheet
Assembly
 - 20 Examples 6 and 7
- III. Further Indications and Configurations for
Hydrophilic Polymer Sponge Structures
 - A. Body Fluid Loss Control (e.g., Burns)
 1. Composite dressing assembly 76
 - 25 B. Anti-Microbial Barriers
Example 8
 - C. Anti-Viral Patches
 - D. Bleeding Disorder Intervention
 - E. Controlled Release of Therapeutic Agents
 - 30 F. Treatment of Mucosal Surfaces

IV. Conclusion

Although the disclosure hereof is detailed and exact
to enable those skilled in the art to practice the
invention, the physical embodiments herein disclosed
35 merely exemplify the invention, which may be embodied in

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other specific structure. While the preferred embodiment has been described, the details may be changed without departing from the invention, which is defined by the claims.

5 I. Tissue Dressing Pad Assembly

A. Overview

Fig. 1 shows a tissue dressing pad assembly 10. In use, the tissue dressing pad assembly 10 is capable of adhering to tissue in the presence of blood, or body
10 fluids, or moisture. The tissue dressing pad assembly 10 can be used to stanch, seal, and/or stabilize a site of tissue injury, or tissue trauma, or tissue access (e.g., a catheter or feeding tube) against bleeding, fluid seepage or weeping, or other forms of fluid loss. The
15 tissue site treated can comprise, e.g., arterial and/or venous bleeding, or a laceration, or an entrance/entry wound, or a tissue puncture, or a catheter access site, or a burn, or a suture. The tissue dressing pad assembly 10 can also desirably form an anti-bacterial and/or anti-
20 microbial and/or anti-viral protective barrier at or surrounding the tissue treatment site.

Fig. 1 shows the tissue dressing pad assembly 10 in its condition prior to use. As Fig. 2 best shows, the tissue dressing pad assembly 10 comprises a tissue
25 dressing matrix 12 and a pad backing 14 that overlays one surface of the tissue dressing matrix 12. Desirably, the tissue dressing matrix 12 and the backing 14 possess different colors, textures, or are otherwise visually and/or tactilely differentiated, to facilitate
30 recognition by a caregiver.

The size, shape, and configuration of the tissue dressing pad assembly 10 can vary according to its intended use. The pad assembly 10 can be rectilinear, elongated, square, round, oval, or a composite or complex
35 combination thereof. Desirably, as will be described

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later, the shape, size, and configuration of pad assembly 10 can be formed by cutting, bending, or molding, either during use or in advance of use. In Fig. 1, a representative configuration of the tissue dressing pad assembly 10 is shown that is very useful for the temporary control of external bleeding or fluid loss. By way of example, its size is 10 cm x 10 cm x 0.55 cm.

1. The Tissue Dressing Matrix

The tissue dressing matrix 12 is preferably formed from a low modulus hydrophilic polymer matrix, i.e., a inherently "uncompressed" tissue dressing matrix 12, which has been densified by a subsequent densification process, which will be described later. The tissue dressing matrix 12, preferably, includes a biocompatible material that reacts in the presence of blood, body fluid, or moisture to become a strong adhesive or glue. Desirably, the tissue dressing matrix also possesses other beneficial attributes, for example, anti-bacterial and/or anti-microbial anti-viral characteristics, and/or characteristics that accelerate or otherwise enhance the body's defensive reaction to injury.

The tissue dressing matrix 12 may comprise a hydrophilic polymer form, such as a polyacrylate, an alginate, chitosan, a hydrophilic polyamine, a chitosan derivative, polylysine, polyethylene imine, xanthan, carrageenan, quaternary ammonium polymer, chondroitin sulfate, a starch, a modified cellulosic polymer, a dextran, hyaluronan or combinations thereof. The starch may be of amylose, amylopectin and a combination of amylopectin and amylose.

In a preferred embodiment, the biocompatible material of the matrix 12 comprises a non-mammalian material, which is most preferably poly [β -(1 $\rightarrow$ 4)-2-amino-2-deoxy-D- glucopyranose, which is more commonly referred to as chitosan. The chitosan selected for the matrix 12

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preferably has a weight average molecular weight of at least about 100 kDa, and more preferably, of at least about 150 kDa. Most preferably, the chitosan has a weight average molecular weight of at least about 300 kDa.

5 In forming the matrix 12, the chitosan is desirably placed into solution with an acid, such as glutamic acid, lactic acid, formic acid, hydrochloric acid and/or acetic acid. Among these, hydrochloric acid and acetic acid are most preferred, because chitosan acetate salt and
10 chitosan chloride salt resist dissolution in blood whereas chitosan lactate salt and chitosan glutamate salt do not. Larger molecular weight (Mw) anions disrupt the para-crystalline structure of the chitosan salt, causing a plasticization effect in the structure (enhanced
15 flexibility). Undesirably, they also provide for rapid dissolution of these larger Mw anion salts in blood.

One preferred form of the matrix 12 comprises an "uncompressed" chitosan acetate matrix 12 of density less than 0.035 g/cm³ that has been formed by freezing and
20 lyophilizing a chitosan acetate solution, which is then densified by compression to a density of from 0.6 to 0.25 g/cm³, with a most preferred density of about 0.20 g/cm³. This chitosan matrix 12 can also be characterized as a compressed, hydrophilic sponge structure. The densified
25 chitosan matrix 12 exhibits all of the above-described characteristics deemed to be desirable. It also possesses certain structural and mechanical benefits that lend robustness and longevity to the matrix during use, as will be described in greater detail later.

30 The chitosan matrix 12 presents a robust, permeable, high specific surface area, positively charged surface. The positively charged surface creates a highly reactive surface for red blood cell and platelet interaction. Red blood cell membranes are negatively charged, and they are
35 attracted to the chitosan matrix 12. The cellular

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membranes fuse to chitosan matrix 12 upon contact. A clot can be formed very quickly, circumventing immediate need for clotting proteins that are normally required for hemostasis. For this reason, the chitosan matrix 12 is effective for both normal as well as anti-coagulated individuals, and as well as persons having a coagulation disorder like hemophilia. The chitosan matrix 12 also binds bacteria, endotoxins, and microbes, and can kill bacteria, microbes, and/or viral agents on contact.

Further details of the structure, composition, manufacture, and other technical features of the chitosan matrix 12 will be described later.

2. The Backing

The tissue dressing pad assemble is sized and configured for manipulation by a caregiver's fingers and hand. The backing 14 isolates a caregiver's fingers and hand from the fluid-reactive chitosan matrix 12 (see, e.g., Fig. 8). The backing 14 permits the chitosan matrix 12 to be handled, manipulated, and applied at the tissue site, without adhering or sticking to the caregiver's fingers or hand. The backing 14 can comprise low-modular meshes and/or films and/or weaves of synthetic and naturally occurring polymers. In a preferred embodiment for temporary external wound applications, the backing 14 comprises a fluid impermeable polymeric material, e.g., polyethylene (3M 1774T polyethylene foam medical tape, 0.056 cm thick), although other comparable materials can be used.

Other polymers suitable for backing use in temporary wound applications include, but are not limited to, cellulose polymers, polyethylene, polypropylene, metallocene polymers, polyurethanes, polyvinylchloride polymers, polyesters, polyamides or combinations thereof

For internal wound applications, a resorbable backing may be used in hydrophilic sponge bandage forms.

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Preferably such bandage forms would use a biodegradable, biocompatible backing material. Synthetic biodegradable materials may include, but are not limited to, poly(glycolic acid), poly(lactic acid), poly(ϵ -caprolactone), poly(β -hydroxybutyric acid), poly(β -hydroxyvaleric acid), polydioxanone, poly(ethylene oxide), poly(malic acid), poly(tartronic acid), polyphosphazene, copolymers of polyethylene, copolymers of polypropylene, and the copolymers of the monomers used to synthesize the above-mentioned polymers or combinations thereof. Naturally occurring biodegradable polymers may include, but are not limited to, chitin, algin, starch, dextran, collagen and albumen.

3. The Pouch

As Fig. 3 shows, the chitosan matrix 12 is desirably vacuum packaged before use with low moisture content, preferably 5% moisture or less, in an air-tight heat sealed foil-lined pouch 16. The tissue dressing pad assembly 10 is subsequently terminally sterilized within the pouch 16 by use of gamma irradiation.

The pouch 16 is configured to be peeled opened by the caregiver (see Figs. 4 and 5) at the instant of use. The pouch 16 provides peel away access to the tissue dressing pad assembly 10 along one end. The opposing edges of the pouch 16 are grasped and pulled apart to expose the tissue dressing pad assembly 10 for use.

B. Use of the Tissue Dressing Pad assembly 10

Once removed from the pouch 16 (see Fig. 6), the tissue dressing pad assembly 10 is immediately ready to be adhered to the targeted tissue site. It needs no pre-application manipulation to promote adherence. For example, there is no need to peel away a protective material to expose an adhesive surface for use. The adhesive surface forms *in situ*, because the chitosan matrix 12 itself exhibits strong adhesive properties once

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in contact with blood, fluid, or moisture.

Desirably, the tissue dressing pad assembly 10 is applied to the injury site within one hour of opening the pouch 16. As Fig. 7 shows, the tissue dressing pad assembly 10 can be pre-shaped and adapted on site to conform to the topology and morphology of the site. As Figs. 14 and 15 show, the tissue dressing pad assembly 10 can be deliberately molded into other configurations, e.g., into a cup-shape, to best conform to the particular topology and morphology of the treatment site. While shaping or otherwise manipulating the tissue dressing pad assembly 10 prior to placement on a treatment site, the caregiver should avoid contact between hand or finger moisture and the chitosan matrix 12. This could cause the chitosan matrix 12 to become sticky and difficult to handle. This is the primary purpose of the backing 14, although the backing 14 also lends added mechanical support and strength to the matrix.

Figs. 8 to 13 show the chitosan tissue dressing pad assembly 10 being applied for treating an arterial and/or venous bleeding injury. As Figs. 8 and 9 show, the tissue dressing pad assembly 10 should be placed with the chitosan matrix 12 laid against on the site of active bleeding or where adherence is otherwise desired. The backing 14 provides a non-stick surface for the caregiver to apply pressure in conventional fashion. Desirably, once applied to a site where adherence is desired, the caregiver should avoid repositioning the tissue dressing pad assembly 10.

Desirably, as Fig. 8 shows, firm pressure is applied for at least two minutes, to allow the natural adhesive activity of the chitosan matrix 12 to develop. The adhesive strength of the chitosan matrix 12 will increase with duration of applied pressure, up to about five minutes. Even pressure applied across the tissue dressing

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pad assembly 10 during this time will provide more uniform adhesion and wound sealing. Applying pressure with a Kerlix roll 18 (see Fig. 10A) has been shown to be very effective.

5 Due to unique mechanical and adhesive characteristics, two or more dressing pad assemblies (see Fig. 11) can be overlapped, if needed, to occupy the wound or tissue site. The chitosan matrix 12 of one pad assembly 10 will adhere to the backing 14 of an adjacent
10 dressing pad assembly 10.

 The dressing pad assembly 10 can also be torn or cut on site (see Fig. 12) to match the size of the wound or tissue site. It is desirable to allow at least a one-half inch larger perimeter of the dressing pad assembly 10
15 over the wound or tissue site to provide good tissue adhesion and sealing. Smaller, patch pieces of a dressing assembly can also be cut to size on site (see Fig. 13), fitted and adhered to the periphery of another pad assembly 10 to best approximate the topology and
20 morphology of the treatment site.

 If the tissue pad dressing assembly fails to stick to the injury site, it can be removed and discarded, and another fresh dressing pad assembly 10 applied. In wounds with substantial tissue disruptions, with deep tissue
25 planes or in penetrating wounds, peeling away the backing 14 and stuffing the chitosan matrix 12 into the wound, followed by covering the wound with a second dressing, has been shown to be very effective.

 Once pressure has been applied for two to five
30 minutes, and/or control of the bleeding has been accomplished with good dressing adhesion and coverage of the wound or tissue site, a second conventional dressing (e.g., gauze) is desirably applied to secure the dressing and to provide a clean barrier for the wound (see Fig.
35 10B). If the wound is to be subsequently submersed

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underwater, a water tight covering should be applied to prevent the dressing from becoming over-hydrated.

Desirably, in the case of FDA cleared temporary dressing forms, the tissue dressing pad assembly 10 is removed within forty-eight hours of application for definitive surgical repair. The tissue dressing pad assembly 10 can be peeled away from the wound and will generally separate from the wound in a single, intact dressing. In some cases, residual chitosan gel may remain, and this can be removed using saline or water with gentle abrasion and a gauze dressing. Chitosan is biodegradable within the body and is broken down into glucosamine, a benign substance. Still, it is desirable in the case of temporary dressings, that efforts should be made to remove all portions of chitosan from the wound at the time of definitive repair. As before discussed, biodegradable dressings can be formed for internal use.

Example 1

Usage Action Reports

Action reports by combat medics in operations in and during freedom operations in Afghanistan and Iraq have shown successful clinical utility for the dressing pad assemblies without adverse effects. The US Army Institute for Surgical Research at Fort Sam Houston in Texas evaluated the dressing pad assembly 10 in trauma models with severe life threatening bleeding and compared this dressing to standard 4 x 4 inch cotton gauze dressings. The tissue dressing pad assembly 10 significantly decreased blood loss and decreased resuscitative fluid requirements. Survival at one hour was increased in the group to which the tissue dressing pad assembly 10 was applied, compared to the cotton gauze survival group. Combat medics have successfully treated bullet wounds, shrapnel, land mine and other injuries, when conventional wound dressings have failed.

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**C. Manufacture of the Tissue Dressing Pad
Assembly**

A desirable methodology for making the tissue dressing pad assembly 10 will now be described. This methodology is shown schematically in Fig. 16. It should be realized, of course, that other methodologies can be used.

1. Preparation of a Chitosan Solution

The chitosan used to prepare the chitosan solution preferably has a fractional degree of deacetylation greater than 0.78 but less than 0.97. Most preferably the chitosan has a fractional degree of deacetylation greater than 0.85 but less than 0.95. Preferably the chitosan selected for processing into the matrix has a viscosity at 25°C in a 1%(w/w) solution of 1%(w/w) acetic acid (AA) with spindle LVI at 30 rpm, which is about 100 centipoise to about 2000 centipoise. More preferably, the chitosan has viscosity at 25°C in a 1%(w/w) solution of 1%(w/w) acetic acid (AA) with spindle LVI at 30 rpm, which is about 125 centipoise to about 1000 centipoise. Most preferably, the chitosan has viscosity at 25°C in a 1%(w/w) solution of 1%(w/w) acetic acid (AA) with spindle LV1 at 30 rpm, which is about 400 centipoise to about 800 centipoise.

The chitosan solution is preferably prepared at 25°C by addition of water to solid chitosan flake or powder and the solid dispersed in the liquid by agitation, stirring or shaking. On dispersion of the chitosan in the liquid, the acid component is added and mixed through the dispersion to cause dissolution of the chitosan solid. The rate of dissolution will depend on the temperature of the solution, the molecular weight of the chitosan and the level of agitation. Preferably the dissolution step is performed within a closed tank reactor with agitating blades or a closed rotating vessel. This ensures

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homogeneous dissolution of the chitosan and no opportunity for high viscosity residue to be trapped on the side of the vessel. Preferably the chitosan solution percentage (w/w) is greater than 0.5% chitosan and less than 2.7% chitosan. More preferably the chitosan solution percentage (w/w) is greater than 1% chitosan and less than 2.3% chitosan. Most preferably the chitosan solution percentage is greater than 1.5% chitosan and less than 2.1% chitosan. Preferably the acid used is acetic acid. Preferably the acetic acid is added to the solution to provide for an acetic acid solution percentage (w/w) at more than 0.8% and less than 4%. More preferably the acetic acid is added to the solution to provide for an acetic acid solution percentage (w/w) at more than 1.5% (w/w) and less than 2.5%.

The structure or form producing steps for the chitosan matrix 12 are typically carried out from solution and can be accomplished employing techniques such as freezing (to cause phase separation), non-solvent die extrusion (to produce a filament), electro-spinning (to produce a filament), phase inversion and precipitation with a non-solvent (as is typically used to produce dialysis and filter membranes) or solution coating onto a preformed sponge-like or woven product. In the case of freezing, where two or more distinct phases are formed by freezing (typically water freezing into ice with differentiation of the chitosan biomaterial into a separate solid phase), another step is required to remove the frozen solvent (typically ice), and hence produce the chitosan matrix 12 without disturbing the frozen structure. This may be accomplished by a freeze-drying and/or a freeze substitution step. The filament can be formed into a non-woven sponge-like mesh by non-woven spinning processes. Alternately, the filament may be produced into a felted weave by conventional spinning and

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weaving processes. Other processes that may be used to make the biomaterial sponge-like product include dissolution of added porogens from a solid chitosan matrix 12 or boring of material from said matrix.

5 **2. Degassing the Aqueous Chitosan Solution**

 Preferably (see Fig. 16, Step B), the chitosan biomaterial is degassed of general atmospheric gases. Typically, degassing is removing sufficient residual gas from the chitosan biomaterial so that, on undergoing a
10 subsequent freezing operation, the gas does not escape and form unwanted large voids or large trapped gas bubbles in the subject wound dressing product. The degassing step may be performed by heating a chitosan biomaterial, typically in the form of a solution, and
15 then applying a vacuum thereto. For example, degassing can be performed by heating a chitosan solution to about 45°C immediately prior to applying vacuum at about 500 mTorr for about 5 minutes while agitating the solution.

 In one embodiment, certain gases can be added back
20 into the solution to controlled partial pressures after initial degassing. Such gases would include but are not limited to argon, nitrogen and helium. An advantage of this step is that solutions containing partial pressures of these gases form micro-voids on freezing. The
25 microvoid is then carried through the sponge as the ice-front advances. This leaves a well defined and controlled channel that aids sponge pore interconnectivity.

3. Freezing the Aqueous Chitosan Solution

 Next (see Fig. 16, Step C), the chitosan
30 biomaterial -- which is typically now in acid solution and degassed, as described above -- is subjected to a freezing step. Freezing is preferably carried out by cooling the chitosan biomaterial solution supported within a mold and lowering the solution temperature from
35 room temperature to a final temperature below the

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freezing point. More preferably this freezing step is performed on a plate freezer whereby a thermal gradient is introduced through the chitosan solution in the mold by loss of heat through the plate cooling surface.

5 Preferably this plate cooling surface is in good thermal contact with the mold. Preferably the temperature of the chitosan solution and mold before contact with the plate freezer surface are near room temperature. Preferably the plate freezer surface temperature is not more than -10 °C

10 before introduction of the mold + solution. Preferably the thermal mass of the mold + solution is less than the thermal mass of the plate freezer shelf + heat transfer fluid. Preferably the molds are formed from, but are not limited to, a metallic element such as iron, nickel,

15 silver, copper, aluminum, aluminum alloy, titanium, titanium alloy, vanadium, molybdenum, gold, rhodium, palladium, platinum and/or combinations thereof. The molds may also be coated with thin, inert metallic coatings such as titanium, chromium, tungsten, vanadium,

20 nickel, molybdenum, gold and platinum in order to ensure there is no reaction with the acid component of the chitosan solution and the chitosan salt matrix. Thermally insulating coatings or elements may be used in conjunction with the metallic molds to control heat

25 transfer in the molds. Preferably the mold surfaces do not bind with the frozen chitosan solution. The inside surface of the mold is preferably coated with a thin, permanently-bound, fluorinated release coating formed from polytetrafluoroethylene (Teflon), fluorinated

30 ethylene polymer (FEP), or other fluorinated polymeric materials. Although coated metallic molds are preferable, thin walled plastic molds can be a convenient alternative for supporting the solution. Such plastic molds would include, but not be limited to, molds prepared by

35 injection molding, machining or thermoforming from

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polyvinylchloride, polystyrene, acrylonitrile-butadiene-styrene copolymers, polyesters, polyamides, polyurethanes and polyolefins. An advantage of the metallic molds combined with local placement of thermally insulating elements is that they also provide opportunity for improved control of heat flow and structure within the freezing sponge. This improvement in heat flow control results from large thermal conductivity differences between thermally conducting and thermally insulating element placements in the mold.

Freezing of the chitosan solution in this way enables the preferred structure of the wound-dressing product to be prepared.

As will be demonstrated below, the plate freezing temperature affects the structure and mechanical properties of the final chitosan matrix 12. The plate freezing temperature is preferably not higher than about -10°C , more preferably not more than about -20°C , and most preferably not more than about -30°C . When frozen at -10°C , the structure of the uncompressed chitosan matrix 12 is very open and vertical throughout the open sponge structure. When frozen at -25°C , the structure of the uncompressed chitosan matrix 12 is more closed, but it is still vertical. When frozen at -40°C , the structure of the uncompressed chitosan matrix 12 is closed and not vertical. Instead, the chitosan matrix 12 comprises more of a reinforced, inter-meshed structure. The adhesive/cohesive sealing properties of the chitosan matrix 12 are observed to improve as lower freezing temperatures are used. A freezing temperatures of about -40°C forms a structure for the chitosan matrix 12 having superior adhesive/cohesive properties.

During the freezing step, the temperature may be lowered over a predetermined time period. For example, the freezing temperature of a chitosan biomaterial

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solution may be lowered from room temperature to -45°C by plate cooling application of a constant temperature cooling ramp of between about $-0.4^{\circ}\text{C}/\text{mm}$ to about $-0.8^{\circ}\text{C}/\text{mm}$ for a period of about 90 minutes to about 160
5 minutes.

4. Freeze Drying the Chitosan/Ice Matrix

The frozen chitosan/ice matrix desirably undergoes water removal from within the interstices of the frozen material (see Fig. 16, Step D). This water removal step
10 may be achieved without damaging the structural integrity of the frozen chitosan biomaterial. This may be achieved without producing a liquid phase, which can disrupt the structural arrangement of the ultimate chitosan matrix
12. Thus, the ice in the frozen chitosan biomaterial
15 passes from a solid frozen phase into a gas phase (sublimation) without the formation of an intermediate liquid phase. The sublimated gas is trapped as ice in an evacuated condenser chamber at substantially lower temperature than the frozen chitosan biomaterial.

20 The preferred manner of implementing the water removal step is by freeze-drying, or lyophilization. Freeze-drying of the frozen chitosan biomaterial can be conducted by further cooling the frozen chitosan biomaterial. Typically, a vacuum is then applied. Next,
25 the evacuated frozen chitosan material may be gradually heated.

More specifically, the frozen chitosan biomaterial may be subjected to subsequent freezing preferably at about -15°C , more preferably at about -25°C , and most
30 preferably at about -45°C , for a preferred time period of at least about 1 hour, more preferably at least about 2 hour, and most preferably at least about 3 hour. This step can be followed by cooling of the condenser to a temperature of less than about -45°C , more preferably at
35 about -60°C , and most preferably at about -85°C . Next, a

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vacuum in the amount of preferably at most about 100 mTorr, more preferably at most about 150 mTorr, and most preferably at least about 200 mTorr, can be applied. The evacuated frozen chitosan material can be heated
5 preferably at about -25°C, more preferably at about -15°C, and most preferably at about -10°C, for a preferred time period of at least about 1 hour, more preferably at least about 5 hour, and most preferably at least about 10 hour.

10 Further freeze drying, maintaining vacuum pressure at near 200 mTorr, is conducted at a shelf temperature of about 20°C, more preferably at about 15°C, and most preferably at about 10°C, for a preferred time period of at least about 36 hours, more preferably at least about
15 42 hours, and most preferably at least about 48 hours.

5. **Densification of the Chitosan Matrix**

The chitosan matrix before densification (density near 0.03 g/cm³) will be called an "uncompressed chitosan matrix." This uncompressed matrix is ineffective in
20 stanching bleeding since it rapidly dissolves in blood and has poor mechanical properties. The chitosan biomaterial is necessarily compressed (see Fig. 16, Step E). Compression loading normal to the hydrophilic matrix polymer surface with heated platens can be used to
25 compress the dry "uncompressed" chitosan matrix 12 to reduce the thickness and increase the density of the matrix. The compression step, which will sometimes be called in shorthand "densification," significantly increases adhesion strength, cohesion strength and
30 dissolution resistance of the chitosan matrix 12. Appropriately frozen chitosan matrices 12 compressed above a threshold density (close to 0.1 g/cm³) do not readily dissolve in flowing blood at 37 °C.

The compression temperature is preferably not less
35 than about 60°C, more preferably it is not less than

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about 75°C and not more than about 85°C.

After densification, the density of the matrix 12 can be different at the base ("active") surface of the matrix 12 (i.e., the surface exposed to tissue) than at the top surface of the matrix 12 (the surface to which the backing 14 is applied). For example, in a typical matrix 12 where the mean density measured at the active surface is at or near the most preferred density value of 0.2 g/cm³, the mean density measured at the top surface can be significantly lower, e.g., at 0.05 g/cm³. The desired density ranges as described herein for a densified matrix 12, are intended to exist at are near the active side of the matrix 12, where exposure to blood, fluid, or moisture first occurs.

The densified chitosan biomaterial is next preferably preconditioned by heating chitosan matrix 12 in an oven to a temperature of preferably up to about 75°C, more preferably to a temperature of up to about 80°C, and most preferably to a temperature of preferably up to about 85°C (Fig. 16, Step F). Preconditioning is typically conducted for a period of time up to about 0.25 hours, preferably up to about 0.35 hours, more preferably up to about 0.45 hours, and most preferably up to about 0.50 hours. This pre-conditioning step provides further significant improvement in dissolution resistance with a small cost in a 20-30% loss of adhesion properties.

6. Secure the Backing to the Densified Chitosan Matrix

The backing 14 is secured to the chitosan matrix 12 to form the tissue dressing pad assembly 10 (see Fig. 16, Step G). The backing 14 can be attached or bonded by direct adhesion with a top layer of chitosan matrix 12. Alternatively, an adhesive such as 3M 9942 Acrylate Skin Adhesive, or fibrin glue, or cyanoacrylate glue can be employed.

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7. Placement in the Pouch

The tissue dressing pad assembly 10 can be subsequently packaged in the pouch 16 (see Fig. 16, Step H), which is desirably purged with an inert gas such as either argon or nitrogen gas, evacuated and heat sealed. The pouch 16 acts to maintain interior contents sterility over an extended time (at least 24 months) and also provides a very high barrier to moisture and atmospheric gas infiltration over the same period.

8. Sterilization

After pouching, the processed tissue dressing pad assembly 10 is desirably subjected to a sterilization step (see Fig. 16, Step I). The tissue dressing pad assembly 10 can be sterilized by a number of methods. For example, a preferred method is by irradiation, such as by gamma irradiation, which can further enhance the blood dissolution resistance, the tensile properties and the adhesion properties of the wound dressing. The irradiation can be conducted at a level of at least about 5 kGy, more preferably at least about 10 kGy, and most preferably at least about 15 kGy.

D. Evaluating the Adhesive/Cohesive Properties of a Hydrophilic Polymer Sponge Structure

1. The Arterial Wound Sealing Test Fixture

The adhesive characteristics of any given hydrophilic polymer sponge structure, of which the tissue dressing pad assembly 10 is but one example, can be reliably tested and verified using a test fixture specially designed for the task. A representative test fixture 20 is shown in Fig. 17.

The test fixture 20 provides a platform that simulates an arterial wound sealing environment. The test fixture 20 makes it possible to assess, for that environment and exposure period, the burst (or rupture) strength of a hydrophilic polymer sponge structure, such

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as the pad assembly 10, or a manufactured lot of such structure, in a reproducible and statistically valid way. The test fixture 20 can be implemented as part of an overall manufacturing process to validate, based upon
5 prescribed, objective burst strength criteria, the relative adhesive and cohesive properties of a tissue dressing pad assembly 10, or a manufactured lot of pad assemblies, prior to final labeling and product release. The test fixture 20 provides burst strength data in
10 reproducible way that statistically correlates with *in vivo* use.

The test fixture 20 comprises a test block 22, which simulates an external arterial wound site. The test block 22 comprises a test surface 24 made of a material that
15 simulates tissue. The test surface 24 can be made, e.g., from rigid polyvinyl chloride plastic. The test surface 24 includes an aperture 44 of about 4mm in diameter, which simulates the arterial wound entrance. The test surface 24 is treated to simulate tissue, e.g., by
20 sanding the test surface 24 surrounding the aperture 44 in small circular motions with 400 grit sandpaper.

A load arm 26 is positioned over the test surface 24 in registry with the aperture. The load arm 26 is part of a pneumatic cylinder that is coupled to a source of
25 pneumatic pressure 28. A controller 30 (e.g., a programmed microprocessor) governs communication with the source of pneumatic pressure, to operate the load arm 26. Pneumatic pressure advances the load arm 26 toward the test surface 24 to apply a prescribed pressure.

30 As Fig. 17 shows, a test-sized sample 32 of a hydrophilic polymer sponge structure (e.g., a tissue dressing pad assembly 10) is pre-soaked in a test fluid 34 and placed upon the test surface 24. The chitosan matrix 12 is situated over the aperture. The load arm 26
35 can then be operated (see Fig. 18A) to initially apply

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pressure upon the pre-soaked test-sized sample 32 on the test surface 24.

The test fluid 34 comprises a fluid that activates the adhesive properties of the chitosan matrix 12. The test fluid 34 can comprise, for example, bovine whole blood which has been anti-coagulated (e.g., with citrate). For the purpose of its use as a test fluid 34 in the test fixture 20, there does not appear to be a significant difference in test results whether the blood is fresh or ten days old.

A supply conduit 36 is coupled to the test block 22. The supply conduit 36 is capable of conveying the test fluid 34 into the test block 22 and through the aperture 44 into contact with the chitosan matrix 12. The other end of the supply conduit 36 is coupled to a syringe drive pump 38.

The syringe drive pump 38 is operated in draw and expel cycles by a motor 40. The motor 40 is, in turn, coupled to the controller 30. Through the motor 40, the controller 30 commands operation of the syringe drive pump 38 in synchrony with the source of pneumatic pressure.

In a draw cycle, the motor 40 operates the syringe drive pump 38 to draw the test fluid 34 from a test fluid source 42 into the syringe drive pump 38. Back flow of blood from the test block 22 to the syringe drive pump 38 during the draw cycle is prevented by an in-line one-way check valve 46B. In an expel cycle, the motor 40 operates the syringe drive pump 38 to expel the test fluid 34 from the syringe drive pump 38 through the aperture 44 in the test surface 24. Back flow of the test fluid to the test fluid source 42 during the expel cycle is prevented by an in-line one-way check valve 46A. The controller 30 governs the rate at which the test fluid 34 is conveyed through the aperture 44 during the expel cycle.

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In use, see Fig. 18A, the test-sized sample 32, pre-soaked in the test fluid 34 (e.g., for no more than about 10 seconds), is placed on the test surface 24. The controller 30 operates the load arm 26 to apply pressure (e.g., about 60 kPa) to the test-sized sample 32 over the aperture. A prescribed load period is desirably observed to simulate actual use conditions, e.g., about 3 minutes. During this period, the controller 30 can operate the syringe drive pump 38 in a draw cycle to conduct the test fluid 32 into the syringe drive pump 38.

At the end of the load period (see Fig. 18B), the controller 30 releases pneumatic pressure on the load arm 26 and withdraws the load arm 26 from the test surface 24. The controller 30 immediately operates the syringe drive pump 38 in an expel cycle. The controller 30 ramps the citrated bovine whole blood pressure into the test block 22 at a prescribed rate, e.g., between 3 and 16 mmHg/s, and preferably 10 mmHg/s. The pressure within the supply conduit 36 is continuously monitored and recorded by the controller 30 over time.

The controller 30 continues ramping blood pressure at the prescribed rate until ultimate failure of the test-sized sample occurs (see Fig. 18C). Ultimate failure is indicated when the highest ramped pressure state is lost, indicating that the test-sized sample has lost adherence with the test surface 24 and can no longer withstand the pressure applied through the aperture. The controller 30 records the highest pressure state at which ultimate failure occurs for test-sized sample. This pressure is the burst strength of the pad assembly 10.

The highest pressure state (burst strength) observed is compared to a prescribed "pass-fail" criteria. In a representative example, burst strengths greater than 750 mmHg indicate a "pass." Burst strengths below 750 mmHg indicate a "fail." This criteria imposes a strict "pass"

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standard, as it represents a pressure level that is generally six times greater than normal human blood systolic pressure.

An alternative to ramping pressure continuously to ultimate failure is to ramp at between 3 and 16 mmHg/s (preferably 10 mmHg/s) to a constant elevated blood pressure (for example 250 mmHg) and hold for a predetermined period (for example 10 minutes). In this test, a pass-fail criteria could treat as a "pass" a test-sized sample that held blood pressure for the 10 minutes hold test period, while treating as a "fail" a test-sized sample that does not hold blood pressure for 10 minutes hold period.

Statistically significant samples of entire production lots of tissue dressing pad assemblies can be validated using the above-described test fixture 20 and test methodology. To expedite validation, several test block 22s, each with a dedicated load arm 26 and test fluid supply conduit 36, coupled by manifolds to a single source of pneumatic pressure and a syringe drive pump 38, can be operated in tandem using a single controller 30. The pass-fail criteria can be defined with a composite pass-fail rate for the entire lot. For example, ultimate burst strengths of 75% or more of the lot of greater than 750 mmHg can correlate to a statistically valid "pass" of the entire lot. Ultimate burst strengths of less than 75% of the lot below 750 mmHg can correlate to a statistically valid "fail" of the entire lot.

2. Discernment of an Aging Phenomenon

Using the test fixture 20 and methodology described above, the existence of a surprising yet beneficial aging phenomenon can be discerned for the densified tissue dressing pad assemblies. Simply stated, with storage time prior to use -- i.e., after manufacturing in the manner described above, sterilization, packaging in the pouch

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16, and storage without use -- the adhesive properties of the densified tissue dressing pad assemblies improves significantly. Due to the aging phenomenon, lots of tissue dressing pad assemblies that failed the pass-fail
5 criteria when tested within days after manufacture, sterilization, and pouching -- when retested two or more months later, pass the pass-fail criteria.

EXAMPLE 2

The Aging Phenomenon

10 A procedure was initiated to retest lots that had failed initial testing, because an apparent increase in adhesive efficacy performance over time had been observed, including better performance at six and twelve months than immediately following production.

15 The following data was derived from seven lots of tissue dressing pad assemblies that had failed final product testing and were retested after a minimum of two months aging. The "Pressure" in Tables 1 and 2 is the highest pressure state at which ultimate failure occurred
20 for test samples (i.e., the burst strength), as described above. As Tables 1 and 2 show, six of seven lots demonstrated an increase in performance, which, for most of them, was a dramatic increase.

Table 1:
Increase in Adhesive Properties Due to Aging Phenomenon

Product Lot #	Original Results			Aged Results		
	Date	Pad Assemblies Above Minimum Pressure	Average Pressure	Date	Pad Assemblies Above Minimum Pressure	Average Pressure
(PL88)	2/25/2004	65%	935	7/23/2004	80%	1031
(PL90)	2/25/2004	65%	924	7/24/2004	90%	1242
(PL97)	3/9/2004	40%	772	7/27/2004	90%	1054
(PL100)	3/17/2004	64%	955	7/23/2004	90%	1139
(PL112)	4/22/2004	70%	919	7/27/2004	60%	867
(PL113)	5/6/2004	60%	849	7/26/2004	90%	1120
(PL124)	5/19/2004	50%	767	7/22/2004	80%	1022
Average		59%	874		83%	1068

Table 2:
Increase in Adhesive Properties Due to Aging Phenomenon

Product Lot #	Percent Change in Passing Pad Assemblies	Pressure Change	Pressure Percent Change
PL88)	15	96	10
(PL90)	25	318	34
(PL97)	50	282	37
(PL100)	26	184	19
(PL112)	-10	-52	-6
(PL113)	30	271	32
(PL124)	30	255	33
Average	24	193	23

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Subsequent lots were evaluated in the same way. The following Table 3 summarizes the lot pass-fail statistics during this subsequent time. Half of the lots passed on the original testing performed as soon as practical after return from sterilization by gamma irradiation. The fifty percent (50%) of lots that did not initially pass were retested after a minimum of two months aging time. Of those lots, seventy-nine percent (79%) passed, confirming the existence of the aging phenomenon, bringing the total pass rate for the lots to ninety percent (90%).

Table 3:
Increase in Adhesive Properties Due to Aging Phenomenon

Lots That Passed First Time	Lots That Failed First Time	Passed After "Aging Effect"	Failed After "Aging Effect"
128	127		127
129	132	132	
130	133		133
131	134	134	
135	136	136	
144	137	137	
146	138	138	
151	139		139
154	140		140
155	141	141	
157	142	142	
158	143	143	
160	145	145	
164	147	147	
166	148	148	
171	149	149	
172	150	150	
173	152	152	
174	153	153	
175	156		156
176	159	159	
177	161	161	
178	162		162
179	163	163	
180	165	165	
181	167	167	
182	168	168	
183	169	169	
184	170	170	
29	29	23	6
% of Retested Lots	N/A	79	21
% of Total Lots	50	40	10

Fourteen of the above referenced lots had the validation data using the test fixture 20 for both the

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initial and aged testing entered into a data template. They are tabulated below in Table 4. The changes in the lot average burst pressures and the percentage of tested pad assemblies 10 that meet the pass-fail criteria demonstrate an increase in efficacy. Table 4 demonstrates that the two lots (156 and 162) that still did not pass after aging nevertheless demonstrate increases in adhesive efficacy. The average percentage increase in burst pressures is thirty-eight percent (38%). The number of tested tissue dressing pad assemblies meeting the pass-fail criteria increased fifty-nine percent (59%) over the initial test data.

Table 4:
Increase in Adhesive Properties Due to Aging Phenomenon

Lot	Initial Average Burst Pressure	Aged Average Burst Pressure	% Change	Initial Percent of Pad Assemblies Meeting Criteria	Aged Percent of Pad Assemblies Meeting Criteria	% Change
136	857	877	2	68	79	16
141	758	1020	35	60	79	32
148	757	1055	39	50	92	84
152	843	986	17	54	92	70
153	974	1096	13	58	92	59
156	776	872	12	50	71	42
159	794	1082	36	50	83	66
161	704	1305	85	42	96	129
162	617	939	52	30	67	123
163	765	1908	149	48	92	92
165	903	899	0	71	83	17
167	813	957	18	67	75	12
168	800	959	20	71	79	11
170	772	1145	48	54	96	78
Average	795	1079	38	55	84	59

The enhancement of performance of the tissue dressing pad assembly 10 over storage time, called the aging phenomenon, is dramatic and real. The aging phenomenon demonstrates the robustness and longevity of resistance to dissolution of the chitosan matrix 12 composition described above, which improves over time.

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3. Discernment of Adhesive/Cohesive Sealing
Properties Among Different Tissue
Dressing Pad Assembly Configurations

Using the test fixture 20 and methodology described
5 above, the differences in densified tissue dressing pad
assemblies manufactured in different ways can be
discerned and quantified.

For example, using the test fixture 20 and
methodology described above, it can be discerned that the
10 temperature at which the chitosan matrix 12 is frozen
during manufacture affects the not only the structure of
the matrix but its adhesive and cohesive properties, as
well.

The differences in the structure of the uncompressed
15 chitosan matrix 12 frozen at different temperatures can
be visually observed. When frozen in Teflon coated, 5 cm
diameter aluminum mold on a shelf at -10°C, the structure
of the uncompressed chitosan matrix 12 has course, openly
spaced and vertical lamella throughout the sponge
20 structure. When frozen in Teflon coated, 5 cm diameter
aluminum mold on a shelf at -25°C, the structure of the
uncompressed chitosan matrix 12 has less course, more
closely spaced, but still vertical lamella. When frozen
in Teflon coated, 5 cm diameter aluminum mold on a shelf
25 at -40°C, the structure of the uncompressed chitosan
matrix 12 has fine, most closely spaced lamella radiating
from the mold edge toward the top middle portion of the
sponge. In this later condition, the uncompressed
chitosan matrix 12 comprises more of a reinforced inter-
30 meshing structure that is better suited to the
densification step where compression load is applied
normal to the matrix surface.

Using the test fixture 20 and methodology described
above to assess the burst strength of the three types of
35 chitosan matrixes, it can be demonstrated that the

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adhesive properties of a given chitosan matrix 12 improve in relation to a decrease in freezing temperature.. Fig. 35 is a graphical demonstration of the underlying data. Three data sets are plotted in Fig. 19 along the x-axis by freezing temperature (-10°C, -25°C, and -40°C), with the temperature decreasing to the right) and along the y-axis by burst pressure (in mmHg) as measured by the test fixture 20 and methodology described above. The ANOVA analysis of the three data sets (n=10, n=10, and n=18 for -10°C, -25°C, and -40°C, respectively) generated a very small p-value ($p = 11.77E-11$). It can be seen from Fig. 35 that the adhesive properties of the chitosan matrix 12 improve as the physical structure of the matrix changes from a course, open, vertical lamella structure to a fine, reinforced cross-meshing lamella structure.

Fig. 19 also demonstrates that the test fixture 20 and methodology described above yield reproducible data that is sensitive enough to distinguish among "less effective" and "more effective" chitosan matrix 12es.

E. Altering the Compliance Properties of a Hydrophilic Polymer Sponge Structure

Immediately prior to use, the tissue dressing pad assembly 10 is removed from its pouch 16 (as shown in Figs. 4 to 6). Due to its low moisture content, the tissue dressing pad assembly 10, upon removed from the pouch 16, can seem to be relatively inflexible and may not immediately mate well with curved and irregular surfaces of the targeted injury site. Bending and/or molding of the pad assembly 10 prior to placement on the targeted injury site has been already described and recommended. The ability to shape the pad assembly 10 is especially important when attempting to control strong bleeding, since apposition of the pad assembly 10 immediately against an injured vessel is necessary to control severe bleeding. Generally, these bleeding

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vessels are deep within irregularly shaped wounds.

In hydrophilic polymer sponge structure, of which the pad assembly 10 is but one example, the more flexible and compliant the structure is, the more resistant it is to tearing and fragmentation as the structure is made to conform to the shape of the wound and achieve apposition of the sponge structure with the underlying irregular surface of the injury. Resistance to tearing and fragmentation is a benefit, as it maintains wound sealing and hemostatic efficacy. Compliance and flexibility provide an ability to load a hydrophilic polymer sponge structure (e.g., the pad assembly 10) against a deep or crevice shaped wound without cracking or significant pad assembly 10 dissolution.

Improved flexibility and compliance by the use of certain plasticizing agents in solution with the chitosan may be problematic, because certain plasticizers can change other structural attributes of the pad assembly 10. For example, chitosan glutamate and chitosan lactate are more compliant than chitosan acetate. However, glutamate and lactate chitosan acid salts rapidly dissolve in the presence of blood, while the chitosan acetate salt does not. Thus, improved compliance and flexibility can be offset by reduced robustness and longevity of resistance to dissolution.

Improved compliance and flexibility can be achieved by mechanical manipulation of any hydrophilic polymer sponge structure after manufacture, without loss of beneficial features of robustness and longevity of resistance to dissolution. Several ways in which such mechanical manipulation can be accomplished after manufacture will now be described. While the methodologies are described in the context of the chitosan matrix 12, it should be appreciated that the methodologies are broadly applicable for use with any

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form of hydrophilic polymer sponge structure, of which the chitosan matrix 12 is but one example.

**1. Controlled Micro-Fracturing of a
Hydrophilic Polymer Sponge Structure**

5 Controlled micro-fracturing of the substructure of a hydrophilic polymer sponge structure such as the chitosan matrix 12 can be accomplished by systematic mechanical pre-conditioning of the dry pad assembly 10. This form of controlled mechanical pre-conditioning of the pad
10 assembly 10 can achieve improved flexibility and compliance, without engendering gross failure of the pad assembly 10 at its time of use.

Desirably, as Fig. 20 shows, pre-conditioning can be performed with the pad assembly 10 sealed within its
15 pouch 16. As Fig. 20 shows, maintaining the active face of the pad assembly 10 (i.e., the chitosan matrix 12) upright, manual repetitive digital impressions 48 of 1 to 1.5 mm depth can be applied over the entire surface. After application of the local pressure, and Fig. 21A
20 shows, one edge of the square pad assembly 10, with active face remaining upright, can be attached to the side of a 7.5 cm diameter x 12 cm long cylinder 50. The cylinder 50 is then rolled onto the pad assembly 10 to produce a 7.5 cm diameter concave in the pad assembly 10.
25 The cylinder 50 can be released and the pad assembly 10 rotated 90° (see Fig. 21B) to enable another 7.5 cm diameter concave to be formed into the pad assembly 10. After this treatment, the pad assembly 10 can be flipped (i.e., with the backing 14 now upright) (see Figs. 21C
30 and 21D) to enable 90° offset, 7.5 cm diameter concaves to be formed in the backing 14 of the pad assembly 10. It is envisioned that the manipulation of the pad assembly 10 described here would be performed mechanically during its processing immediately prior to its loading and
35 sealing into the final shipment package.

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The mechanical pre-conditioning described above is not limited to the pre-conditioning by digital probing and/or drawing over cylinders. The pre-conditioning may also include any technique which provides for mechanical change inside any hydrophilic polymer sponge structure resulting in enhanced sponge flexural modulus without significant loss of sponge hemostatic efficacy. Such pre-conditioning would include mechanical manipulations of any hydrophilic sponge structure including, but not limited to, mechanical manipulations by bending, twisting, rotating, vibrating, probing, compressing, extending, shaking and kneading.

Example 3

Swine Femoral Artery Injury Study

Chitosan pad assemblies were mechanically pre-conditioned for improved flexibility and compliance, as described above, for use in a 240 minute, severe-bleeding injury model. Swine (N=14), of near 45 kg each, were anaesthetized (Telazol induction, buprenorphine, isoflurane in oxygen) with monitoring of mean arterial pressure and cardiovascular support with crystalloids and hypertonic saline. Transverse skin and muscular incisions to simulate a wound, not following tissue planes as would occur in normal surgery, were made in left and right groin areas of each animal to expose and partially isolate left and right femoral arteries. The exposed femoral arteries were 2.5 cm to 4.0 cm below the external tissue surface. Bupivacaine was administered over the exposed femoral artery, prior to making the injury, as an analgesic, and also to reduce vasospasm. The femoral artery injury, at 1-2 cm from the inguinal canal, was made, by perforation with a 2.7 mm vascular punch, resulting in persistent strong bleeding after release of gauze held over the injury for 1 minute. Two sponges of Medline Gauze Sponge (7.5 cm x 7.5 cm & 12 ply) were

- 40 -

doubled over to give a control test piece of 48 ply gauze with dimensions 7.5 cm x 3.8 cm; hence referred to as 48PG. The pre-conditioned chitosan pad assembly 10 was cut into 4 test pieces of 5 cm x 5 cm x 0.55 cm; hence referred to as HCB. Two of the four HCB pieces of each chitosan pad assembly 10 were randomly selected for possible use in each injury trial. In attempting to achieve hemostasis, the HCB or 48PG was applied immediately over the perforation with support from a 7.5 cm roll of gauze and held firmly over the injury for 3 minutes. The pressure used to control the injury was just sufficient to stop arterial blood flow as observed by monitoring the pulse, distal to the injury. Pressure was released after 3 minutes with the 7.5 cm gauze roll left in place over the test piece. Time of hemostasis was recorded for each test piece. If the first test piece attempt did not achieve hemostasis within 30 minutes, a second test piece attempt with the same pad assembly 10 was allowed. If the second attempt was also unable to achieve and maintain hemostasis for at least 240 minutes, then the HCB or 48PG application was recorded as a failure. If 48PG had been used in the first application and it had been unsuccessful in the first 30 minutes, then the HCB pad assembly 10 could be used as a rescue pad assembly 10. Conversely, if the HCB had been used first and it had been unsuccessful in the first 30 minutes then 48PG could be used as a rescue pad assembly 10. If neither HCB nor 48PG were successful in achieving hemostasis in the one injury over at least 30 minutes, then the injury would be clamped to allow the other artery to be used. In cases of 240 minutes of hemostasis, test pieces were evaluated for chronic intra-operative success. The pulse was checked distally to establish whether the artery was patent and the test piece (HCB or 48PG) was removed to check for clot durability or

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bleeding. Test pieces were examined for integrity, gelling and adhesion to tissue. Blood loss from the femoral artery was recorded. Samples were collected for histology. The order of application in the second femoral injury on the animal was the opposite of the order in the first femoral injury. All fourteen animals (28 injuries) were tested in this way.

In this study, 100% of the HCB tests (N=25) were hemostatic after 30 minutes while only 21% of the 48PG (N=14) were hemostatic after the same time. As a result of the 100% and 21% hemostasis of the HCB and 48PG tests respectively at 30 minutes, there were no rescue applications with 48PG, while there were 11 rescue applications with the HCB. At 240 minutes, 84% of the HCB tests were hemostatic while only 7% of the 48PG were hemostatic. Statistical analysis by Fischer's Exact Test demonstrates a significant ($P < 0.001$) difference in hemostatic efficacy between the 48PG and HCB groups in this model. The results are summarized below in Table 5 and Table 6.

TABLE 5:
Summary of Test Hemostasis Results in Femoral Artery Study

Test Type	Hemostasis at 30 mins.		Hemostasis at 240 mins.	
	Success	Failure	Success	Failure
48PG 1st App	3	11	1	13
48PG Rescue	0	0	0	0
HCB 1 st App	14	0	12	2
HCB Rescue	11	0	9	2

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TABLE 6:
Summary of All Test Piece Time to Hemorrhage in
Femoral Artery Study

Injury Indice #	TIME TO HEMORRHAGE (mins.)					
	HCB 1st App		48PG		HCB Rescue	
	Test piece 1	Test piece 2	Test piece 1	Test piece 2	Test piece 1	Test piece 2
1	5	240	0	5	5	240
2	5	240	5	5	5	240
3	10	240	5	5	12	240
4	25	240	5	5	235	
5	130		5	5	240	
6	210		5	5	240	
7	240		5	5	20	240
8	240		5	5	240	
9	240		5	92		
10	240		5	5	240	
11	240		10	5	240	
12	240		20	3	205	
13	240		45			
14	240		240			

5

Also flexural testing and acute in vitro simulated arterial wound seal test (using the test fixture 20 and methodology described above, which will also sometimes be called in shorthand "SAWS" or "the SAWS test") were performed on manipulated pad assemblies and non-manipulated pad assemblies. Two strips of 10 cm x 1.27 cm x 0.55 cm were removed from one half of each pad assembly 10. These were used to test flexural modulus in a three-point bend test. Three point flexural testing on an Instron uniaxial mechanical tester, model number 5844; with a 50 N load cell was performed to determine flexural modulus for the 0.55 cm thick test pieces with span 5.8 cm and crosshead speed of 0.235 cm/s. The other halves of the pad assemblies were used in the SAWS test. The results of flexural testing are shown below in Table 7. The flexural testing demonstrates a significant improvement in flexibility with the mechanical pre-

20

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conditioning. The results of the SAWS testing are shown below in Table 8.

The SAWS test results indicate that there is a 32.4% loss in mean resistance to rupture pressure from 1114 mmHg to 753.7 mmHg in the treated test samples compared to the untreated controls. This in vitro testing is on the flat test bed surface of the SAWS tester; however, on the irregular curved surface of an injury, as demonstrated in the femoral artery model, the treated sample exhibited a high level of efficacy. The 63% reduction in stiffness, afforded by the mechanical manipulation, allows ready apposition of chitosan matrix to injury; and this demonstrably offsets the 32.4% loss in SAWS efficacy.

15

TABLE 7:
Summary of Flexural Modulus Testing

<i>Groups</i>	<i>Count</i>	<i>Sum</i>	<i>Average (MPa)</i>	<i>Variance (MPa²)</i>
Untreated control pieces	12	84.1	7.01	2.56
Treated test pieces	12	28.7	2.39	0.56

ANOVA $\alpha = 0.05$

<i>Source of Variation</i>	<i>P-value</i>	<i>F crit</i>
Between Groups	7.13E-09	4.30

20

TABLE 8:
Summary of SAWS Testing of Mechanically Pre-Conditioned Samples

		<i>Rupture Pressure (mmHg)</i>	
		<i>Untreated control</i>	<i>Treated test pieces</i>
	Mean (N=16)	1114.75	753.69
	Standard Deviation	364.38	215.21

25

2. Controlled Macro-Texturing of a Hydrophilic Polymer Sponge Structure

Controlled macro-texturing (by the formation of deep relief patterns) in a given hydrophilic polymer sponge structure can achieve improved flexibility and

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compliance, without engendering gross failure of the pad assembly 10 at its time of use. With regard to the chitosan matrix 12, the deep relief patterns can be formed either on the active surface of the chitosan matrix 12, or on the backing 14, or both sides.

As Figs. 23A and 23B show, deep (0.25-0.50 cm) relief surface patterns 52 (macro-textured surfaces) can be created in the pad assembly 10 by sponge thermal compression at 80 °C. The sponge thermal compression can be performed using a positive relief press platen 54, which includes a controlled heater assembly 56. Various representative examples of the types of relief patterns 52 that can be used are shown in Figs. 24A to 24D. The relief pattern negative is formed from a positive relief attached to the heated platen 54.

The purpose of the patterns 52 is to enhance dry pad assembly compliance by reduction in flexural resistance orthogonal to the relief 52, so that the relief pattern acts much like a local hinge to allow enhanced flexure along its length.

It is preferred that this relief 52 is applied in the backing 14 of the pad assembly 10 and not in the chitosan matrix 12, whose role is to provide hemostasis by injury sealing and promoting local clot formation. Macro-textured deep relief patterns 52 in the base chitosan matrix 12 can provide for loss of sealing by providing channels for blood to escape through the chitosan matrix 12.

In order to mitigate this possibility, alternative relief patterns 52 of the type shown in Fig. 24E and 24F may be used in a base relief, which would be less likely to cause loss of sealing. It is therefore possible that the relief 52 may be use in the base of the matrix, however this is still less preferred compared to its use in the backing 14 or top surface of the matrix. By using

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two positive relief surfaces attached to top and bottom platens during sponge compression, it is also possible to apply relief patterns in top and bottom surfaces of the pad assembly 10 simultaneously. However it is more preferable that a single, deep relief is created by use of one positive relief in the top surface of the chitosan matrix 12, as Figs 18A and 18B show.

Example 4

Mechanical flexure testing was carried out on a test pad assemblies (each 10 cm x 10 cm x 0.55 cm, with adherent backing 14 -- 3M 1774T polyethylene foam medical tape 0.056 cm thick). One pad assembly 10 (Pad 1) comprised a chitosan matrix 12 having a predominantly vertical lamella structure (i.e., manufactured at a warmer relative freezing temperature, as described above). The other pad assembly 10 (Pad 2) comprised a chitosan matrix 12 having a predominantly horizontal, intermeshed lamella structure (i.e., manufactured at a colder relative freezing temperature, as described above).

Each Pad 1 and 2 was cut in half. Two halves (5 cm x 10 cm x 0.55 cm) of each compressed chitosan pads 1 and 2, were locally compressed at 80 °C to produce the relief pattern on the backing 14, in the form of Fig. 19A. The other halves of the pads 1 and 2 were left untreated to be used as controls.

Three test pieces (10 cm x 1.27 cm x 0.55 cm) were cut from each half of the pad assembly 10 using a scalpel. These test pieces were subjected to three point flex testing. The test pieces had relief indentations 0.25 cm deep and 0.25 cm wide at the top surface. Each indentation was separated from its neighbor by 1.27 cm. Three point flex testing on an Instron uniaxial mechanical tester, model number 5844, with a 50 N load cell was performed to determine flexural modulus for the

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0.55 cm thick test pieces with span 5.8 cm and crosshead speed of 0.235 cm/s. Flexural load was plotted against mid-point flexural displacement for the two pads 1 and 2 (treated and untreated) and are shown, respectively, in Figs. 25A and 25B. Flexural moduli of treated versus untreated test pieces for Pads 1 and 2 (treated and untreated) are shown in Tables 9A and 9B, respectively.

The flexural testing demonstrates a significant improvement in flexibility with controlled macro-texturing of either type of the dry pad assembly 10.

Table 9A:
Summary of Mechanical Testing of
Pad Type 1 (Vertical Lamella)

	Flexure load at Maximum Flexure stress (N)	Modulus (Automatic) (MPa)	Modulus (Young's - Cursor) (MPa)
1	0.5	2.7	2.7
2	0.5	2.3	2.3
3	0.6	3.1	3.1
4	1.2	8.3	8.2
5	1.1	9.5	9.5
6	1.1	8.5	8.5

Specimen Label 1	Right Edge - Hinged w/Flex
Specimen Label 2	Inside Right Edge - Hinged w/Flex
Specimen Label 3	Middle - Hinged w/Flex
Specimen Label 4	Middle - Control
Specimen Label 5	Inside Left Edge - Control
Specimen Label 6	Left Edge - Control

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Table 9B:
Summary of Mechanical Testing of
Pad Type 2 (Horizontal Lamella)

	Flexure load at Maximum Flexure stress (N)	Modulus (Automatic) (MPa)	Modulus (Young's - Cursor) (MPa)
1	0.4	2.1	2.0
2	0.5	2.7	2.7
3	0.5	3.0	3.0
4	0.9	6.1	6.1
5	0.9	5.6	5.7
6	0.8	6.3	6.3

5

Specimen Label 1	Right Edge - Hinged
Specimen Label 2	Inside Right Edge - Hinged
Specimen Label 3	Middle - Hinged
Specimen Label 4	Middle - Control
Specimen Label 5	Inside Left Edge - Control
Specimen Label 6	Left Edge - Control

3. Controlled Formation of Vertical Channels in a Hydrophilic Polymer Sponge Structure

A controlled introduction of blood into, and
 10 through the bulk of a given hydrophilic polymer sponge
 structure, of which the chitosan matrix 12 is but one
 example, is desirable for improved initial structural
 compliance and also for longevity of resistance to
 structure dissolution. Controlled formation of vertical
 15 channels into a given hydrophilic polymer sponge
 structure can achieve improved flexibility and
 compliance, without engendering gross failure of the
 structure at its time of use.

A controlled introduction of blood into, and
 20 through the bulk of a hydrophilic polymer sponge
 structure is desirable for improved initial compliance of
 the structure and also for longevity of resistance to
 dissolution of the structure. Improved absorption of
 blood into a hydrophilic polymer sponge structure can be
 25 accomplished by the introduction of vertical channels
 into the structure. Channel cross sectional area, channel
 depth and channel number density can be controlled to
 ensure an appropriate rate of blood absorption and
 distribution of blood absorption into the hydrophilic

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polymer sponge structure. With respect to the chitosan matrix 12, typically, a 200% increase in chitosan matrix 12 mass associated with blood absorption from 5 g to 15 g can cause a flexural modulus reduction of near 72%, from 5 7 MPa to 2 MPa. Also, controlled introduction of blood into the chitosan matrix 12 can result in a more cohesive matrix.

This improvement in the strength of a hydrophilic polymer matrix is a consequence of reaction of blood 10 components, such as platelets and erythrocytes, with the same matrix. After introduction of blood into the sponge structure and allowance for time for the sponge structure and blood components to react to produce a blood and hydrophilic polymer sponge structure "amalgam," the 15 subsequent sponge structure is resistant to dissolution in body fluids and cannot be dissolved readily, especially in the case of a chitosan acid salt matrix, by the introduction of saline solution. Typically, prior to the reaction between blood and the hydrophilic polymer 20 sponge structure, especially in the case of a chitosan acid salt matrix, the introduction of saline causes rapid swelling, gelling and dissolution of the hydrophilic polymer sponge structure.

Still, excessive introduction of blood into a given 25 hydrophilic polymer sponge structure such as the chitosan matrix 12 can result in fluidized collapse. Therefore, mean channel cross-sectional area, mean channel depth and channel number density should be controlled to ensure that rate of blood absorption does not overwhelm the 30 structure of the hydrophilic polymer sponge structure.

Controlled distribution of vertical channels in the hydrophilic polymer sponge structure can be achieved during the freezing step of the sponge structure preparation, or alternatively it may be achieved 35 mechanically by perforation of the sponge structure

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during the compression (densification) step.

During the base nucleated freezing step, vertical channels can be introduced in the freezing solution by super-saturation of the same solution with residual gas.

5 The same gas nucleates bubbles at the base of the solution in the mold as it begins to freeze. The bubbles rise through the solution during the freezing step leaving vertical channels. Sublimation of the ice around the channels during the lyophilization preserves the
10 channels within the resultant sponge matrix.

Alternatively, channels may also be formed during the freezing step by the positioning of vertical rod elements in the base of the molds. Preferably the molds are formed from, but are not limited to, a metallic
15 element such as iron, nickel, silver, copper, aluminum, aluminum alloy, titanium, titanium alloy, vanadium, molybdenum, gold, rhodium, palladium, platinum and/or combinations thereof. The metallic rod elements are preferably formed from, but not limited to, a metallic
20 element such as iron, nickel, silver, copper, aluminum, aluminum alloy, titanium, titanium alloy, vanadium, molybdenum, gold, palladium, rhodium or platinum and/or combinations thereof. The molds may also be coated with thin, inert metallic coatings such as titanium, chromium,
25 tungsten, vanadium, nickel, molybdenum, gold and platinum in order to ensure there is no reaction with the acid component of the chitosan solution and the chitosan salt matrix. Thermally insulating coatings or elements may be used in conjunction with the metallic molds and vertical
30 rod elements to control heat transfer in the molds and in the vertical rod elements. Although metallic molds and vertical metallic rod elements are preferable, plastic molds and vertical plastic mold rod elements can be a convenient alternative for creating channels. An
35 advantage of the metallic molds and their metallic rod

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elements combined with local placement of thermally insulating elements is that they also provide opportunity for improved control of heat flow and structure within the freezing sponge structure. This improvement in heat
5 flow control results from large thermal conductivity differences between thermally conducting and thermally insulating elements in the mold and also the ability to create local thermal gradients within the bulk of the hydrophilic polymer sponge structure solution through the
10 rod elements.

After lyophilization of the sponge structure, vertical channels can be introduced during the compression (densification) process. For example, as shown in Figs. 26A and 26B, a compression fixture 58
15 carries a pincushion geometrical patterned device 60 for placing short (2.5 mm depth) equally spaced perforations 62 in the base of the sponge structure (as shown in Fig. 27).

The intent of the perforations 62 is to allow local
20 infiltration of blood at a slow controlled rate into and through the base of the hydrophilic polymer sponge structure. The purpose of this infiltration is first to allow for a more rapid flexural change in the matrix by plasticization of the dry sponge with blood. Secondly, it
25 is intended to provide for a more uniform dispersion and mixing of blood through the matrix in order to stabilize the matrix to resist subsequent dissolution agents present within the body cavity. In the absence of the perforated base surface, it is seen after 1, 6, 16 and 31
30 minutes that blood only penetrates superficially into the sponge structure (< 1.5 mm depth) while in the presence of the perforations that blood penetrates from 1.8 to 2.3 mm depth after 31 minutes. There is a resultant more rapid decrease in flexural modulus in the perforated
35 matrix compared to a matrix without perforations.

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Absorption properties of respective matrix types at 1, 6, 16, and 31 minutes are demonstrated in Fig. 28.

Example 5

In vitro SAWS testing of both perforated and non-perforated chitosan matrixes, demonstrates that both matrix types are effective in sealing strong blood flow, as Table 10 demonstrates.

Table 10:
Summary of SAWS *in vitro* Testing of Perforated and Non-Perforated Test Pieces>

	<i>Rupture Pressure (mmHg)</i>	
	<i>Treated Test pieces</i>	<i>Untreated Controls</i>
Mean (N = 8)	835.6	1125.5
Standard Deviation	324.8	294.3

The results of the testing of samples perforated with the pin-cushion design of Fig. 27 demonstrate a significantly improved rate of absorption of blood compared to the non-perforated control. The rate of blood absorption in the perforated test pieces over the first 30 seconds of application of the pad assembly 10 is two to three times higher than that in the control sample, thus providing for a more rapid enhancement of compliance of the pad assembly 10 when perforated and allowing for improved apposition of hydrophilic polymer sponge structures on seriously bleeding injuries in complex wound areas.

II. Tissue Dressing Sheet Assembly

A. Overview

Fig. 29 shows a tissue dressing sheet assembly 64. Like the tissue dressing pad assembly 10 previously described and shown in Fig. 1, the tissue dressing sheet assembly 64 is capable, in use, of adhering to tissue in the presence of blood or body fluids or moisture. The tissue dressing sheet assembly 64 can thus also be used to stanch, seal, and/or stabilize a site of tissue injury

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or trauma or access against bleeding or other forms of fluid loss. As for the tissue dressing pad assembly 10, the tissue site treated by the tissue dressing sheet assembly 64 can comprise, e.g., arterial and/or venous
5 bleeding, or laceration, or entrance/entry wound, or tissue puncture, or catheter access site, or burn, or suturing. The tissue dressing sheet assembly 64 can also form an anti-bacterial and/or anti-microbial and/or anti-viral protective barrier at or about the tissue treatment
10 site.

Fig. 29 shows the tissue dressing sheet assembly 64 in its condition prior to use. As Fig. 30 best shows, the tissue dressing sheet assembly 64 comprises a sheet 66 of woven or non-woven mesh material enveloped between layers
15 of a tissue dressing matrix 68. The tissue dressing matrix 68 impregnates the sheet 66. The tissue dressing matrix 68 desirably comprises a chitosan matrix 12 as described in connection with the tissue dressing pad assembly 10. However, other hydrophilic polymer sponge
20 structures can be used.

The size, shape, and configuration of the tissue dressing sheet assembly 64 can vary according to its intended use. The sheet assembly 64 can be rectilinear, elongated, square, round, oval, or composite or complex
25 combinations thereof.

The tissue dressing sheet assembly 64 achieves rapid compliance of the hydrophilic polymer sponge structure in a bleeding field. The tissue dressing sheet assembly 64 is preferably thin (compared to the pad assembly 10),
30 being in the range of between 0.5 mm to 1.5 mm in thickness. A preferred form of the thin reinforced structure of the sheet assembly 64 comprises a chitosan matrix 12 or sponge, at the typical chitosan matrix density of 0.10 to 0.20 g/cm³, reinforced by absorbable
35 bandage webbing such as cotton gauze and the resultant

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bandage thickness is 1.5 mm or less.

The sheet assembly 64 can be prepared as a compact sheet form (e.g. 10 cm x 10 cm x 0.1 cm) for packaging in a multi-sheet flat form 70 (as Fig. 31A shows) or as an elongated sheet form (e.g. 10 cm x 150 cm x 0.1 cm) for packaging in a compact rolled sheet form 72 (as Fig. 31B shows). The sheet 66 provides reinforcement throughout the assembly 64, while also presenting significant specific hydrophilic polymer sponge structure surface area availability for blood absorption. The presence of the woven or non-woven sheet 66 also serves to reinforce the overall hydrophilic polymer sponge structure.

The sheet 66 can comprise woven and non-woven mesh materials, formed, e.g., from cellulose derived material such as gauze cotton mesh. Examples of preferred reinforcing materials include absorbent low-modulus meshes and/or porous films and/or porous sponges and/or weaves of synthetic and naturally occurring polymers. Synthetic biodegradable materials may include, but are not limited to, poly(glycolic acid), poly(lactic acid), poly(ϵ -caprolactone), poly(β -hydroxybutyric acid), poly(β -hydroxyvaleric acid), polydioxanone, poly(ethylene oxide), poly(malic acid), poly(tartronic acid), polyphosphazene, polyhydroxybutyrate and the copolymers of the monomers used to synthesize the above-mentioned polymers. Naturally occurring polymers may include, but are not limited to, cellulose, chitin, algin, starch, dextran, collagen and albumen. Non-degradable synthetic reinforcing materials may include but are not limited to polyethylene, polyethylene copolymers, polypropylene, polypropylene copolymers, metallocene polymers, polyurethanes, polyvinylchloride polymers, polyesters and polyamides.

B. Use of the Tissue Dressing Sheet Assembly

The thin sheet assembly 64 possesses very good

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compliance and allows for excellent apposition of the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) immediately against the injury site. Also the reinforcement of the sheet enables the overall assembly to resist dissolution in a strong bleeding field. The sheet assembly 64 accommodates layering, compaction, and/or rolling -- i.e., "stuffing" (as Fig. 32 shows) -- of the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) within a wound site using pressure to further reinforce the overall structure against strong arterial and venous bleeding. By stuffing of the sheet structure over itself, as Fig. 32 shows, the interaction of the blood with the hydrophilic polymer (e.g., chitosan) infused within the webbing provides advantages for the application when the wounds are particularly deep or otherwise apparently inaccessible. The stuffing of the sheet assembly 64 into a bleeding wound and its compression on itself provide for a highly adhesive, insoluble and highly conforming bandage form.

C. Manufacture of the Tissue Dressing Sheet Assembly

A tissue dressing sheet assembly 64 (10 cm x 10 cm x 0.15 cm), with chitosan matrix 12 density near 0.15 gm/cm³, can be prepared by filling 11 cm x 11 cm x 2 cm deep aluminum mold with a two percent (2%) chitosan acetate solution (see Fig. 33, Step A) to a depth of 0.38 cm.

As Fig. 33 (Step B) shows, the sheet 66 -- comprising, e.g., a layer of absorbent gauze webbing 10 cm x 10 cm -- can be placed over the top of the solution in the mold and allowed to soak with chitosan. The chitosan impregnates the sheet 66.

As Fig. 33 (Step C) shows, a further 0.38 cm depth of chitosan can be poured over the top of the impregnated gauze sheet 66.

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As Fig. 33 (Step D) shows, the mold is placed in, e.g., a Virtis Genesis 25XL freeze dryer on a shelf at -30 °C. The solution is allowed to freeze, after which the ice is sublimated by lyophilization.

5 As Fig. 33 (Step E) shows, the resultant gauze reinforced sheet assembly 64 is pressed between platens at 80 °C to a thickness of 0.155 cm. The pressed sheet assembly 64 is then baked at 80 °C for thirty minutes (Fig. 33, Step F). The resulting sheet assemblies can
10 sterilized in a manner previously described. One or more sheet assemblies can be packaged within in a heat sealed foil lined pouch 74 or the like (see Fig. 34), either in sheet form or roll form for terminal sterilization and storage.

15

Example 6

Flexural Characteristics of the Tissue Dressing Sheet Assembly

Flexural three point bend testing of a tissue dressing sheet assembly 64 was performed. The three point
20 flexural testing was performed on an Instron uniaxial mechanical tester, model number 5844, with a 50 N load cell to determine flexural modulus test pieces with span 5.8 cm and crosshead speed of 0.235 cm/s. The results are shown in Fig. 35. Fig. 35 demonstrates that the 1.5 mm
25 thick tissue dressing sheet assemblies that were tested are significantly more compliant than the 5.5 mm thick tissue dressing pad assemblies.

Example 7

Adhesion Characteristics of the 30 Tissue Dressing Sheet Assembly

Test pieces (5 cm x 5 cm x 0.15 cm) of the tissue dressing sheet assembly 64 were cut within ninety-six hours of their production. The sheet assembly 64 was not subjected gamma radiation sterilization before testing.
35 The test pieces were soaked in citrated bovine whole

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blood for 10 seconds and immediately subjected to SAWS testing. During the test, three test pieces were layered together, presenting a composite chitosan density near 0.15 g/cm³. The result of this testing is shown in Fig.

5 36.

As Fig. 36a shows, the three layers of tissue dressing sheet assembly 64 held substantial physiological blood pressure of near 80 mmHg for an extended period (i.e., about 400 seconds). This indicates the presence of
10 sealing and clotting.

Based upon experience with the pad assemblies, better adhesion/cohesion properties were expected to result after the tissue dressing sheet assembly 64 underwent gamma irradiation. Fig. 36B confirms this:
15 after gamma-irradiation, three layers of tissue dressing sheet assembly 64 performed significantly like a 0.55 cm thick chitosan tissue pad 10.

III. Further Indications and Configurations for Hydrophilic Polymer Sponge Structures

20 The foregoing disclosure has focused upon the use of the tissue dressing pad assembly 10 and the tissue dressing sheet assembly 64 principally in the setting of stanching blood and/or fluid loss at a wound site. Other indications have been mentioned and certain of these and
25 other additional indications now will be described in greater detail.

Of course, it should be appreciated by now that the remarkable technical features that a compressed hydrophilic polymeric sponge structure, of which the
30 chitosan matrix is but one example, possesses can be incorporated into dressing structures of diverse shapes, sizes, and configurations, to serve a diverse number of different indications. As will be shown, the shapes, sizes, and configurations that a given compressed
35 hydrophilic polymer sponge structure (e.g., the chitosan

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matrix 12) can take are not limited to the pad assembly 10 and sheet assembly 64 described, and can transform according to the demands of a particular indication. Several representative examples follow, which are not
5 intended to be all inclusive of limiting.

A. Body Fluid Loss Control (e.g., Burns)

The control of bleeding represents but one indication where preservation of a body fluid is tantamount to preserving health and perhaps life. Another
10 such indication is in the treatment of burns.

Burns can occur by exposure to heat and fire, radiation, sunlight, electricity, or chemicals. Thin or superficial burns (also called first-degree burns) are red and painful. They swell a little, turn white when you
15 press on them, and the skin over the burn may peel off in one or two days. Thicker burns, called superficial partial-thickness and deep partial-thickness burns (also called second-degree burns), have blisters and are painful. There are also full-thickness burns (also called
20 third-degree burns), which cause damage to all layers of the skin. The burned skin looks white or charred. These burns may cause little or no pain if nerves are damaged.

The presence of a tissue burn region compromises the skin's ability in that region to control fluid loss
25 (leading to dehydration), as well as block entry of bacteria and microbes. Therefore, in the treatment of all burns, dressings are used to cover the burned area. The dressing keeps air off the area, reduces pain and protects blistered skin. The dressing also absorbs fluid
30 as the tissue burn heals. Anti-microbial creams or ointments and/or moisturizers are also used to prevent drying and to ward off infection.

A hydrophilic polymer sponge structure (e.g., a chitosan matrix 12 of the type already described), in
35 either the form of a pad assembly 10 or a sheet assembly

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64, can be used to treat a tissue burn region. The hydrophilic polymer sponge structure (e.g., chitosan matrix 12) will absorb fluids and adhere to cover the burn region. The hydrophilic polymer sponge structure
5 (e.g., the chitosan matrix 12) can also serve an anti-bacterial/anti-microbial protective barrier at the tissue burn region.

1. Composite Dressing Assembly

Figs. 37 and 38 show a composite dressing assembly
10 76 that can also be used in the treatment of a tissue burn region, as well as other injured tissue regions where relative large volumes of fluid seepage and/or bleeding may be anticipated. The composite dressing assembly 76 includes a fluid absorbent component 78 or
15 carrier and a hydrophilic polymer sponge structure (e.g., a chitosan matrix 12) that is carried by the fluid absorbent component 78.

The fluid absorbent component 78 can comprise a woven and non-woven mesh material, formed, e.g., from
20 cellulose derived material such as gauze cotton mesh. Other examples of the fluid absorbent component 78 include absorbent low-modulus meshes and/or porous films and/or porous sponges and/or weaves of synthetic and naturally occurring polymers. Synthetic biodegradable
25 materials may include, but are not limited to, poly(glycolic acid), poly(lactic acid), poly(ϵ -caprolactone), poly(β -hydroxybutyric acid), poly(β -hydroxyvaleric acid), polydioxanone, poly(ethylene oxide), poly(malic acid), poly(tartronic acid),
30 polyphosphazene, polyhydroxybutyrate and the copolymers of the monomers used to synthesize the above-mentioned polymers. Naturally occurring polymers may include, but are not limited to, cellulose, chitin, algin, starch, dextran, collagen and albumen. Non-degradable synthetic
35 reinforcing materials may include but are not limited to

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polyethylene, polyethylene copolymers, polypropylene, polypropylene copolymers, metallocene polymers, polyurethanes, polyvinylchloride polymers, polyesters and polyamides.

5 The hydrophilic polymer sponge structure can, e.g., comprise a chitosan matrix 12 of the type previously described, which desirably has undergone densification. Still, other types of a chitosan structure or other forms of hydrophilic polymer sponge structures or tissue
10 dressing matrixes in general can be used. The hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) can be secured to the adsorbent component by, e.g., direct adhesion to the hydrophilic polymer sponge structure and/or adhesive, or fibrin glue, or
15 cyanoacrylate glue.

 The primary function of the absorbent component 78, when placed in association with the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12), is to absorb residual fluids at or near the tissue burn region
20 (or other wound site). In this way, the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) need not bear the full fluid retention function of the composite assembly. As Fig. 37 shows, the periphery of the fluid absorbent component 78 desirably extends beyond
25 the periphery of the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12), to increase the reach and capacity of the fluid absorption function of the absorbent component 78.

 The absorbent component 78 thereby complements and
30 shares the fluid retention function of the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12). The absorbent component 78 serves to moderate the fluid retention load of the hydrophilic polymer sponge structure (e.g., the chitosan material), so that the
35 hydrophilic polymer sponge structure does not too quickly

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over-hydrate or become super-saturated with fluid or blood, thereby compromising its structural integrity.

As Fig. 39 shows, the interface between the absorbent component 78 and the hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) can be perforated 80 or otherwise rendered permeable, so that fluid retained within the hydrophilic polymer sponge structure can be readily transported into the absorbent component 78, thereby reducing the fluid-bearing load of the hydrophilic polymer sponge structure.

In use, the fluid absorbent component 78 can carry an adhesive to adhere to tissue. Alternatively, or in combination, a second conventional dressing (e.g., gauze) can be applied to secure the composite dressing assembly 76 and to provide a clean barrier for the wound. If the wound is to be subsequently submersed underwater, a water tight covering should be applied to prevent the composite dressing assembly 76 from becoming over-hydrated.

B. Antimicrobial Barriers

In certain indications, the focus of treatment becomes the prevention of ingress of bacteria and/or microbes through a tissue region that has been compromised, either by injury or by the need to establish an access portal to an interior tissue region. Examples of the latter situation include, e.g., the installation of an indwelling catheter to accommodate peritoneal dialysis, or the connection of an external urine or colostomy bag, or to accomplish parenteral nutrition, or to connect a sampling or monitoring device; or after the creation of an incision to access an interior region of the body during, e.g., a tracheotomy, or a laparoscopic or endoscopic procedure, or the introduction of a catheter instrument into a blood vessel.

In Figs. 40 and 41, one representative embodiment of an antimicrobial gasket assembly 82 is shown. The gasket

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assembly 82 is sized and configured to be placed over an access site, and, in particular, an access site where an indwelling catheter 88 resides. The antimicrobial gasket assembly 82 includes a tissue adhering carrier component 84, to which an anti-microbial component is secured. Desirably, the anti-microbial component comprises the chitosan matrix 12 of the type previously described, which has undergone densification. Still, other types of a chitosan structure, or other hydrophilic polymer sponge structures, or tissue dressing matrixes in general can be used.

The carrier component 84 desirably includes an adhesive surface 86, to attach the anti-microbial component (desirably, the chitosan matrix 12) over the access site. In Figs. 40 and 41, the anti-microbial component 12 and carrier 84 include a pass-through hole 90, which allows passage of the indwelling catheter 88 through it. In this arrangement, the interior diameter of the pass-through hole 90 approximates the exterior diameter of the indwelling catheter 88, to provide a tight, sealed fit. It should be appreciated that, in situations where there is only an incision or access site without a resident catheter, the anti-microbial component will not include the pass-through hole.

In an alternative arrangement (see Fig. 42), a tissue dressing pad assembly 10 as previously described is sized and configured proportionate to the area of the access site to comprise an anti-microbial gasket assembly 82. In this configuration, the pad assembly 10 can be provided with a pass-through hole 90 to accommodate passage of an indwelling catheter, if present.

In another alternative arrangement (see Fig. 43), a tissue dressing sheet assembly 64 as previously described is sized and configured proportionate to the area of the access site to comprise an anti-microbial gasket assembly

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82. In this configuration, the sheet assembly 64 can be provided with a pass-through hole 90 to accommodate passage of the indwelling catheter, if present.

Example 8

5

Anti-Microbial Feature

The densified chitosan acetate matrix and diverse forms of dressings that can incorporate the densified chitosan acetate matrix have anti-microbial efficacy as demonstrated by *in vitro* testing, as summarized in Table 11.

TABLE 11:
Results of USP 27<51> Testing of the Densified Chitosan Acetate Matrix.

Organism	Log ₁₀ Reduction at						
	0 hrs	24 hrs	48 hrs	72 hrs	7 days	14 days	28 days
<i>S. Aureus</i>	0.9	5.8	3.8	5.8	5.8	5.8	5.8
<i>P. Aeruginosa</i>	3.8	5.8	5.8	5.8	5.8	5.8	5.8
<i>E. coli</i>	0.0	2.8	5.1	5.1	5.1	5.1	5.1
<i>C. albicans</i>	5.5	5.5	5.5	5.5	5.5	5.5	5.5
<i>A. niger</i>	0.2	-0.3	0.8	0.6	-0.6	-0.3	-0.7

15

The excellent adhesive and mechanical properties of the densified chitosan matrix 12 make it eminently suitable for use in anti-microbial applications on the extremity (epidermal use) and inside the body. Such applications would include short to medium term (0-120 hour) control of infection and bleeding at catheter lead entry/exit points, at entry/exit points of biomedical devices for sampling and delivering application, and at severe injury sites when patient is in shock and unable to receive definitive surgical assistance.

25

C. Antiviral Patches

There are recurrent conditions that are caused by viral agents.

30

For example, herpes simplex virus type 1 ("HSV1") generally only infects those body tissues that lie above the waistline. It is HSV1 that causes cold sores in the majority of cases. Cold sores (or lesions) are a type of

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facial sore that are found either on the lips or else on the skin in the area near the mouth. Some equivalent terminology used for cold sores is "fever blisters" and the medical term "recurrent herpes labialis".

5 Herpes simplex virus type 2 ("HSV2") typically only infects those body tissues that lie below the waistline." It is this virus that is also known as "genital herpes". Both HSV 2 (as well as HSV1) can produce sores (also called lesions) in and around the vaginal area, on the
10 penis, around the anal opening, and on the buttocks or thighs. Occasionally, sores also appear on other parts of the body where the virus has entered through broken skin.

 Figs. 44 and 45 show a representative embodiment of an anti-viral patch assembly. The anti-viral patch
15 assembly 92 is sized and configured to be placed over a surface lesion of a type associated with HSV1 or HSV2, or other forms of viral skin infections, such as molluscum contagiosum and warts. The anti-viral patch assembly 92 includes a tissue adhering carrier component 94, to which
20 an anti-viral component is secured. Desirably, the anti-viral component comprises the chitosan matrix 12 of the type previously described, which has undergone densification. Still, other types of a chitosan structure, or other hydrophilic polymer sponge
25 structures, or tissue dressing matrixes in general can be used.

 The carrier component 94 includes an adhesive surface 96, to attach the anti-viral component (desirably, the chitosan matrix 12) over the lesion site.

30 In alternative arrangements (not shown), a tissue dressing pad assembly 10 or a tissue dressing sheet assembly 64 or a composite dressing assembly 76 as previously described can be sized and configured proportionate to the area of the lesion site to comprise
35 an anti-viral patch assembly. The excellent adhesive and

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mechanical properties of the densified compressed chitosan matrix 12 make it eminently suitable for use in anti-viral applications on the extremity (epidermal use) and inside the body. The presence of the anti-viral patch assembly 92 can kill viral agents and promote healing in the lesion region.

D. Bleeding Disorder Intervention

There are various types of bleeding or coagulation disorders. For example, hemophilia is an inherited bleeding, or coagulation, disorder. People with hemophilia lack the ability to stop bleeding because of the low levels, or complete absence, of specific proteins, called "factors," in their blood that are necessary for clotting. The lack of clotting factor causes people with hemophilia to bleed for longer periods of time than people whose blood factor levels are normal or work properly. Idiopathic thrombocytopenic purpura (ITP) is another blood coagulation disorder characterized by an abnormal decrease in the number of platelets in the blood. A decrease in platelets can result in easy bruising, bleeding gums, and internal bleeding.

A hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) incorporated into a tissue dressing pad assembly 10 or a tissue dressing sheet assembly 64 or a composite dressing assembly 76, all as previously described, can be sized and configured to be applied as an interventional dressing, to intervene in a bleeding episode experience by a person having hemophilia or another coagulation disorder. As previously described, the presence of the chitosan matrix 12 attracts red blood cell membranes, which fuse to chitosan matrix 12 upon contact. A clot can be formed very quickly and does not need the clotting proteins that are normally required for coagulation. The presence of the chitosan matrix 12 during a bleeding episode of a person having hemophilia

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or other coagulation disorder can accelerate the clotting process independent of the clotting cascade, which, in such people, is in some way compromised. For this reason, the presence of the chitosan matrix 12 on a dressing can be effective as an interventional tool for persons having a coagulation disorder like hemophilia.

E. Controlled Release of Therapeutic Agents

A hydrophilic polymer sponge structure (e.g., the chitosan matrix 12 as previously described) can provide a topically applied platform for the delivery of one or more therapeutic agents into the blood stream in a controlled release fashion. The therapeutic agents can be incorporated into the hydrophilic polymer sponge structure, e.g., either before or after the freezing step, and before the drying and densification steps. The rate at which the therapeutic agents are released from the hydrophilic polymer sponge structure can be controlled by the amount of densification. The more densified the hydrophilic polymer sponge structure is made to be, the slower will be the rate of release of the therapeutic agent incorporated into the structure.

Examples of therapeutic agents that can be incorporated into a hydrophilic polymer sponge structure (e.g., the chitosan matrix 12) include, but are not limited to, drugs or medications, stem cells, antibodies, anti-microbials, anti-virals, collagens, genes, DNA, and other therapeutic agents; hemostatic agents like fibrin; growth factors; and similar compounds.

F. Mucosal Surfaces

The beneficial properties of chitosan matrix 12 includes adherence to mucosal surfaces within the body, such as those lining the esophagus, gastro-intestinal tract, urinary tract, the mouth, nasal passages and airways, and lungs. This feature makes possible the incorporation of the chitosan matrix 12, e.g., in systems

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and devices directed to treating mucosal surfaces where the adhesive sealing characteristics, and/or accelerated clotting attributes, and/or anti-bacterial/anti-viral features of the chitosan matrix 12, as described, provides advantages. Such systems and methods can include the anastomosis of bowels and other gastro-intestinal surgical procedures, repairs to esophageal or stomach function, sealing about sutures, etc.

IV. Conclusion

It has been demonstrated that a hydrophilic polymer sponge structure like the chitosan matrix 12 can be readily adapted for association with dressings or platforms of various sizes and configurations -- in pad form, in sheet form, in composite form, in laminated form, in compliant form - such that a person of ordinary skill in the medical and/or surgical arts could adopt any hydrophilic polymer sponge structure like the chitosan matrix 12 to diverse indications on, in, or throughout the body.

Therefore, it should be apparent that above-described embodiments of this invention are merely descriptive of its principles and are not to be limited. The scope of this invention instead shall be determined from the scope of the following claims, including their equivalents.

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What is claimed is:

1. A tissue dressing comprising a hydrophilic polymer sponge structure that includes at least one of
5 (i) micro-fracturing of a substantial portion of the structure by mechanical manipulation prior to use, or
(ii) a surface relief pattern formed on a substantial portion of the structure prior to use, or (iii) a pattern of fluid inlet channels formed in a substantial portion of the structure prior to use.
- 10 2. A tissue dressing according to claim 1 wherein the hydrophilic polymer sponge structure includes a chitosan biomaterial.
3. A tissue dressing according to claim 1 wherein the hydrophilic polymer sponge structure has been
15 densified by compression prior to use to a density of between 0.6 to 0.1 g/cm³.
4. A tissue dressing according to claim 1, wherein the micro-fracturing results from at least one of bending, twisting, rotating, vibration, probing,
20 compressing, extending, shaking, or kneading.
5. A tissue dressing according to claim 1, wherein the surface relief pattern results from thermal compressing.
6. A tissue dressing according to claim 1,
25 wherein the hydrophilic polymer sponge structure includes a base surface and a top surface, and wherein the surface relief pattern is formed on the top surface and not on the base surface.
7. A tissue dressing according to claim 1,
30 wherein the pattern of fluid inlet channels comprises perforations.
8. A tissue dressing according to claim 1, wherein the hydrophilic polymer sponge structure includes a base surface and a top surface, and wherein the fluid
35 inlet channels are formed on the base surface.

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9. A tissue dressing according to claim 1, wherein the hydrophilic polymer sponge structure includes a base surface and a top surface, and further including a fluid impermeable backing joined to the top surface.

5 10. A tissue dressing according to claim 1, wherein the hydrophilic polymer sponge structure includes a base surface and a top surface, and further including a fluid adsorbent material joined to the top surface.

10 11. A method of making a tissue dressing as defined in claim 1.

12. A method of using a tissue dressing as define in claim 1 to perform at least one of (i) stanch, seal, or stabilize a site of tissue injury, tissue trauma, or tissue access; or (ii) form an anti-microbial barrier; or
15 (iii) form an antiviral patch; or (iv) intervene in a bleeding disorder; or (v) release a therapeutic agent; or (vi) treat a mucosal surface; or (vii) a combination thereof.

13. A tissue dressing comprising a hydrophilic
20 polymer sponge structure and at least one woven or non-woven or permeable membranous sheet present within the hydrophilic sponge structure, the hydrophilic polymer sponge structure having been densified by compression to a density of between 0.6 to 0.1 g/cm³.

25 14. A tissue dressing according to claim 1 wherein the hydrophilic polymer sponge structure includes a chitosan biomaterial.

15. A method of making a tissue dressing as defined in claim 13.

30 16. A method of using a tissue dressing as define in claim 13 to perform at least one of (i) stanch, seal, or stabilize a site of tissue injury, tissue trauma, or tissue access; or (ii) form an anti-microbial barrier; or (iii) form an antiviral patch; or (iv) intervene in a
35 bleeding disorder; or (v) release a therapeutic agent; or

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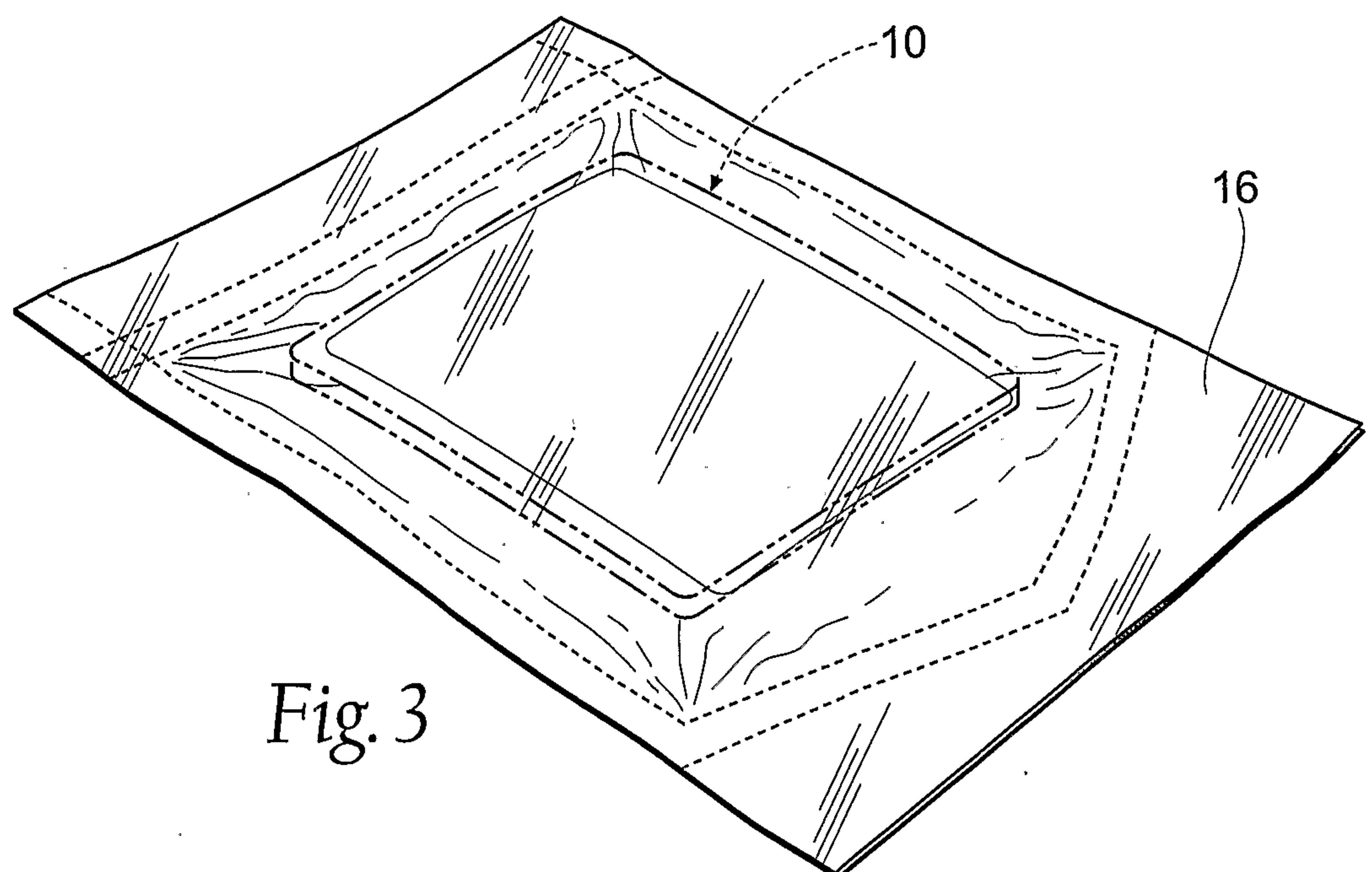
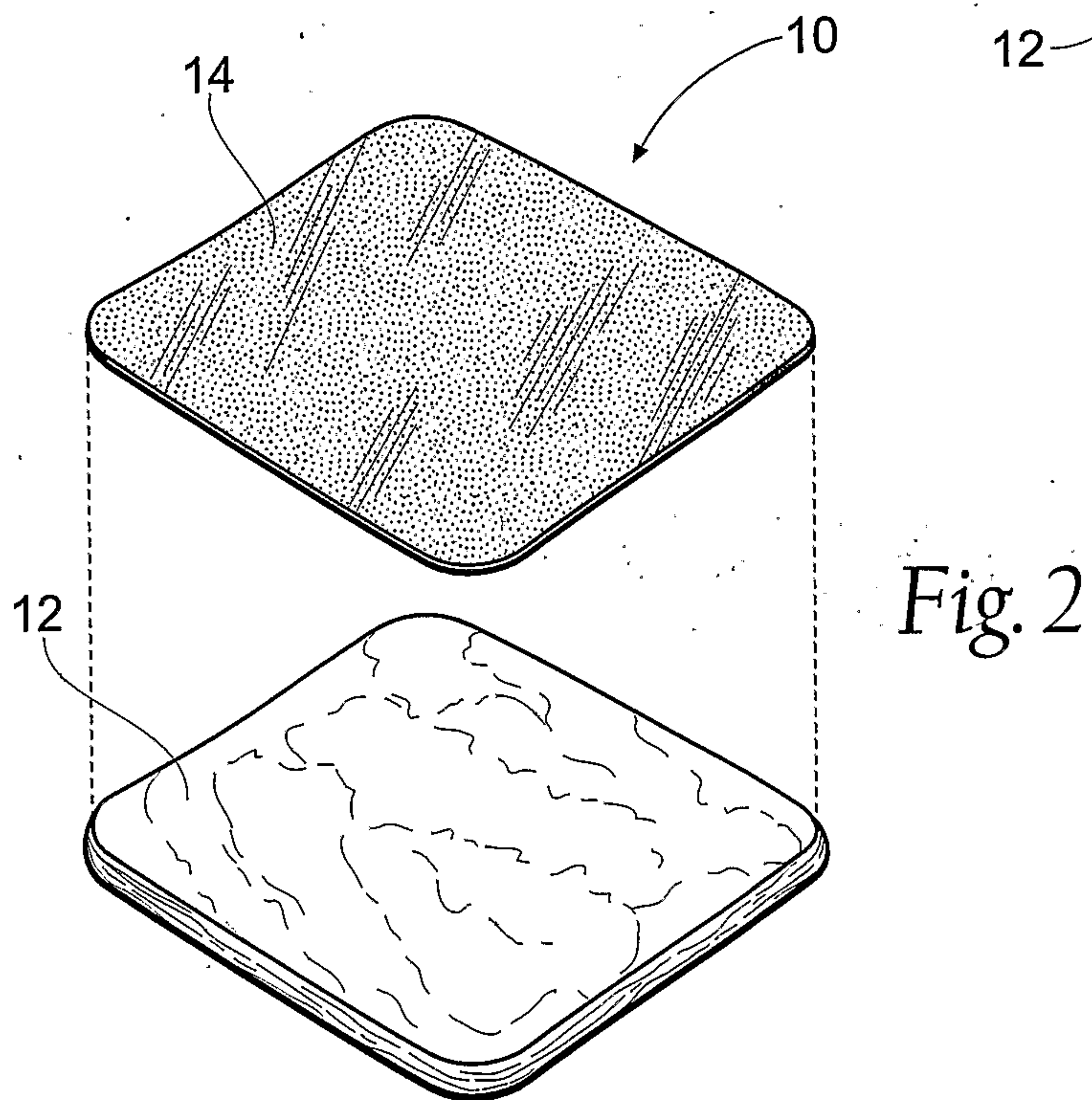
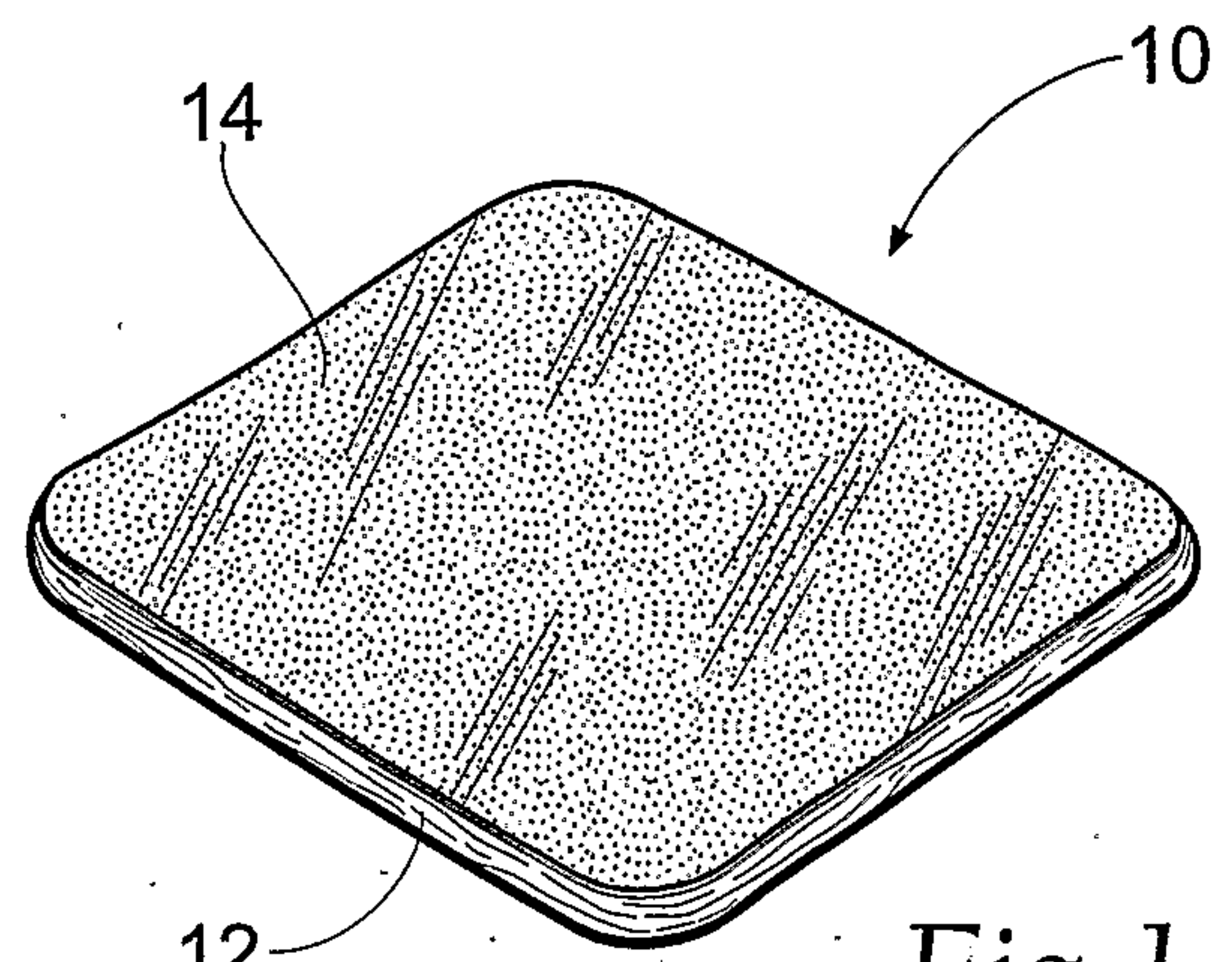
(vi) treat a mucosal surface; or (vii) a combination thereof.

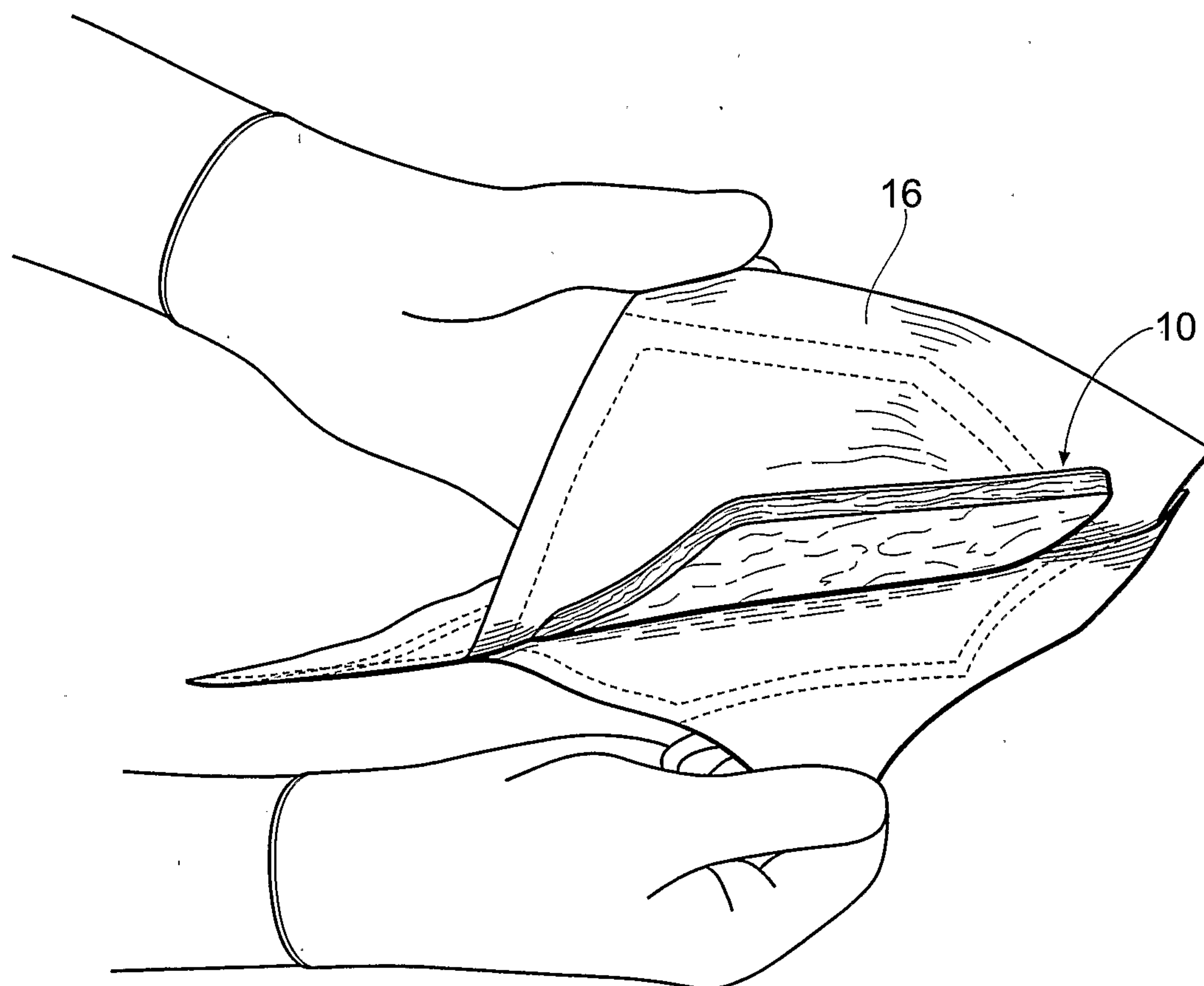
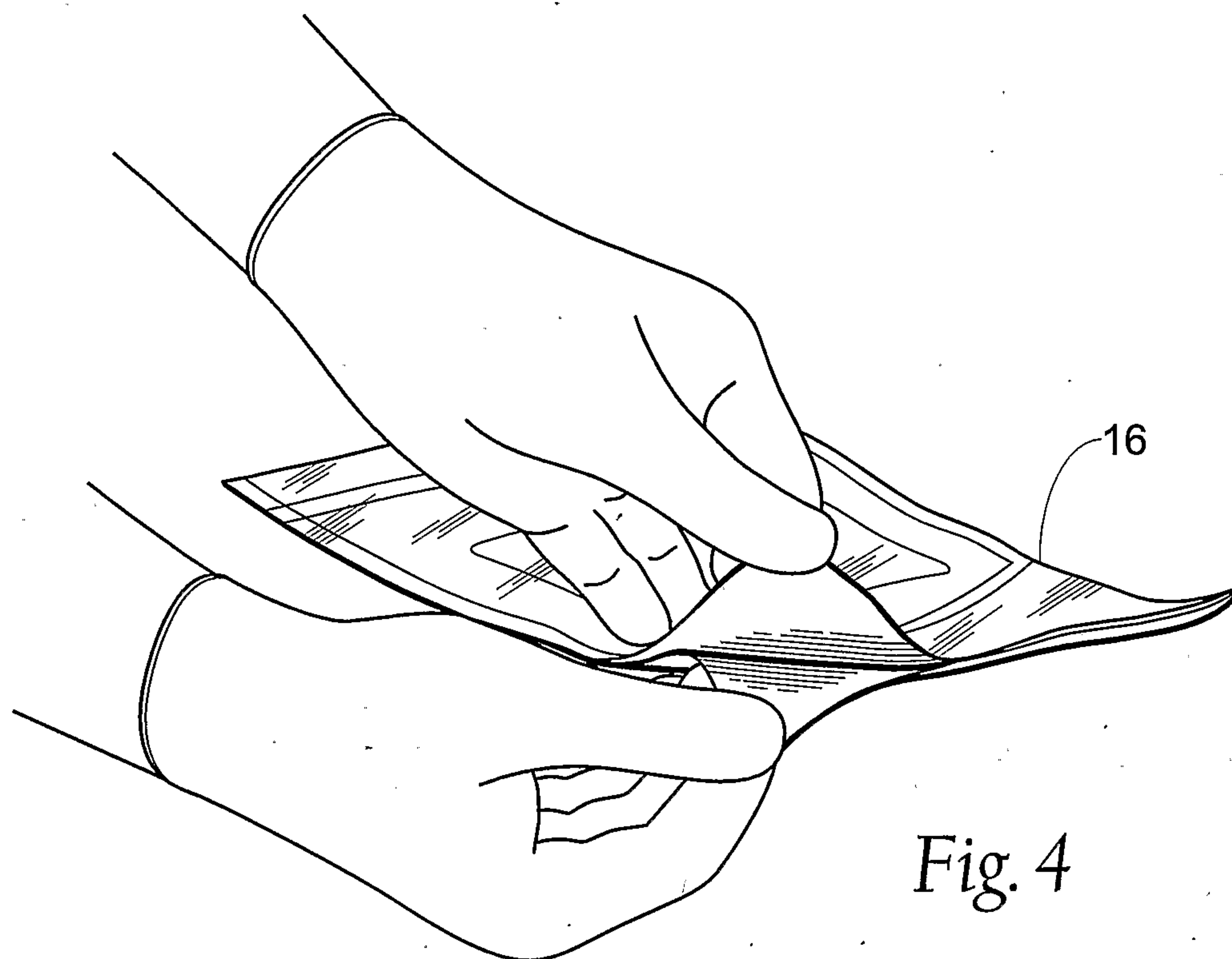
17. A tissue dressing comprising a hydrophilic polymer sponge structure and an absorbent component
5 secured to the hydrophilic sponge structure, the hydrophilic polymer sponge structure having been densified by compression to a density of between 0.6 to 0.1 g/cm³.

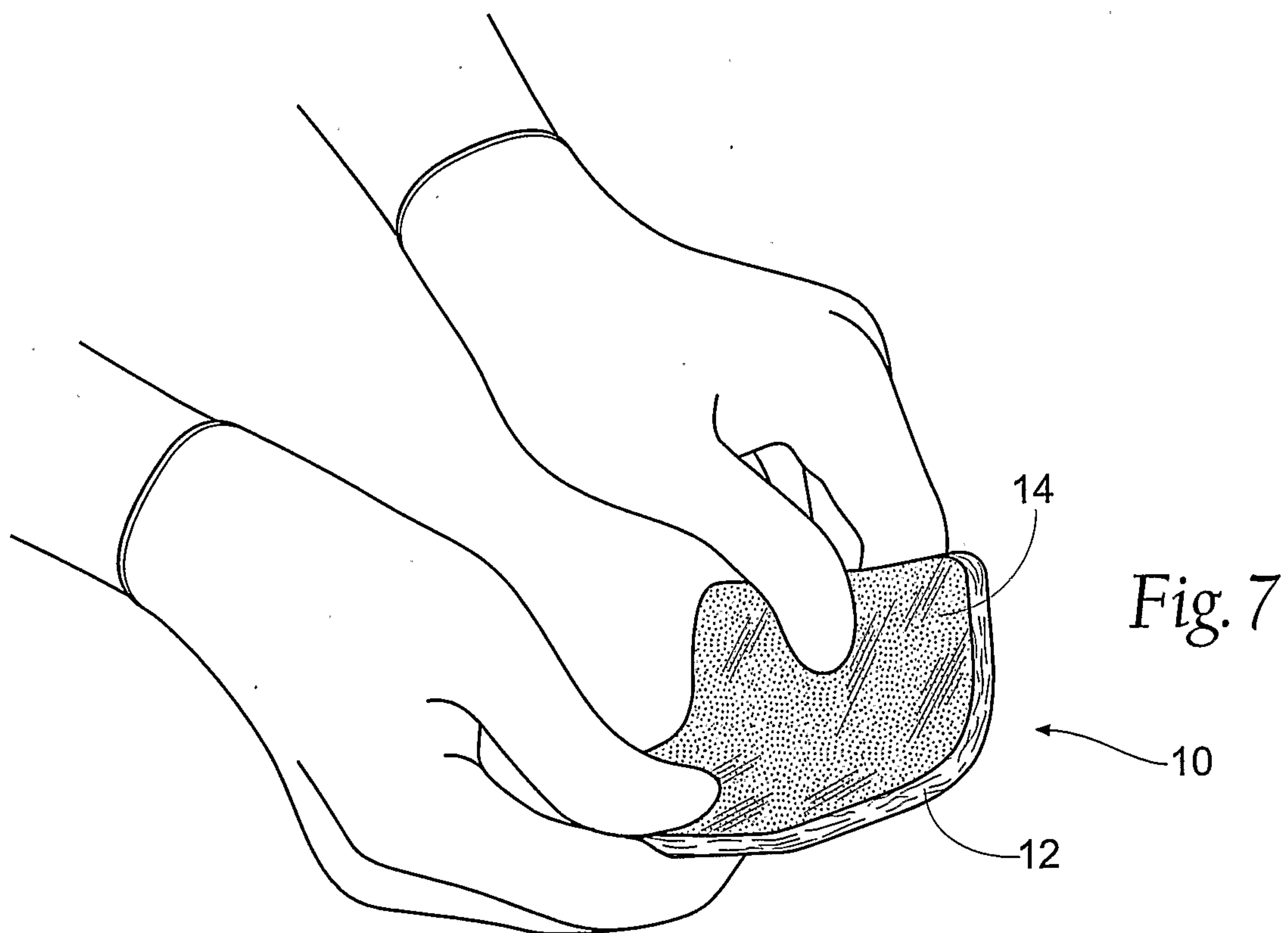
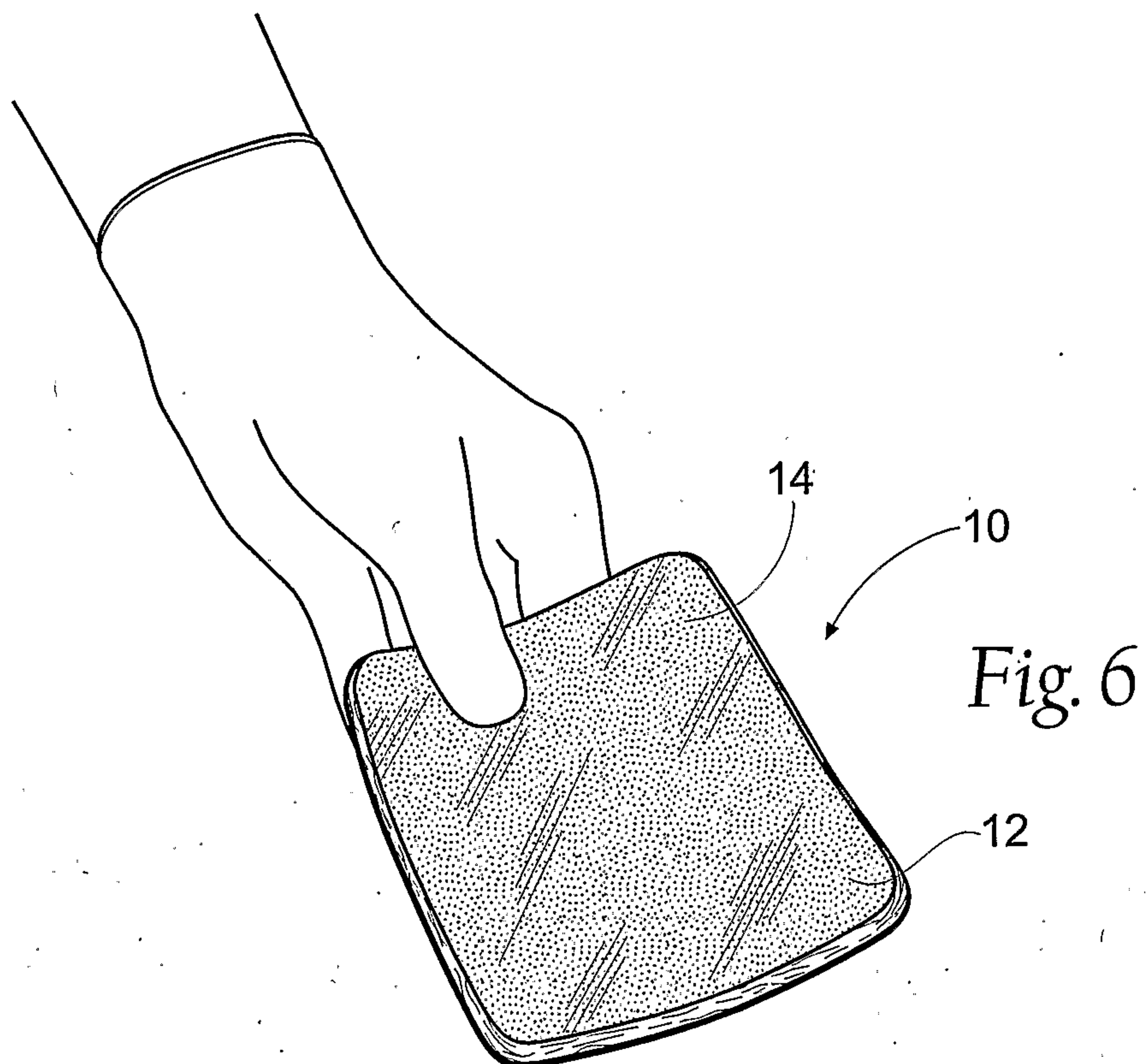
18. A tissue dressing according to claim 17
10 wherein the hydrophilic polymer sponge structure includes a chitosan biomaterial.

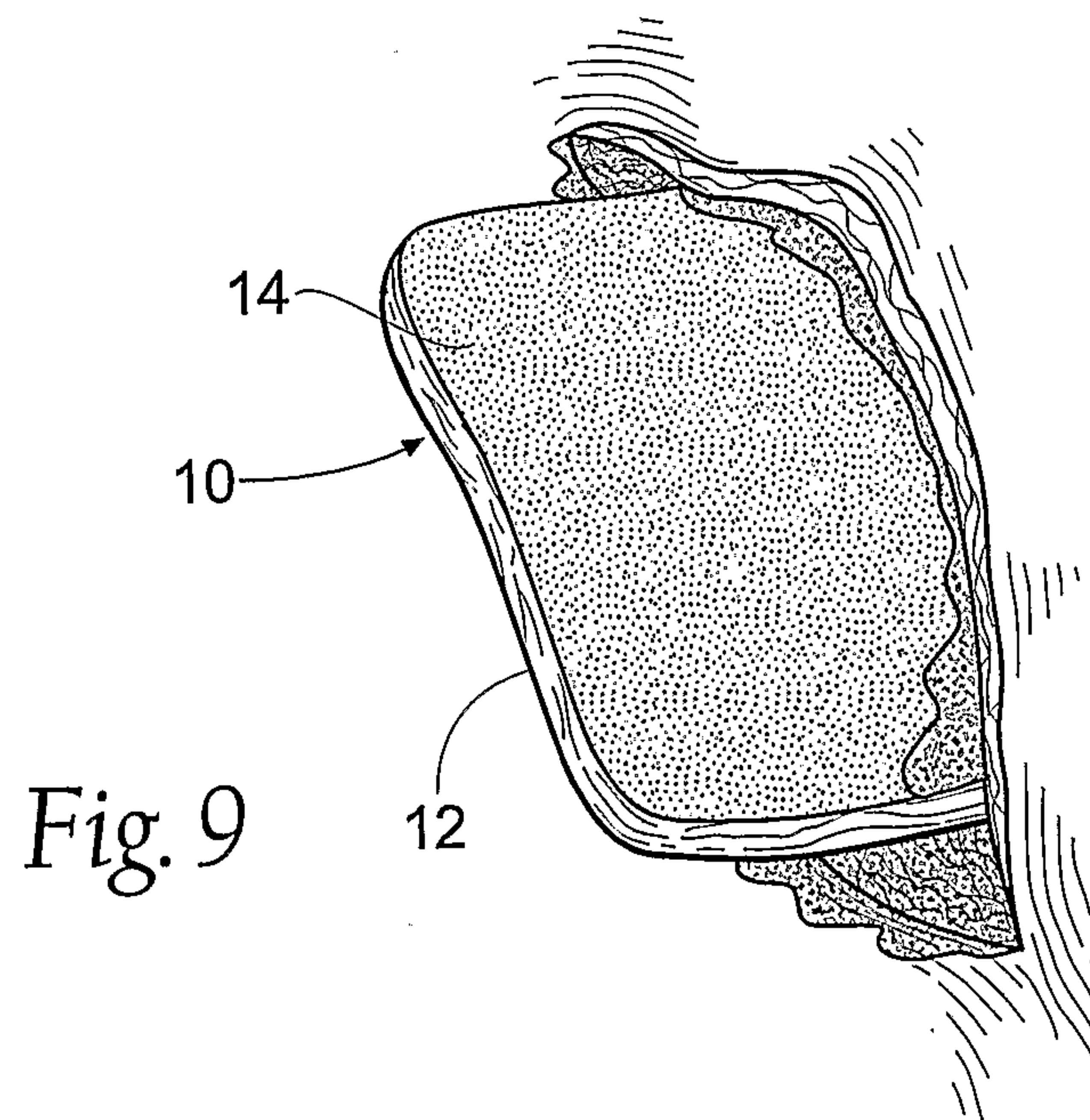
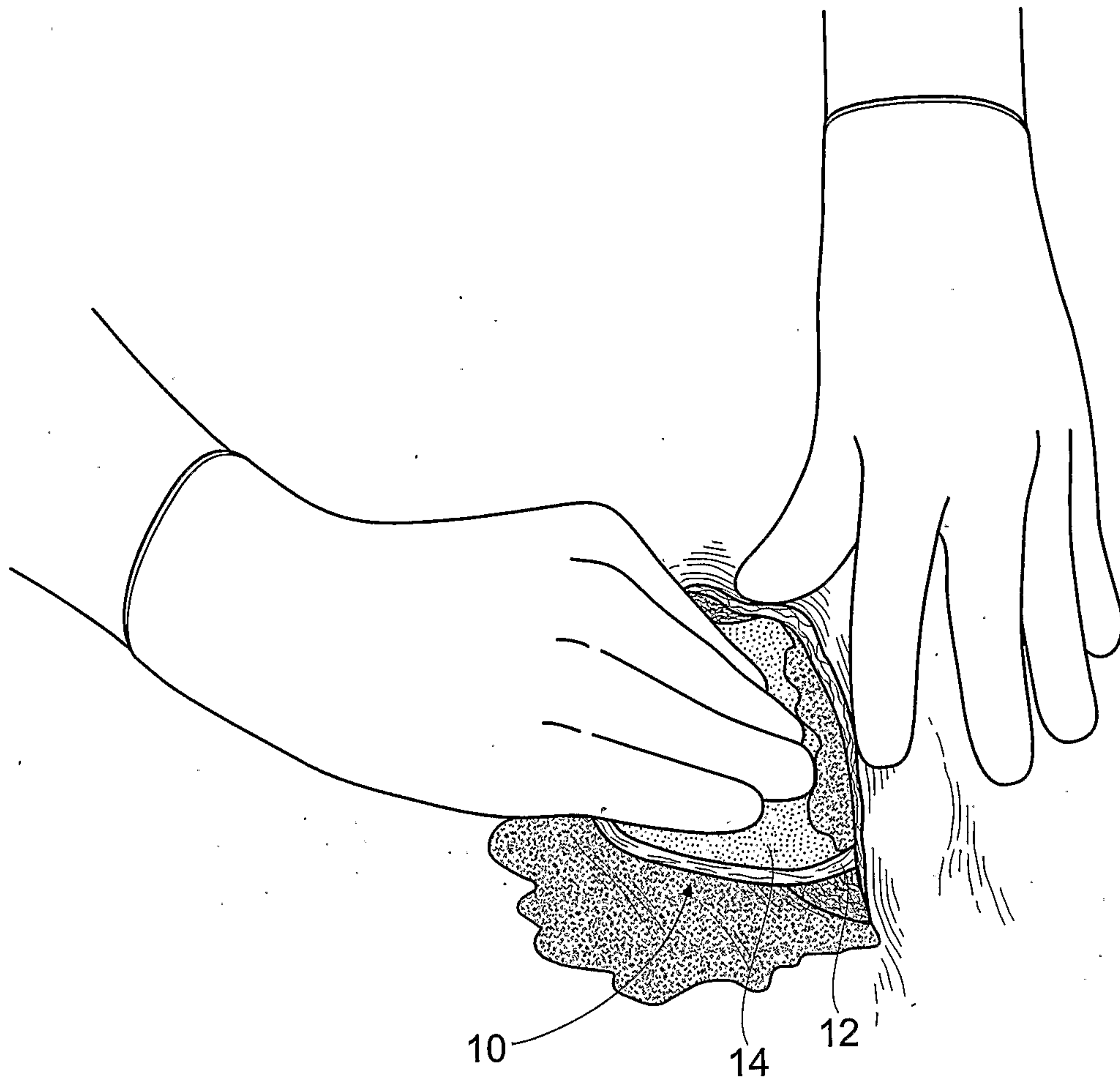
19. A method of making a tissue dressing as defined in claim 17.

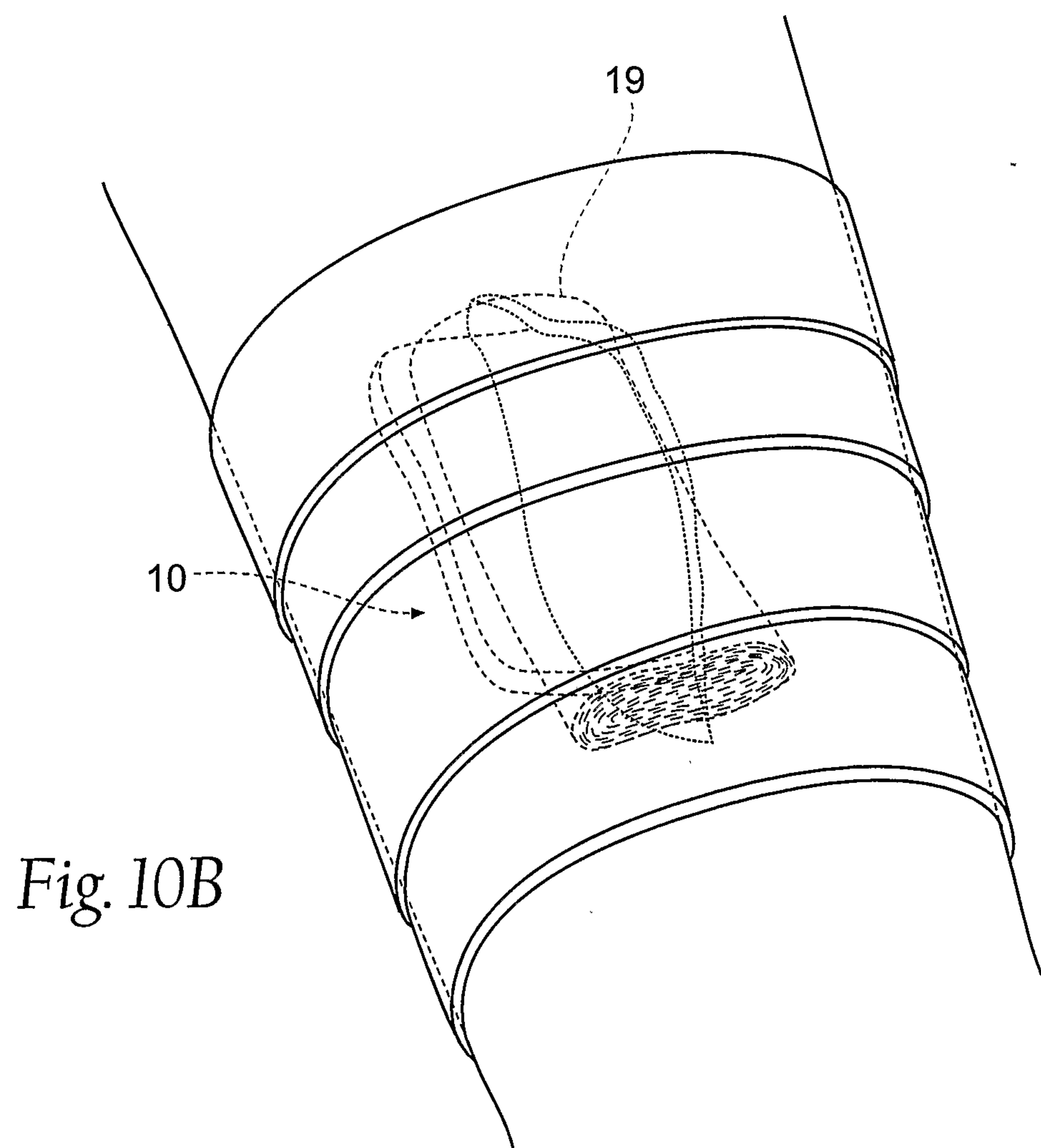
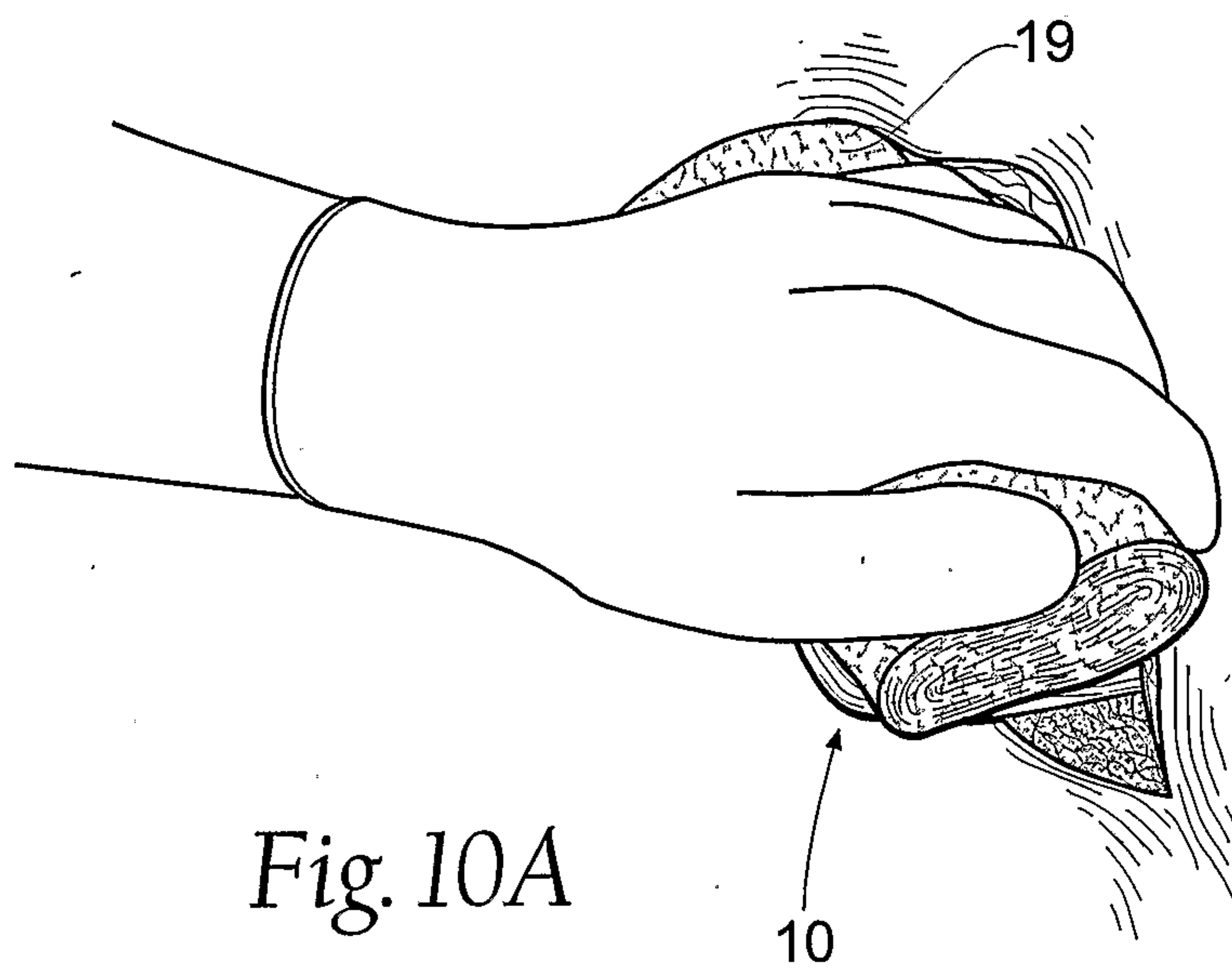
20. A method of using a tissue dressing as define
15 in claim 17 to perform at least one of (i) stanch, seal, or stabilize a site of tissue injury, tissue trauma, or tissue access; or (ii) form an anti-microbial barrier; or (iii) form an antiviral patch; or (iv) intervene in a bleeding disorder; or (v) release a therapeutic agent; or
20 (vi) treat a mucosal surface; or (vii) a combination thereof.

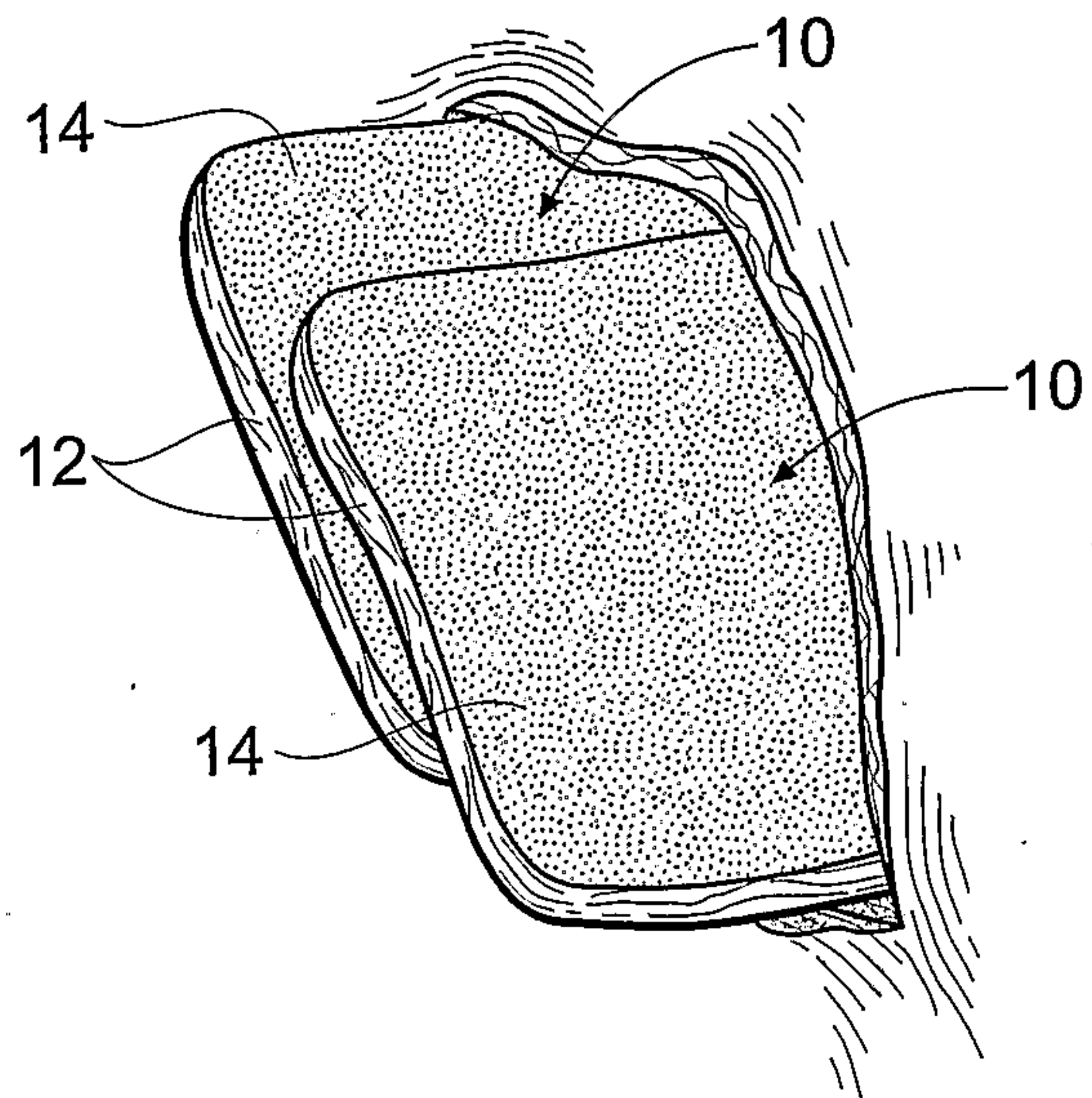
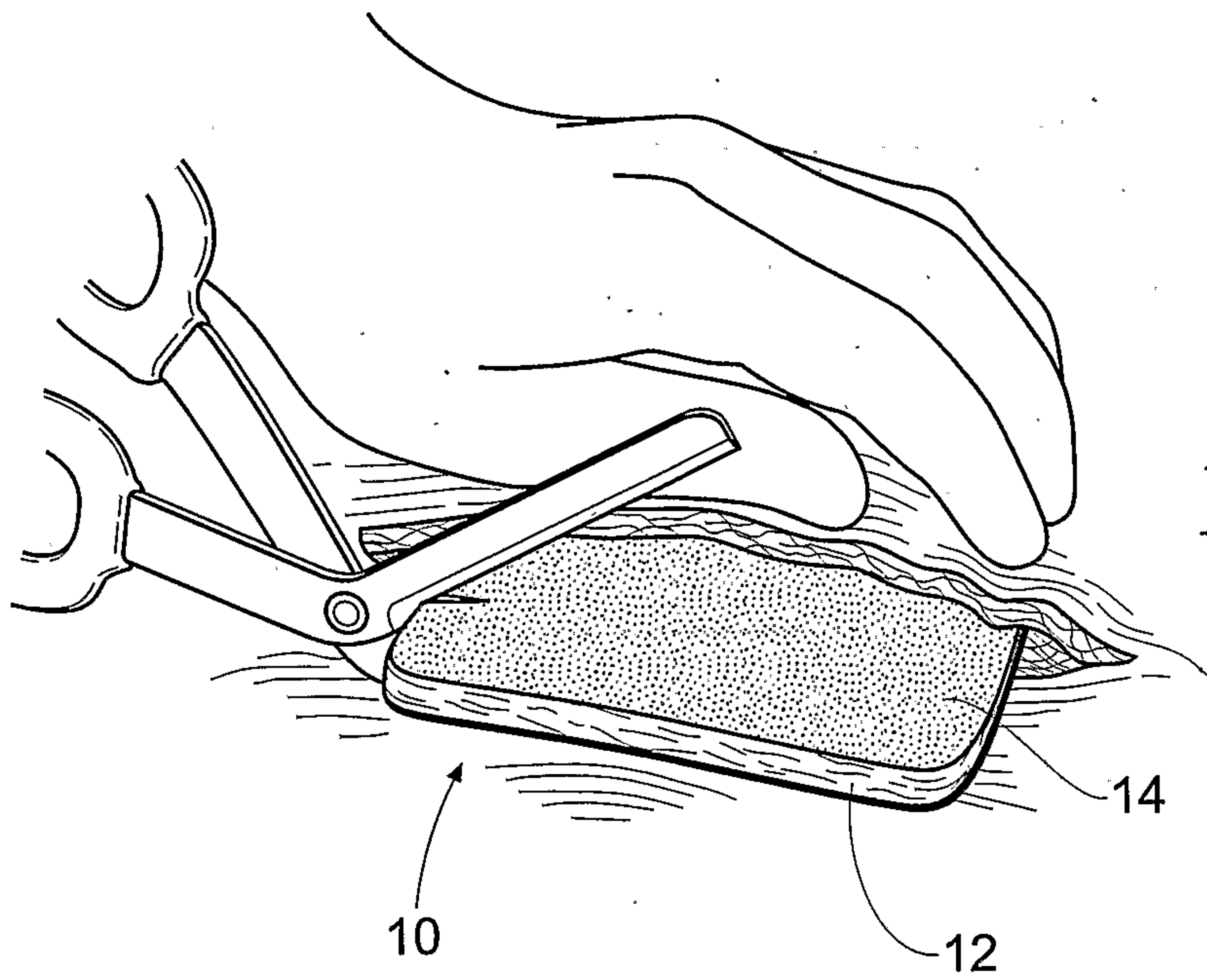
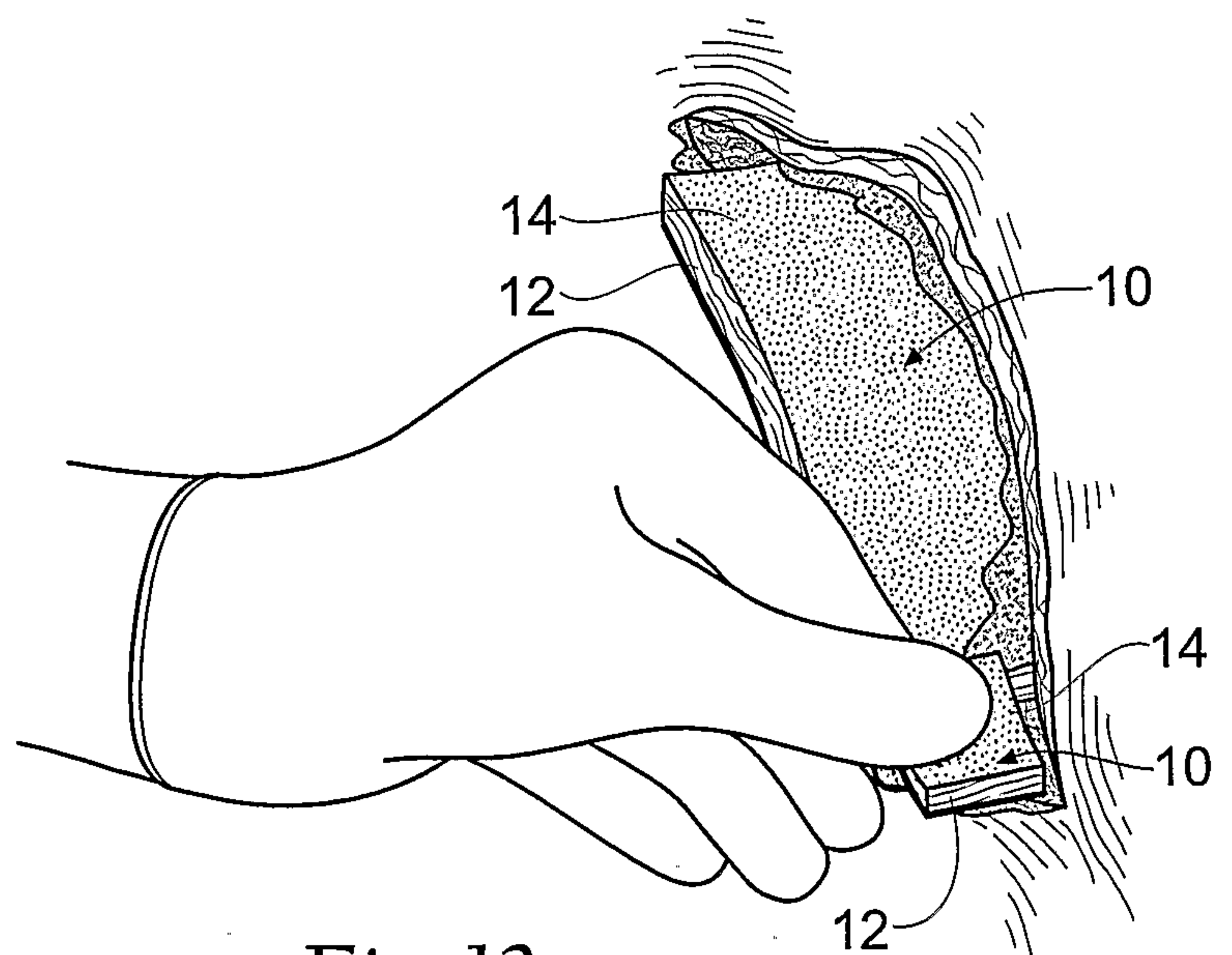










*Fig. 11**Fig. 12**Fig. 13*

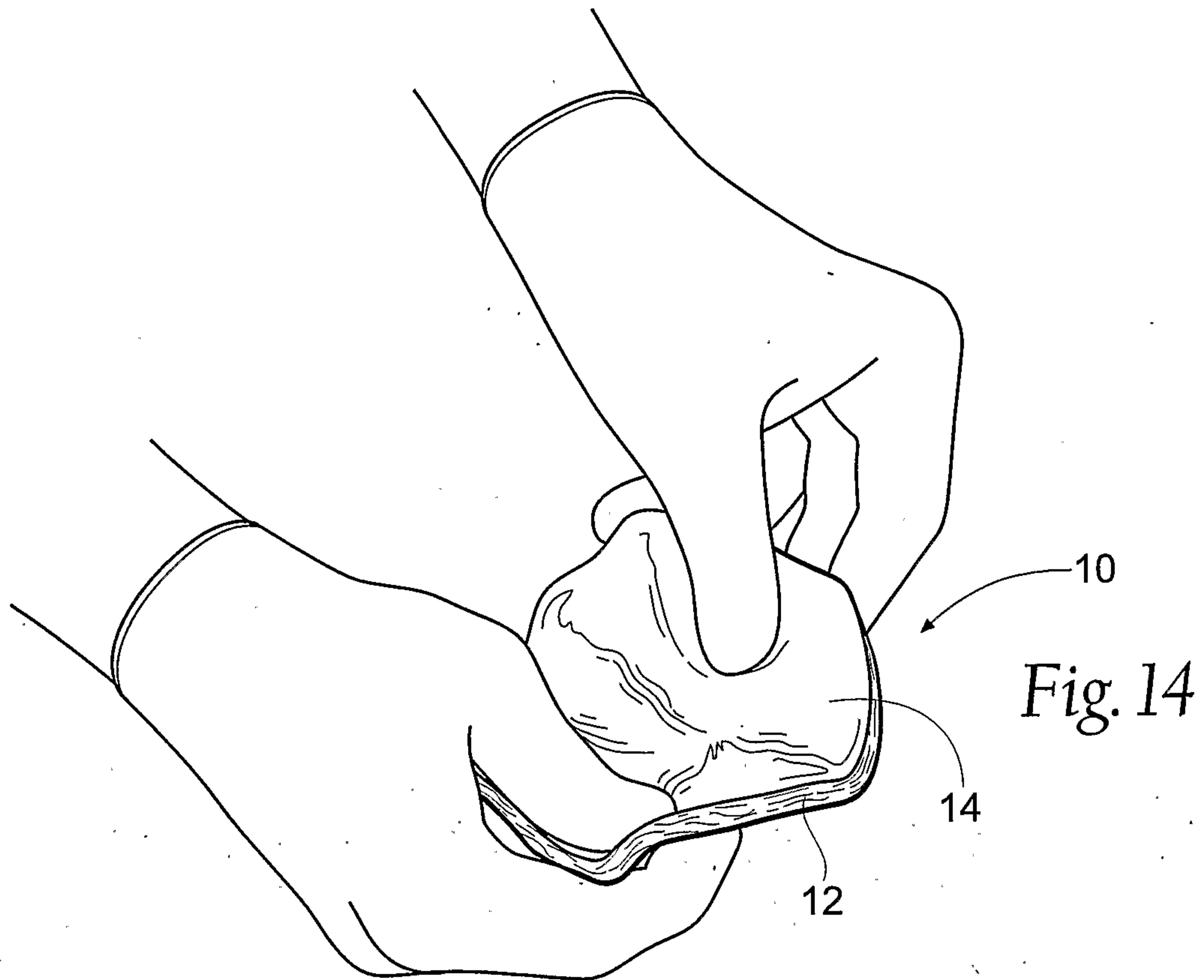
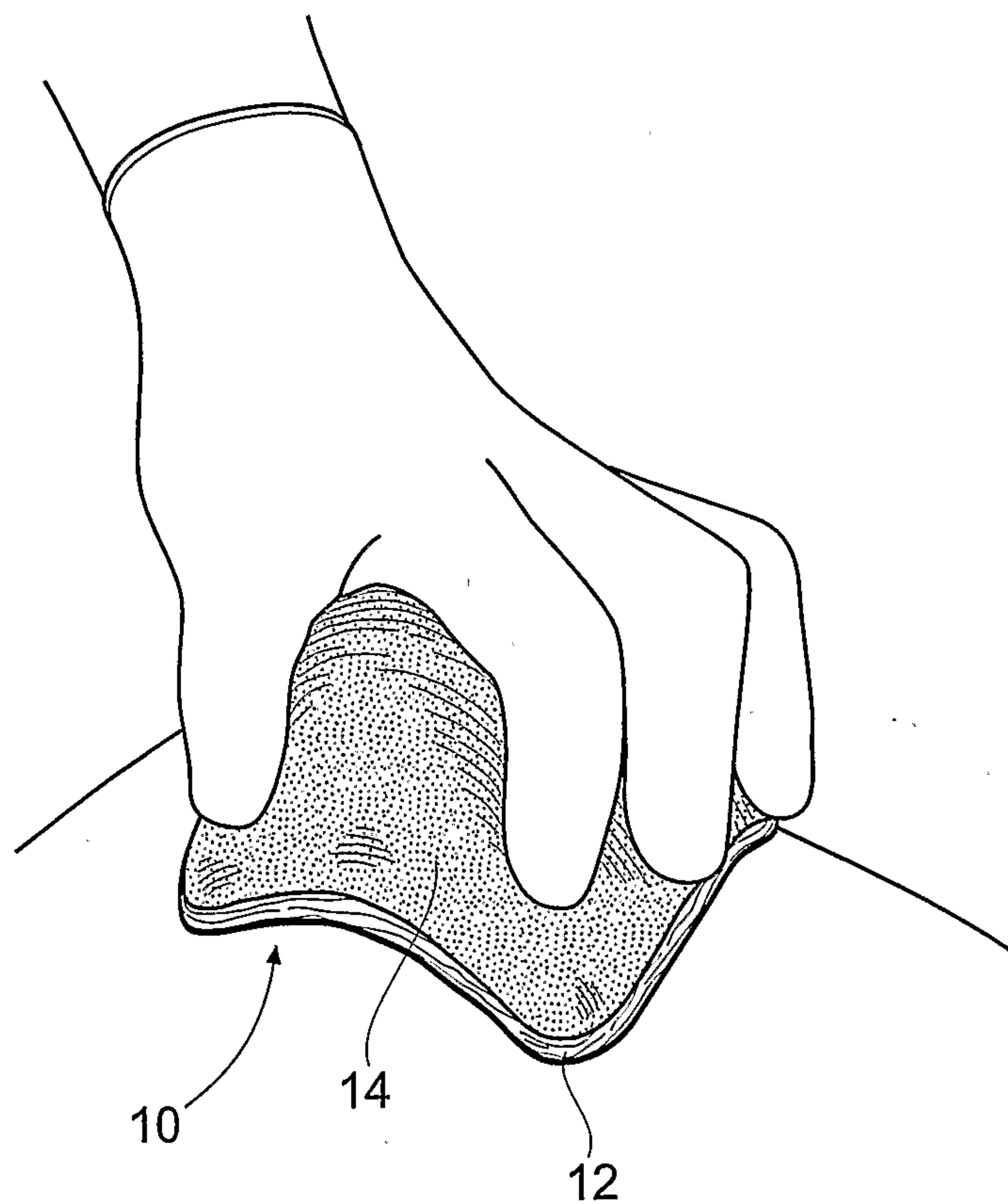


Fig. 15



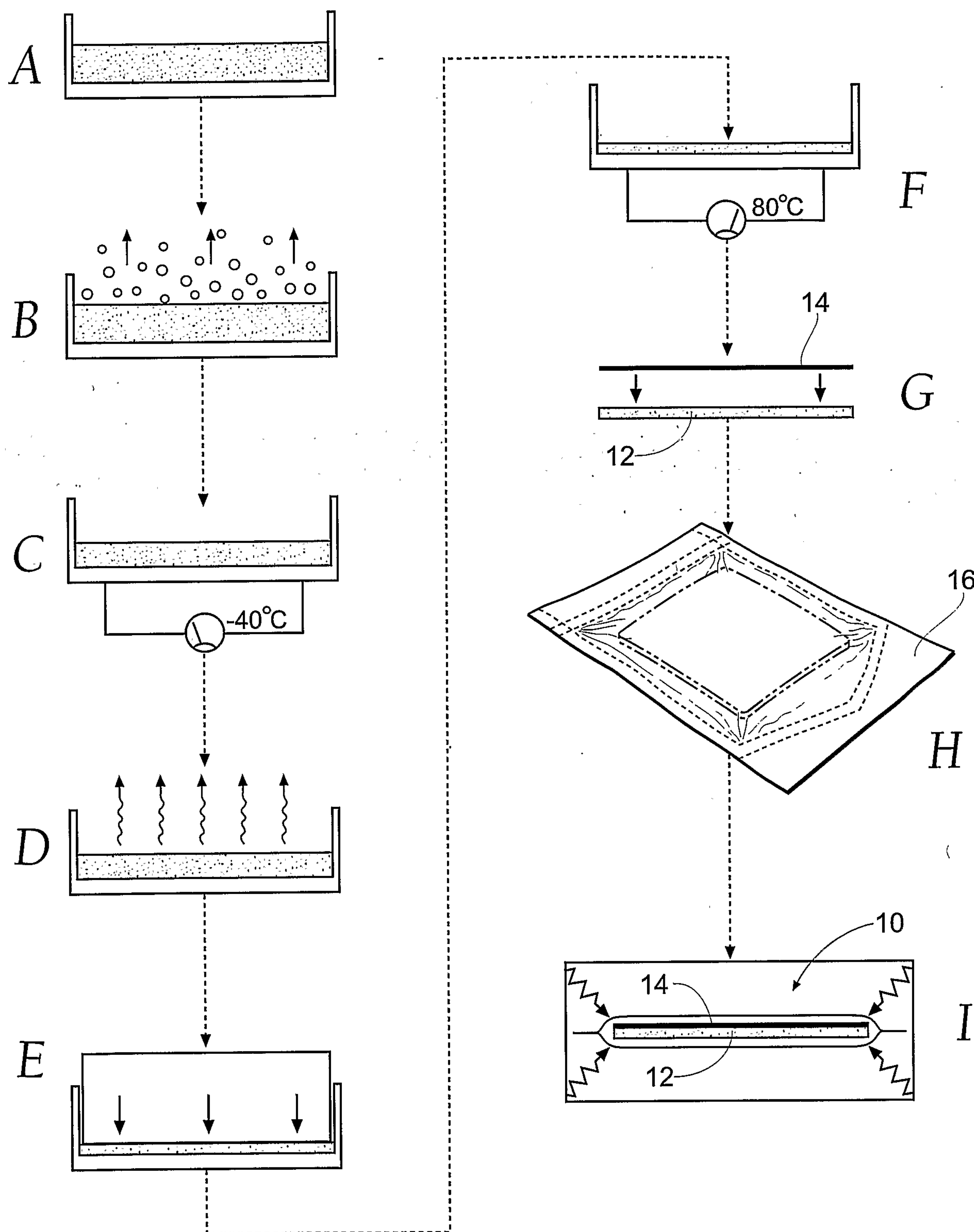


Fig. 16

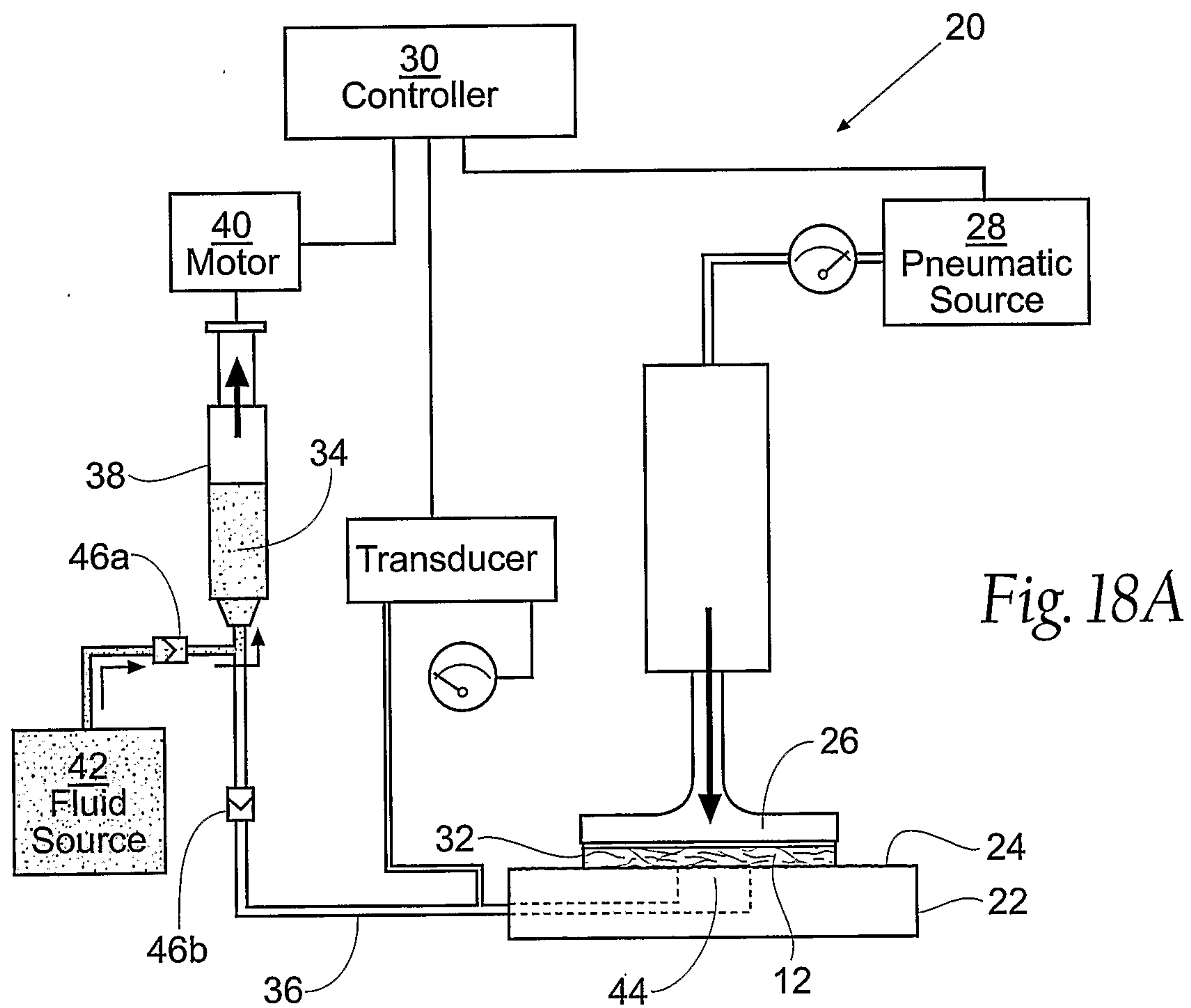
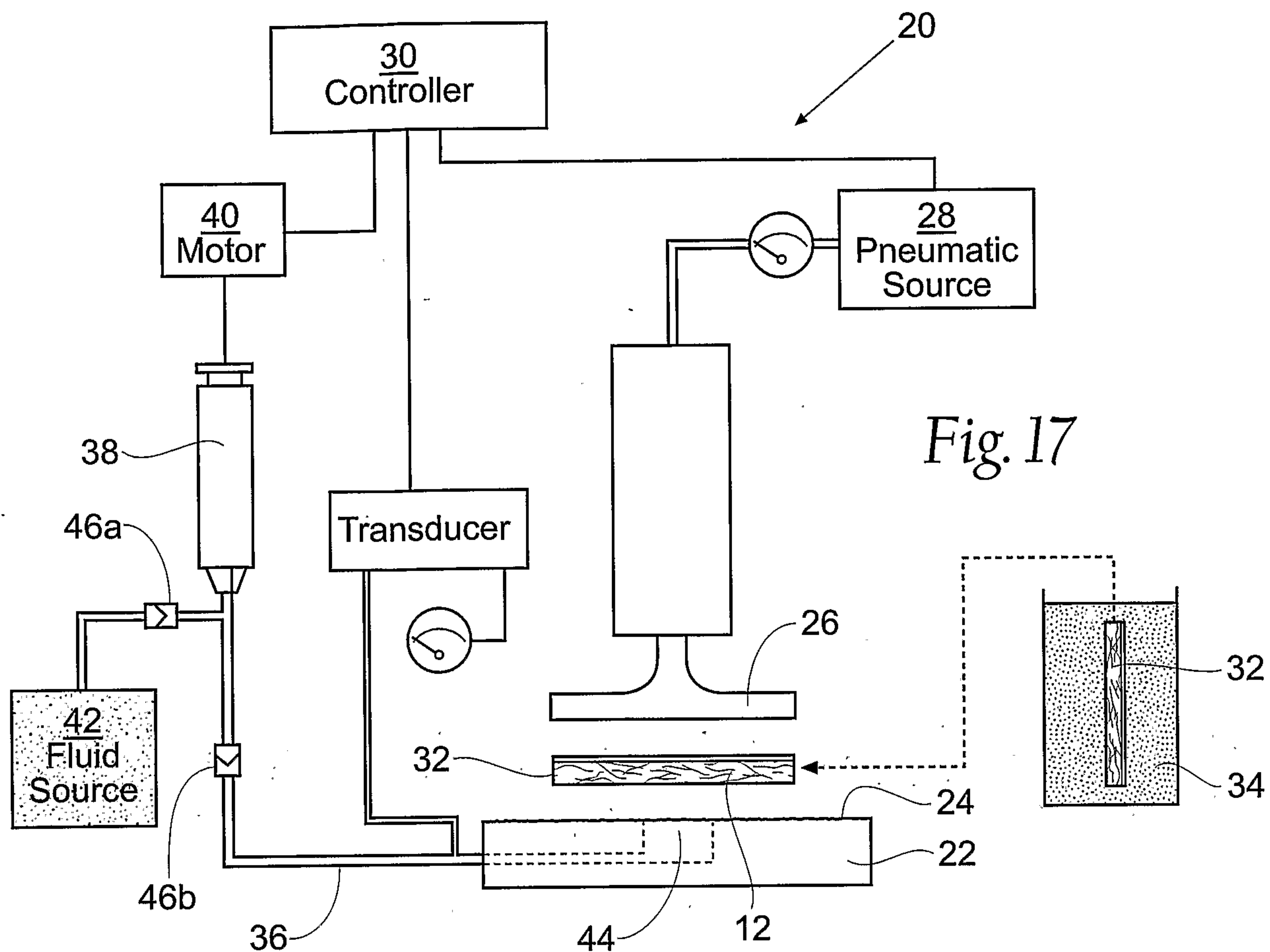
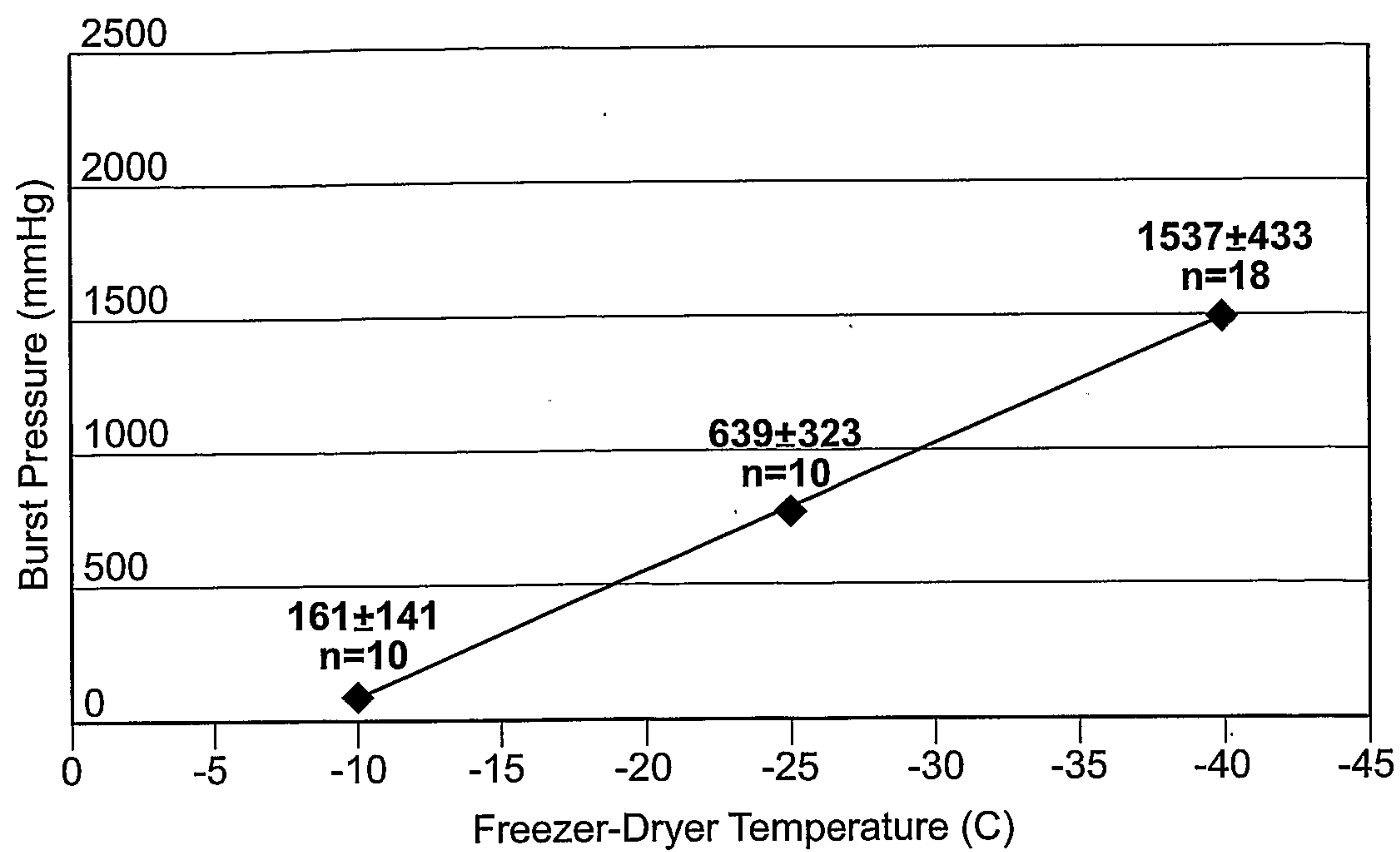
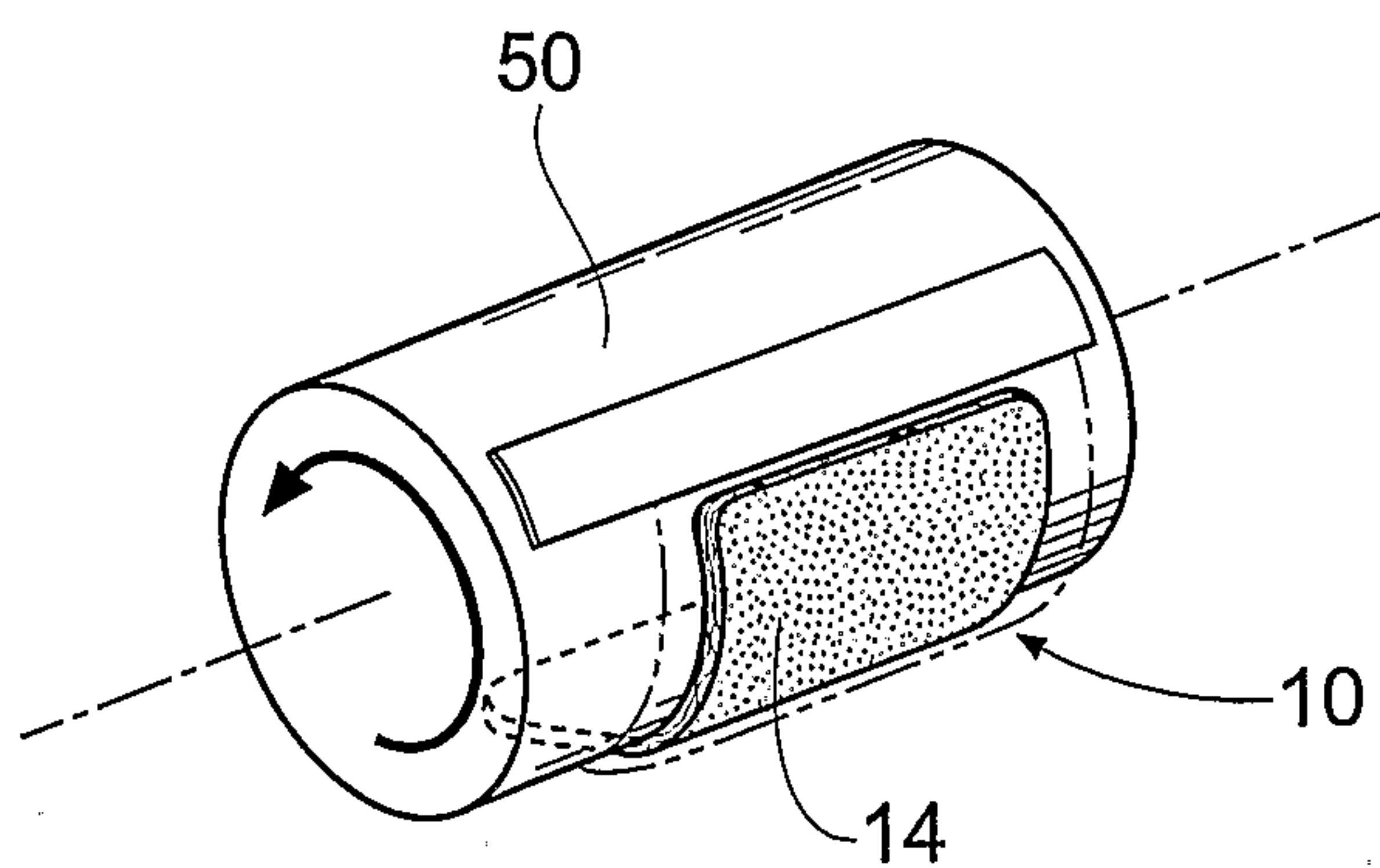
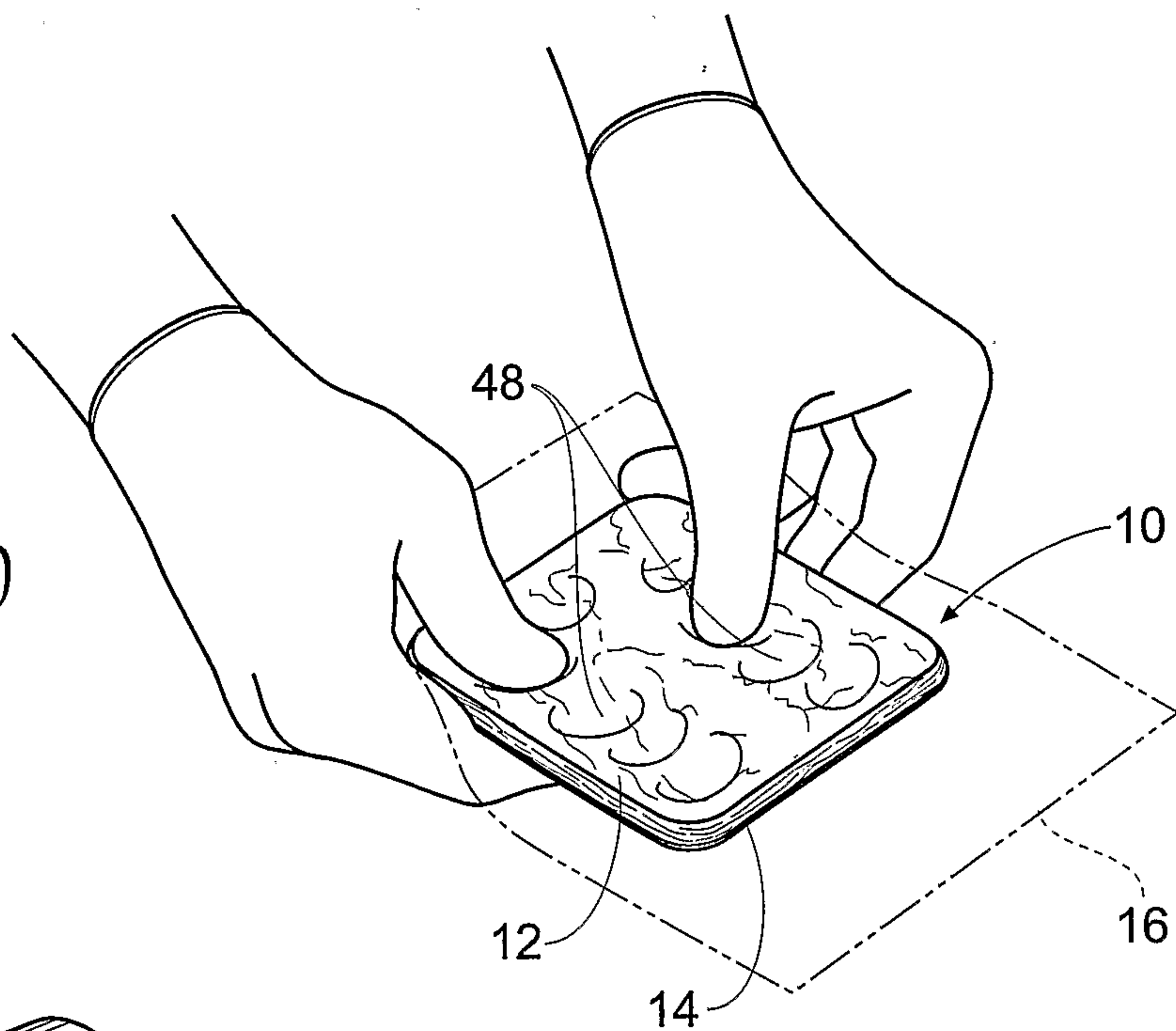
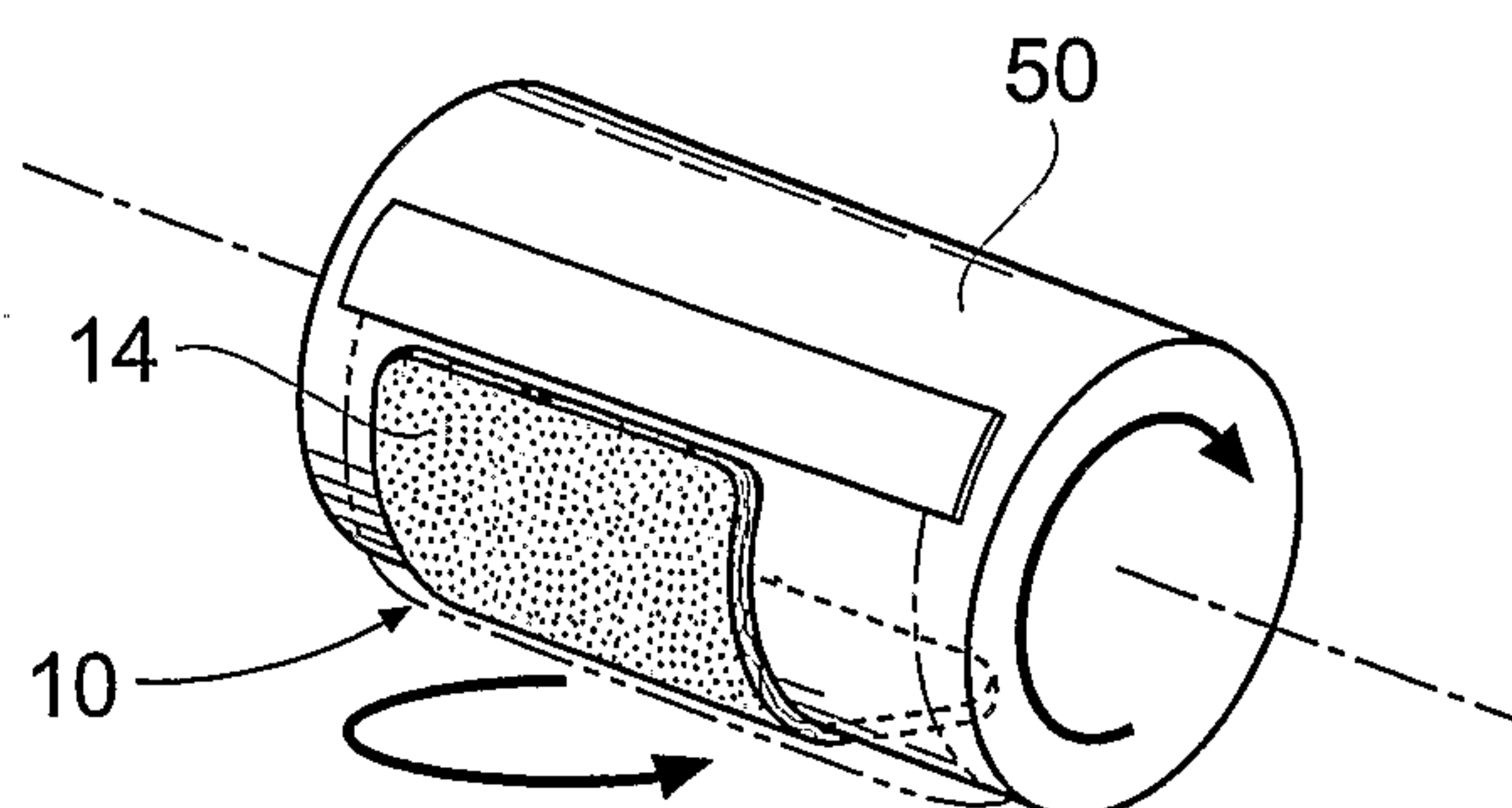
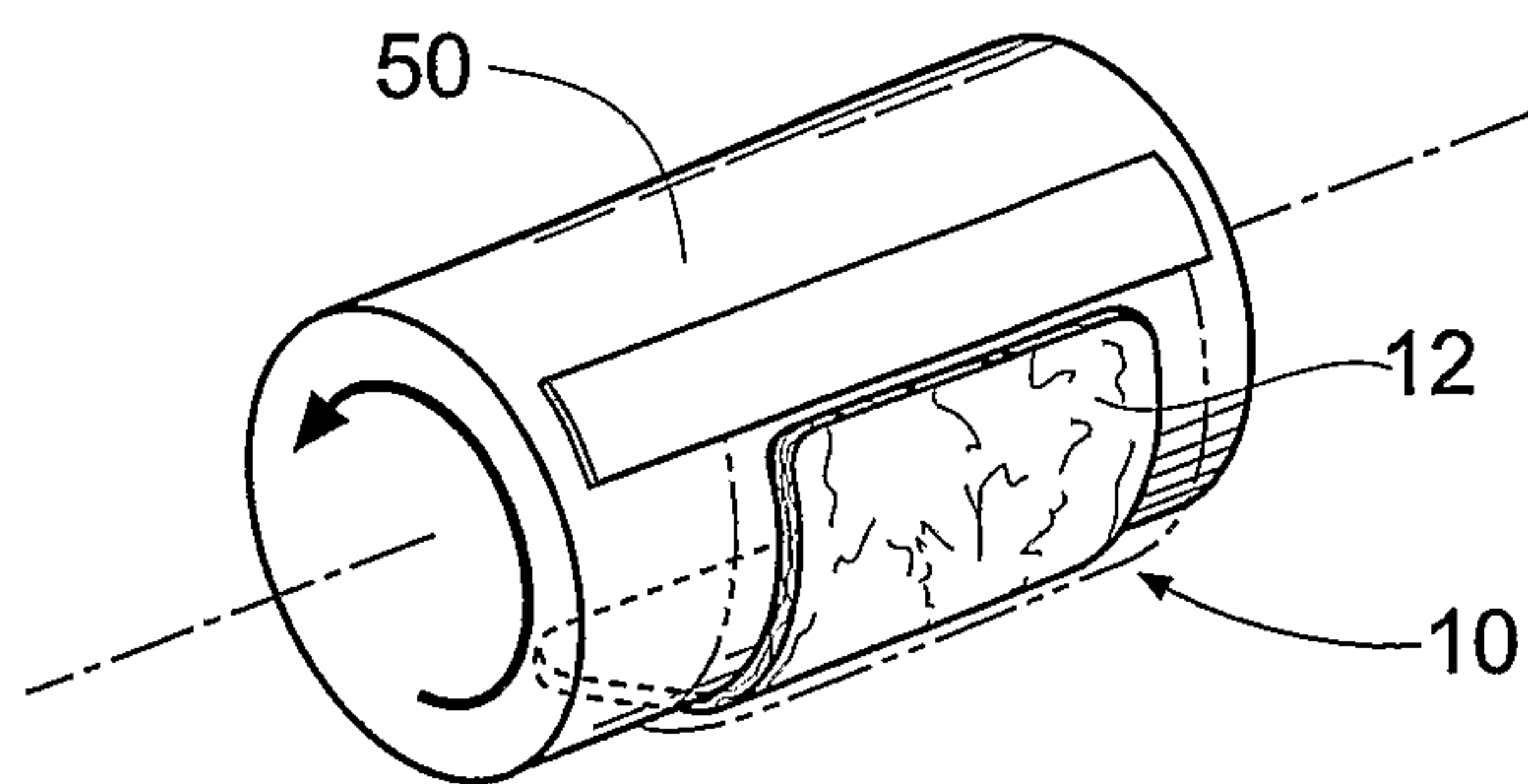
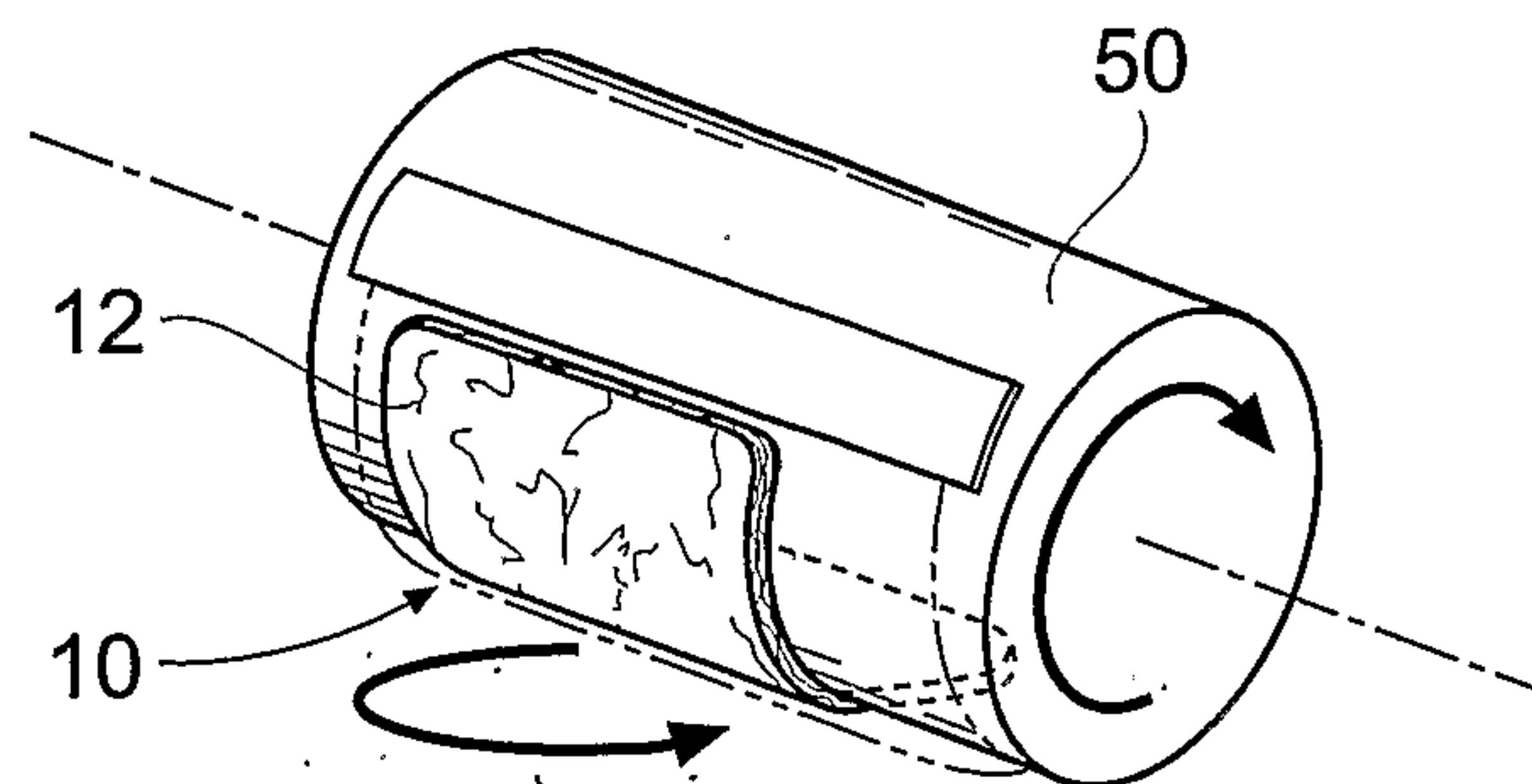
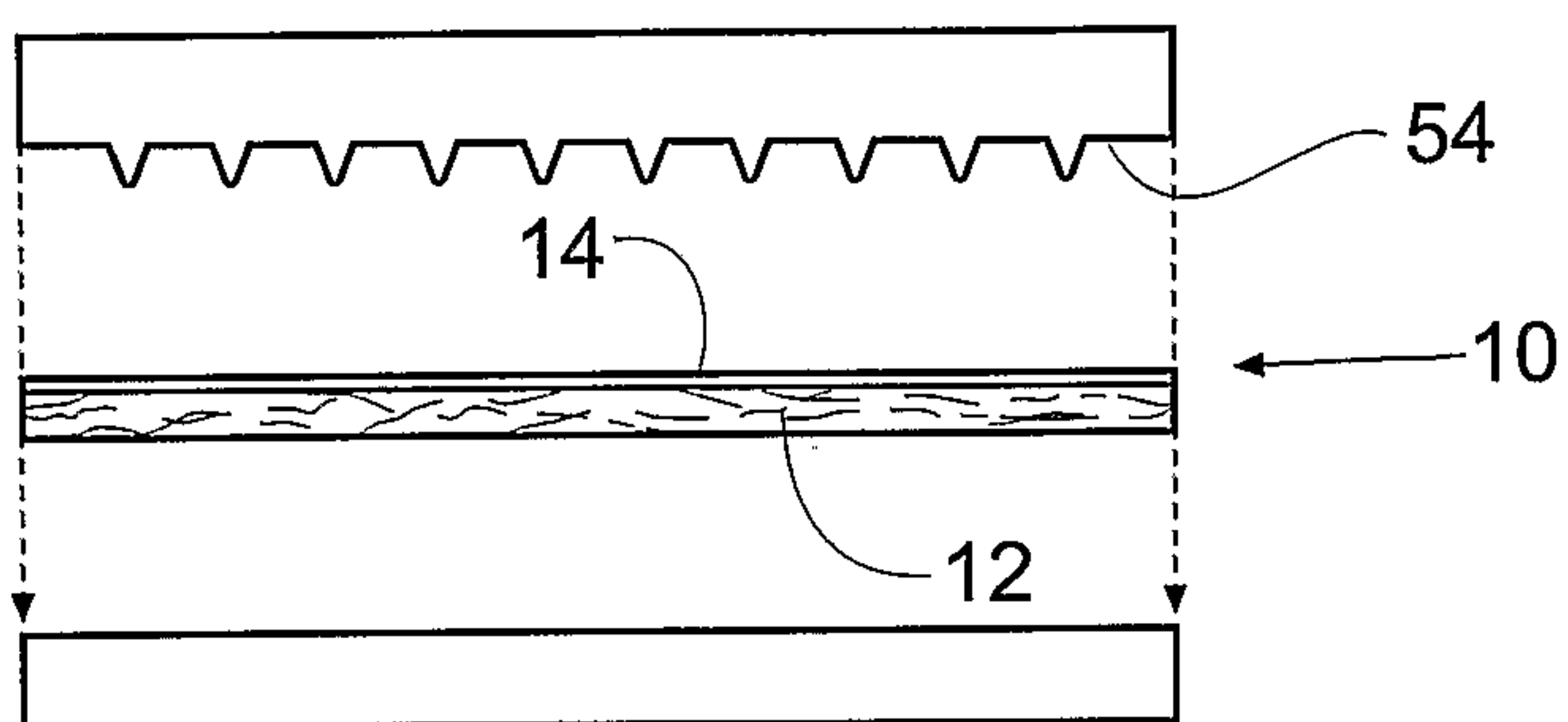
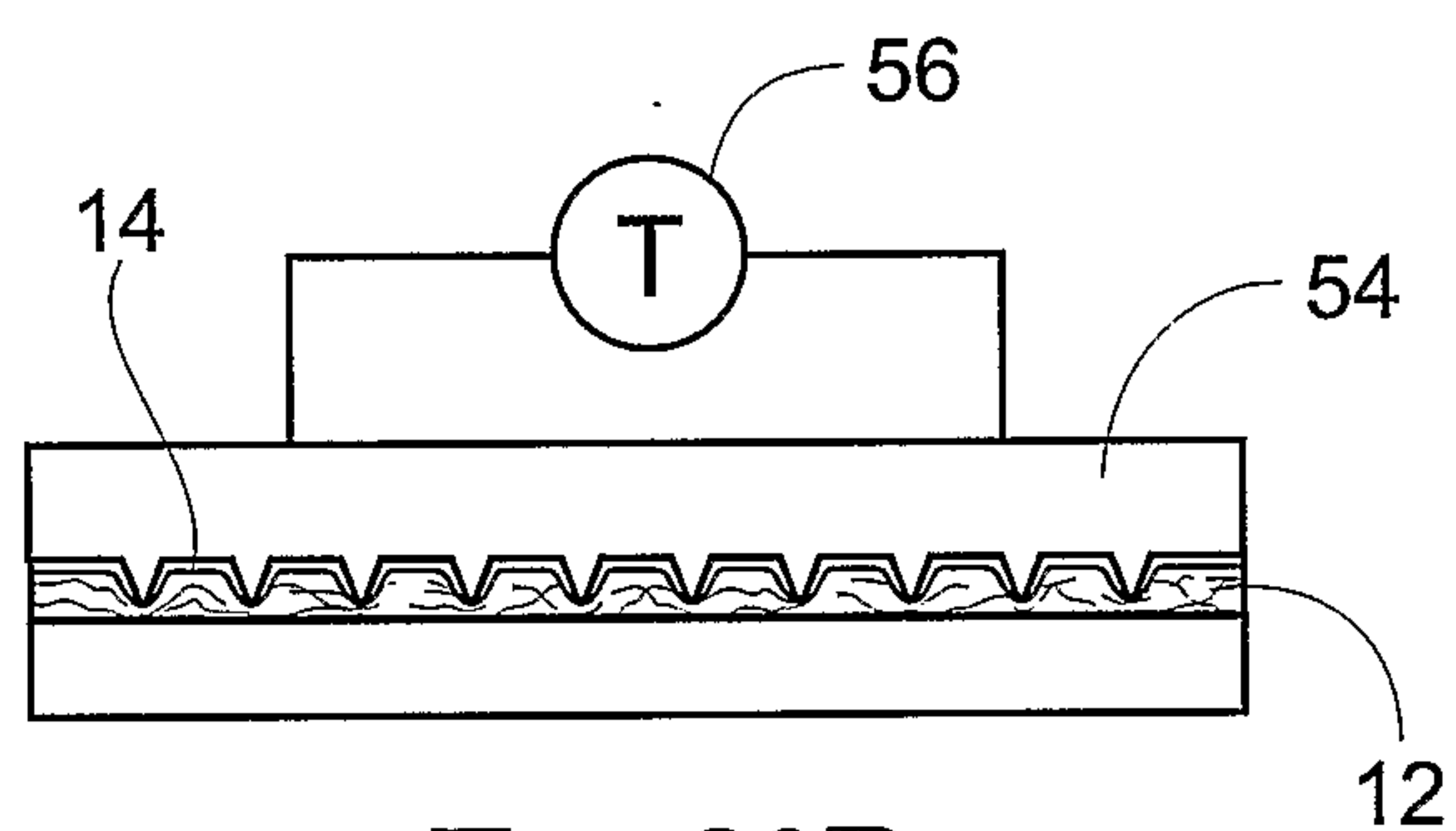
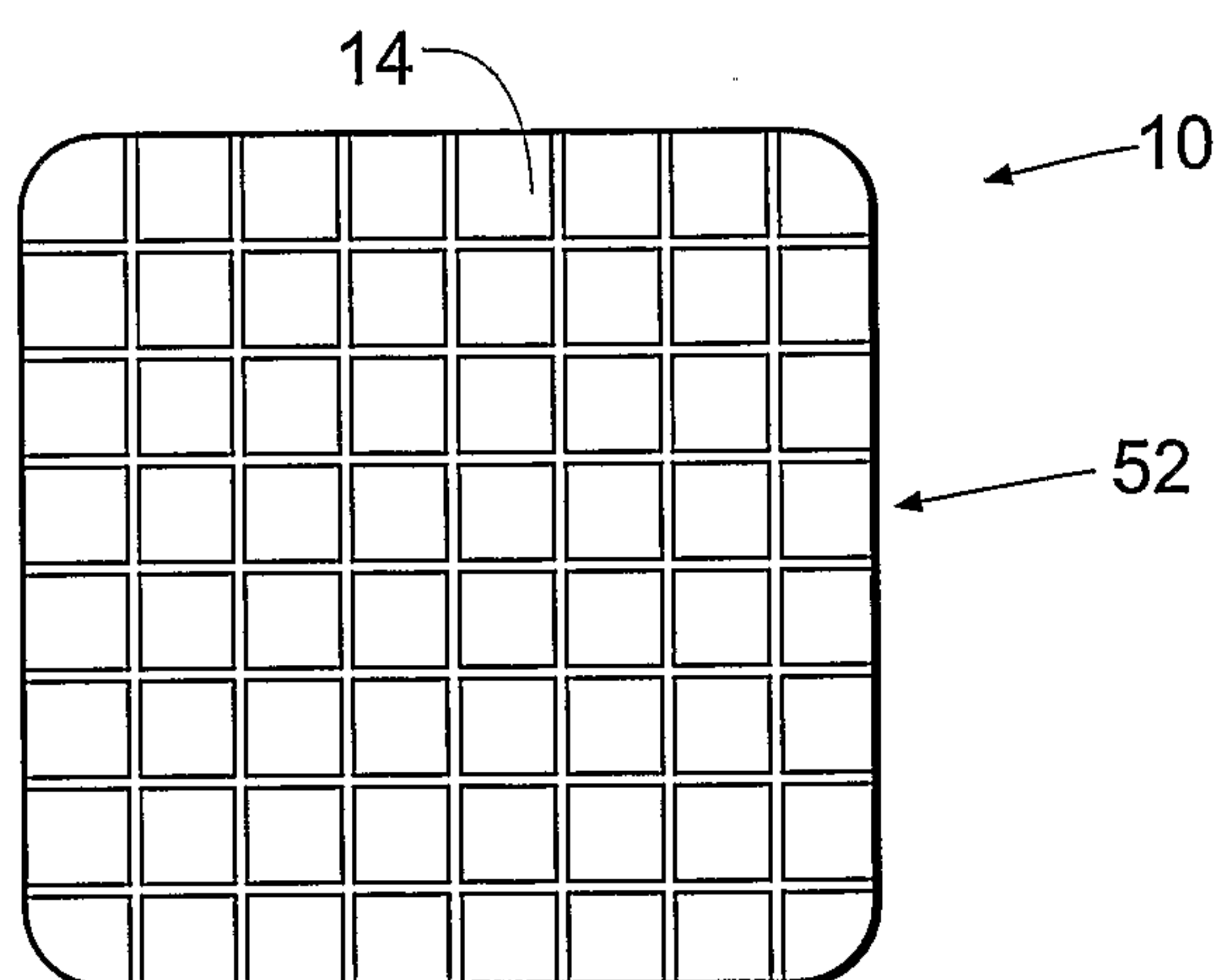
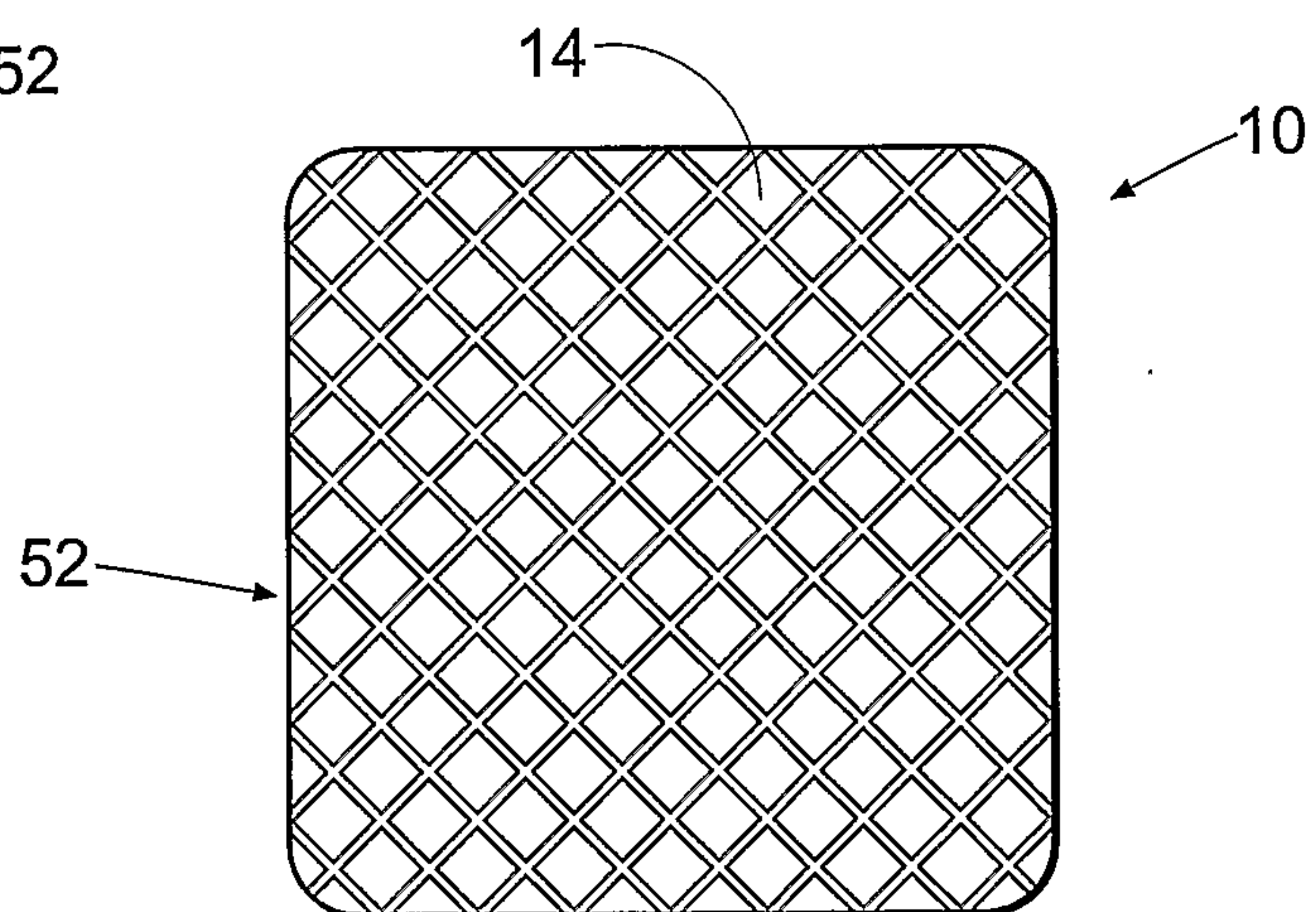
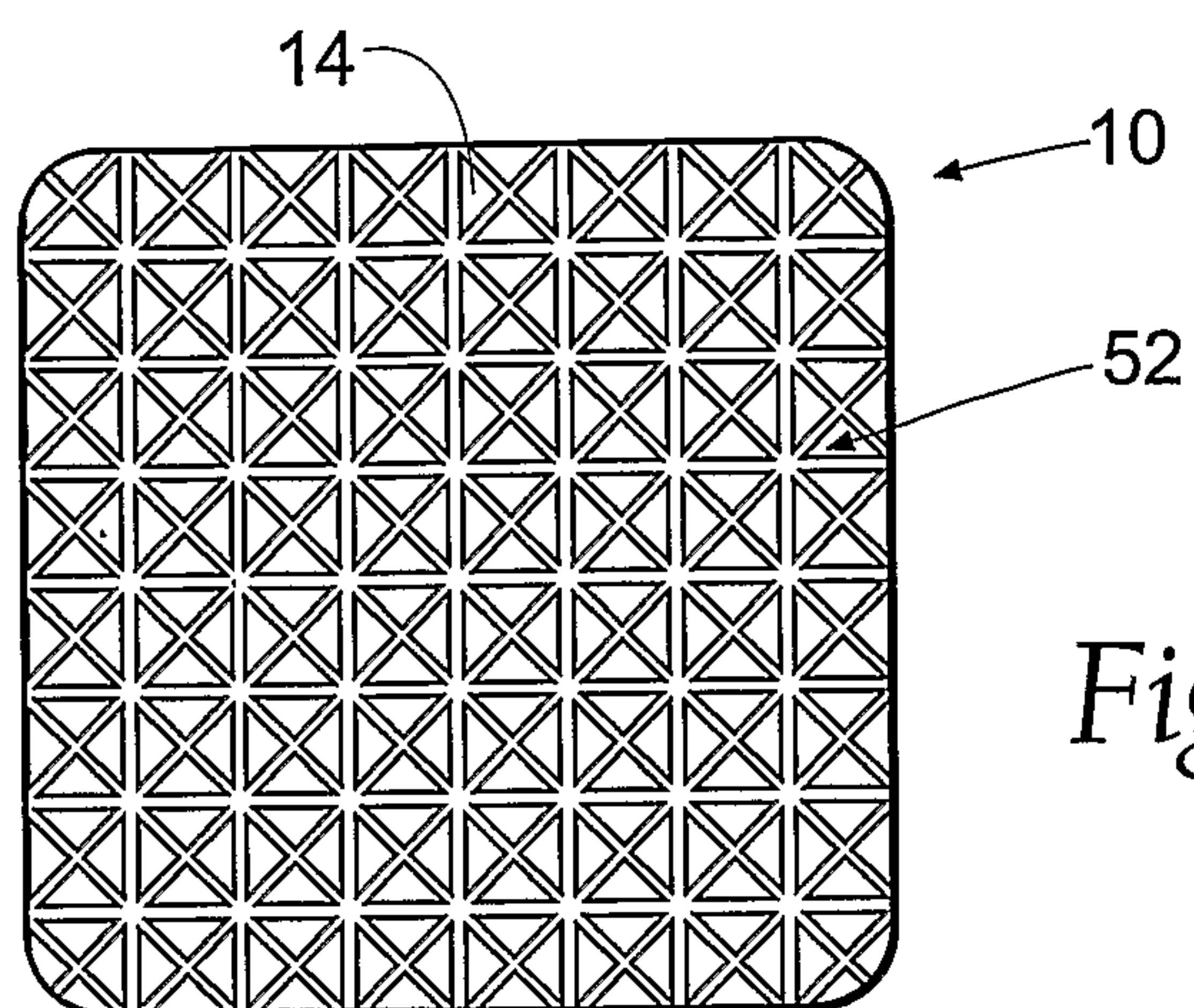
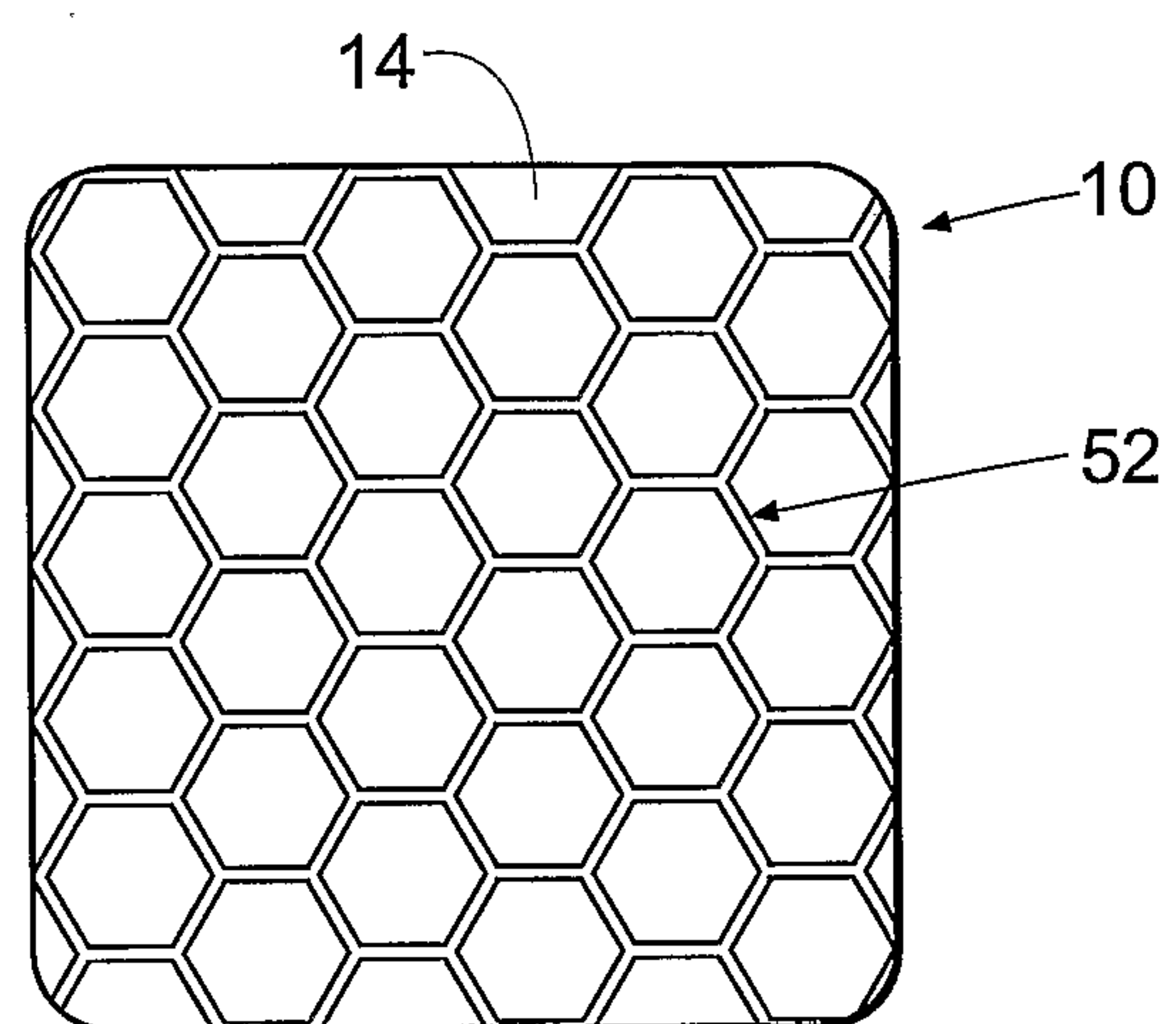
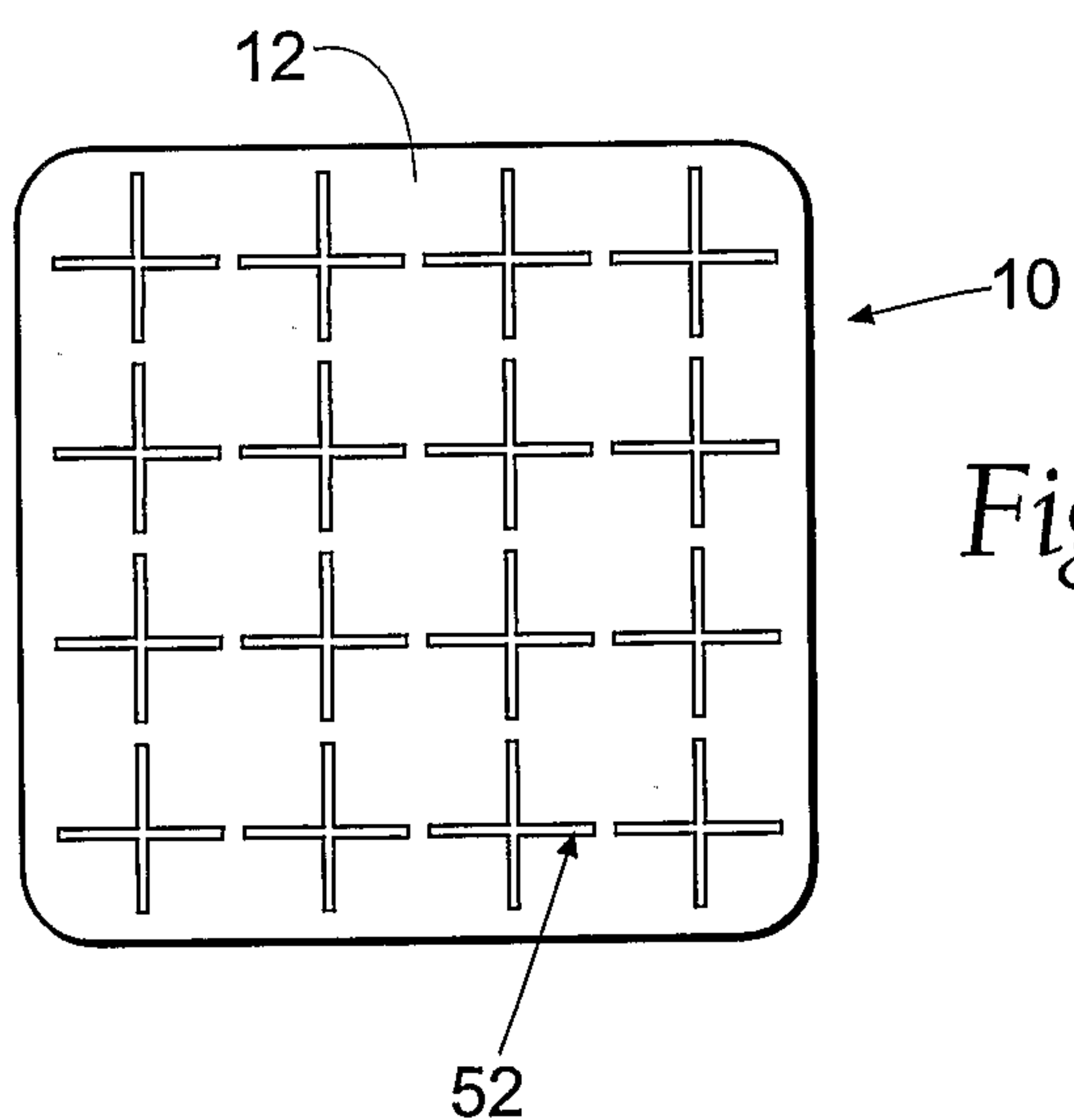
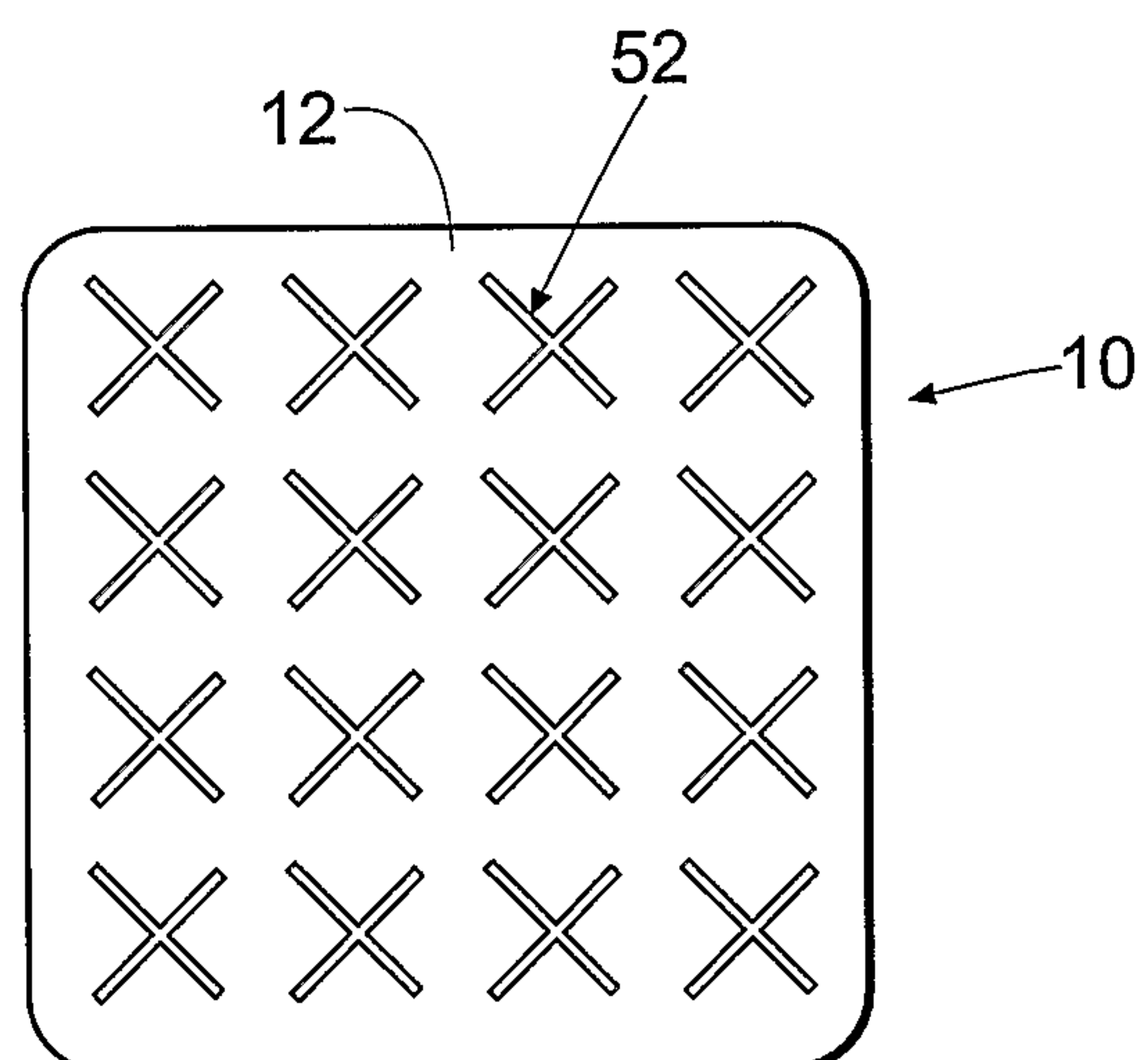


Fig. 1

Fig. 18C

*Fig. 19**Fig. 20**Fig. 21A**Fig. 21B*

*Fig. 22A**Fig. 22B**Fig. 23A**Fig. 23B**Fig. 24A**Fig. 24B*

*Fig. 24C**Fig. 24D**Fig. 24E**Fig. 24F*

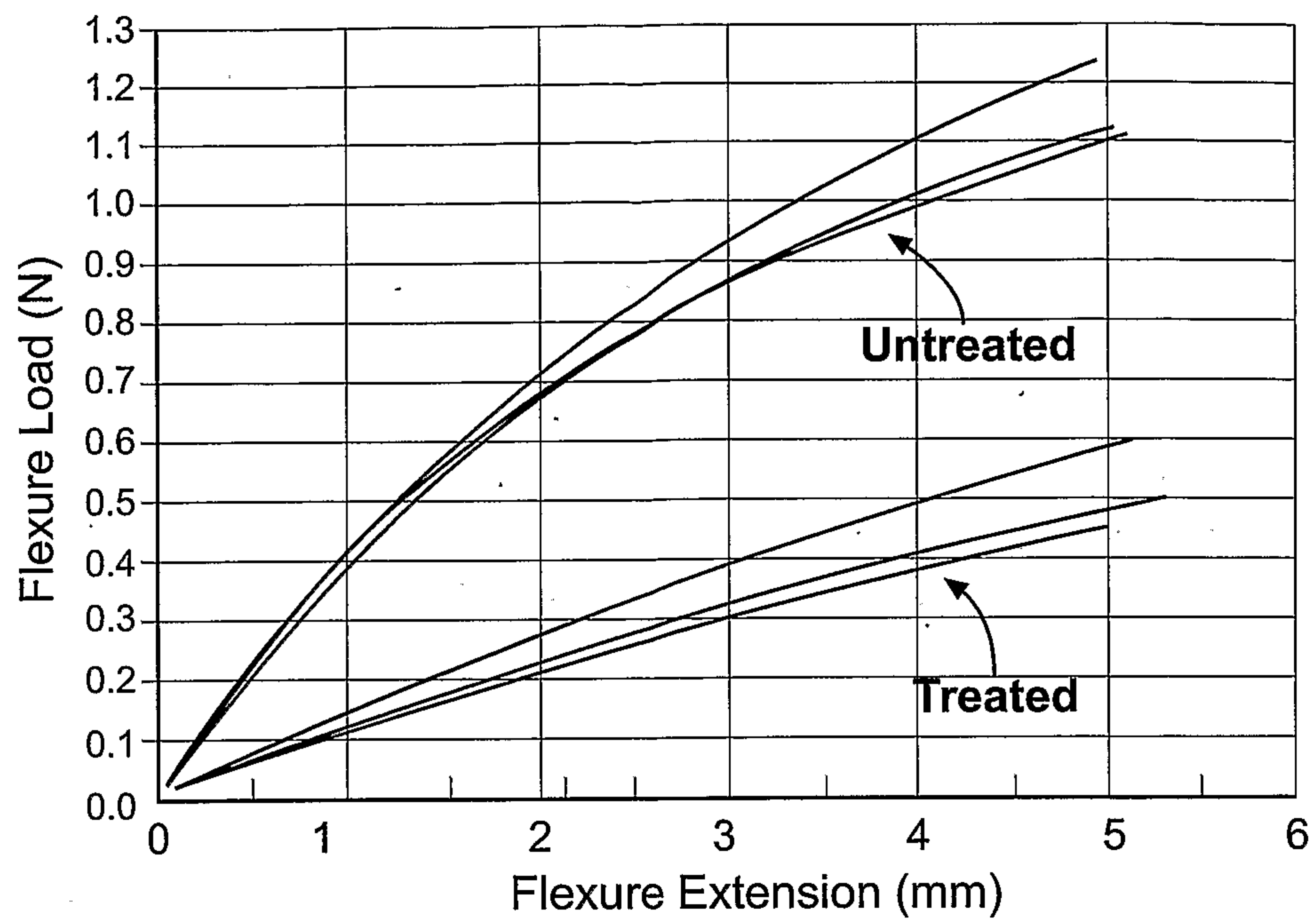


Fig. 25A

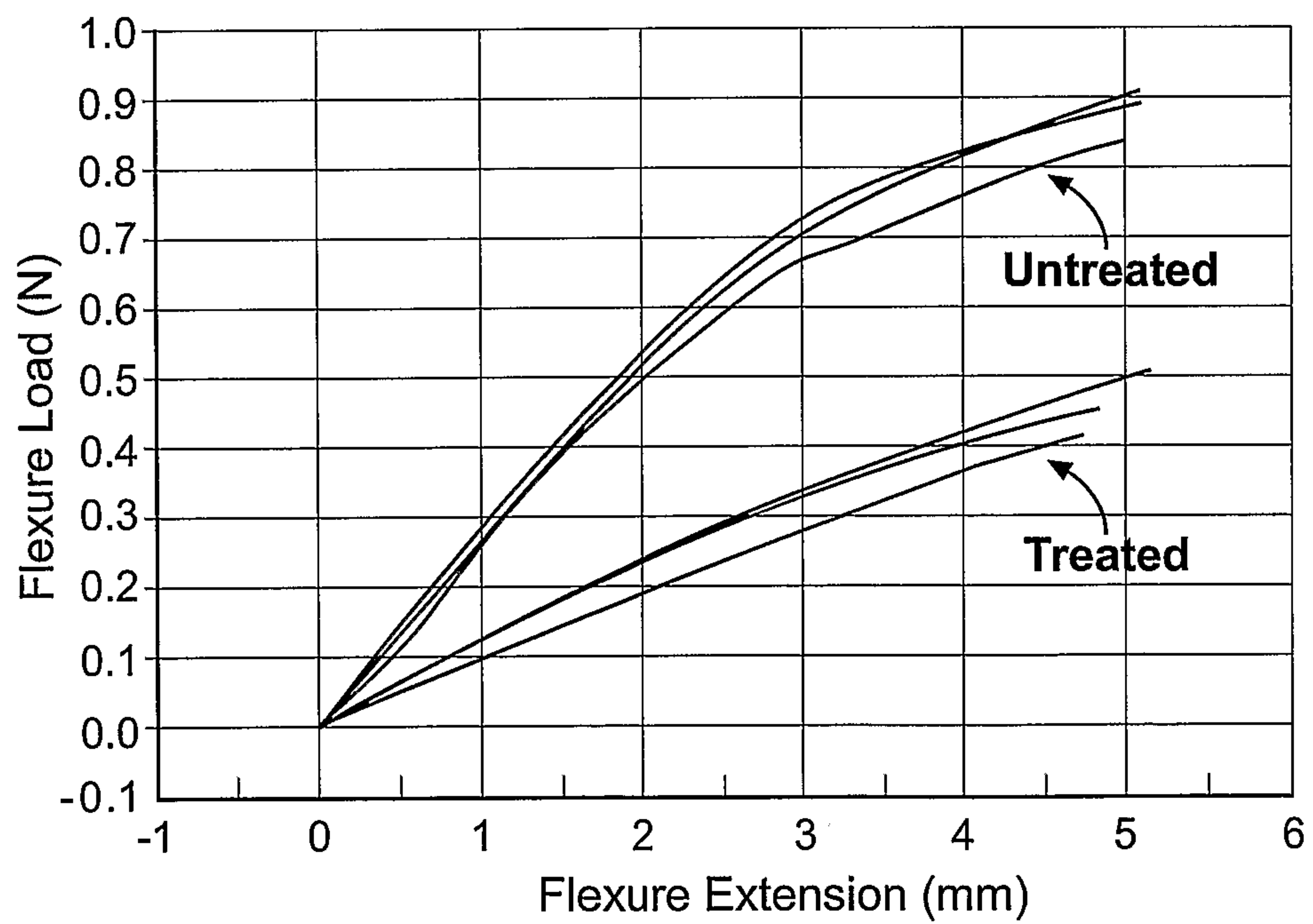
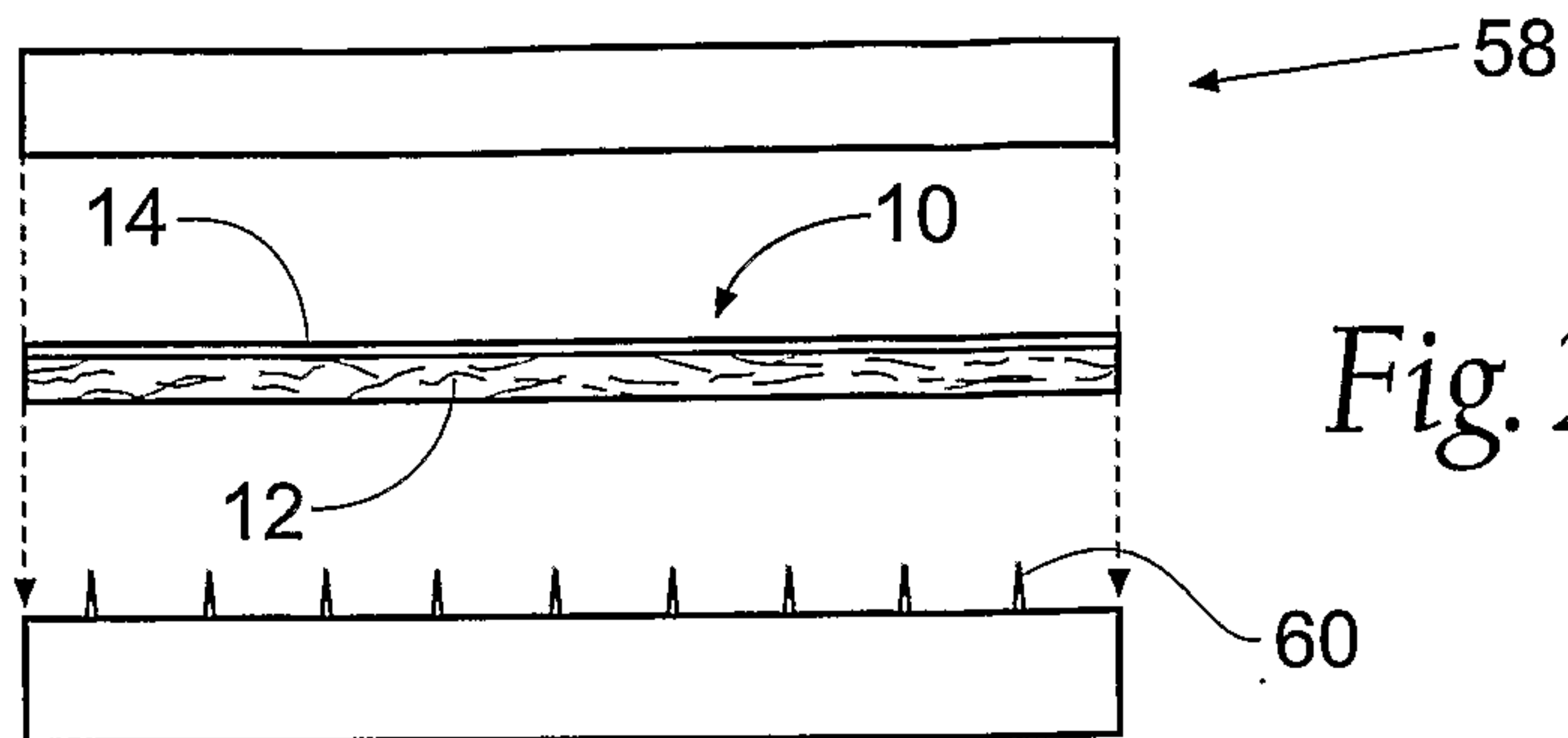
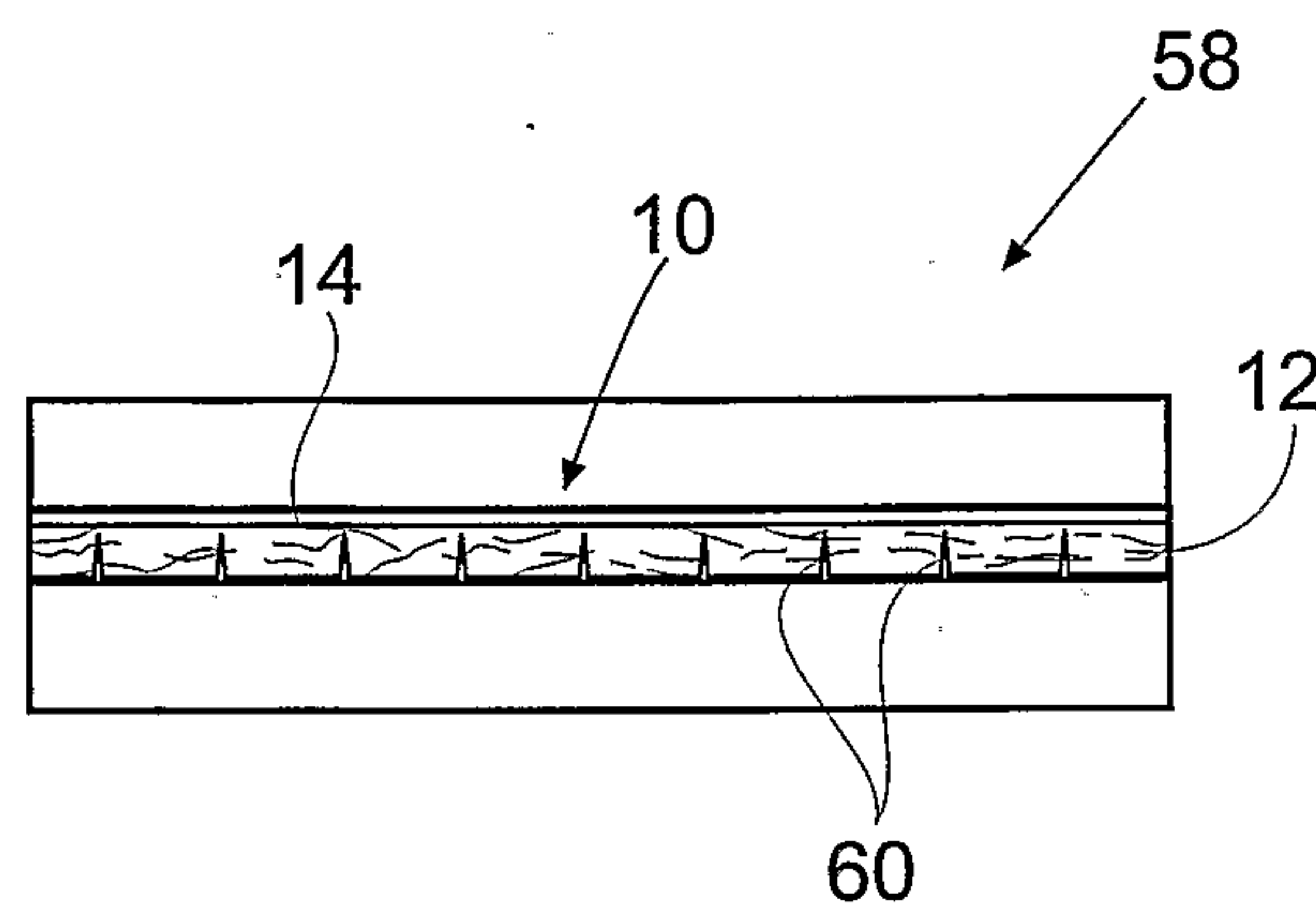
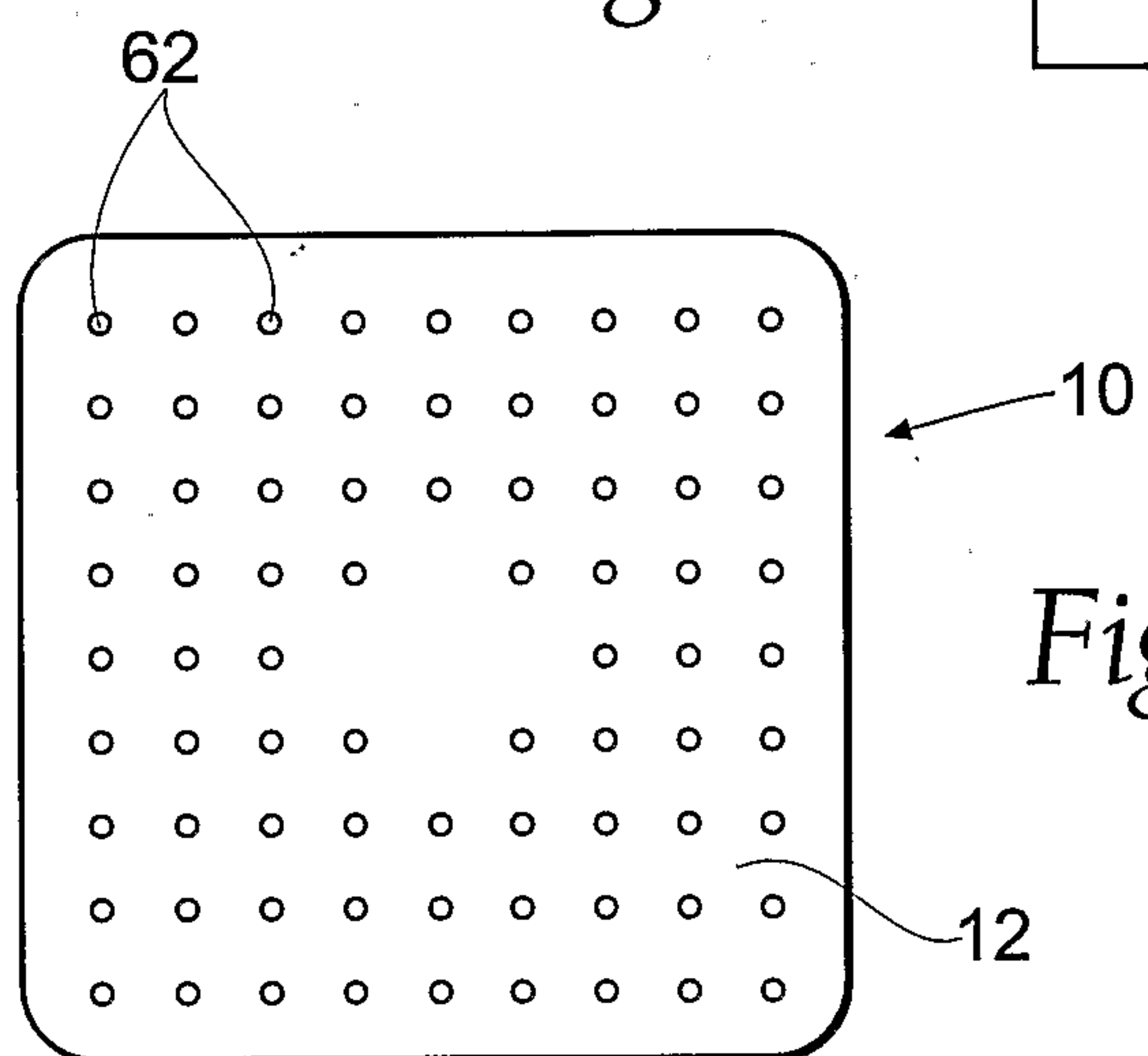
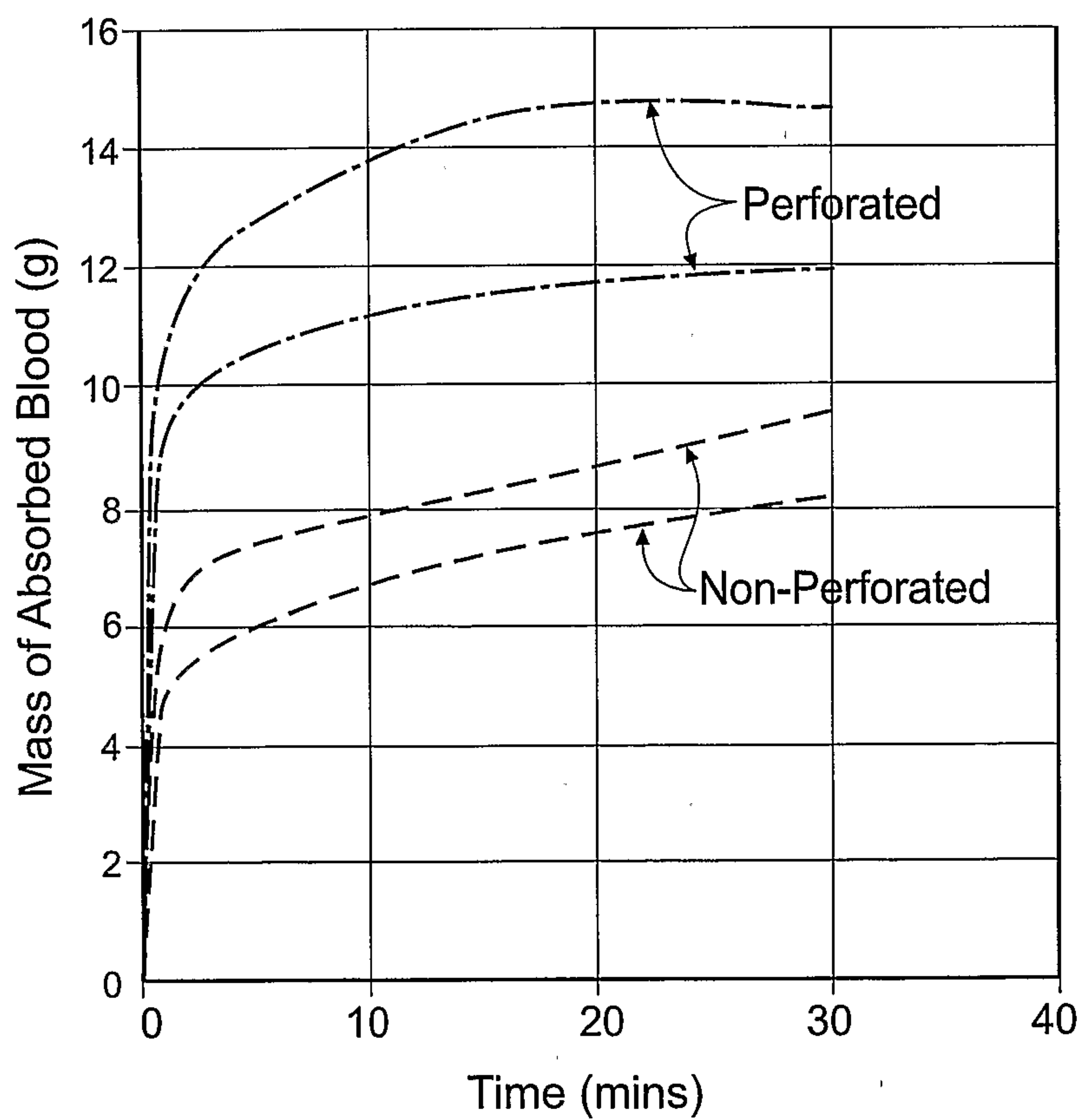
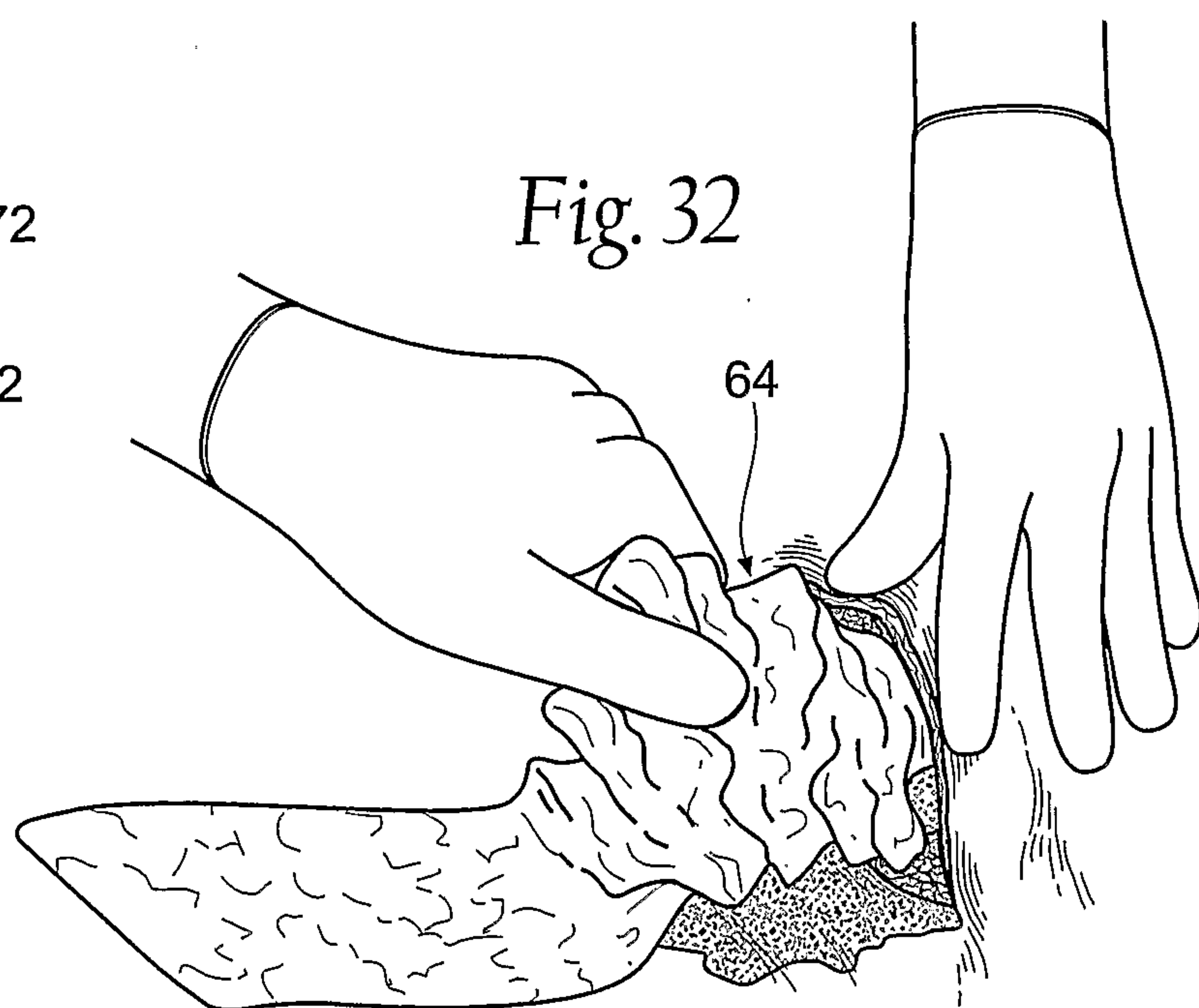
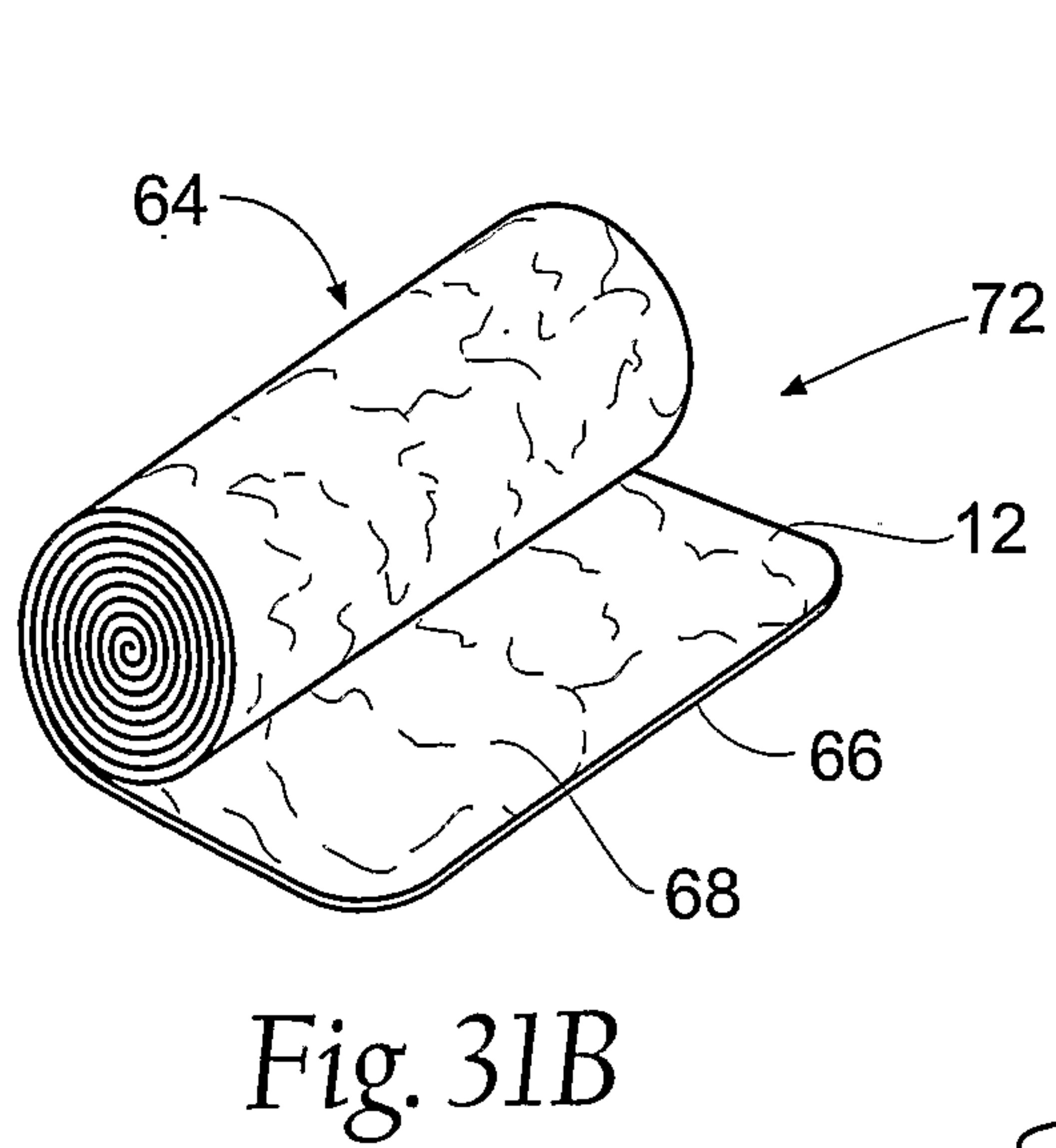
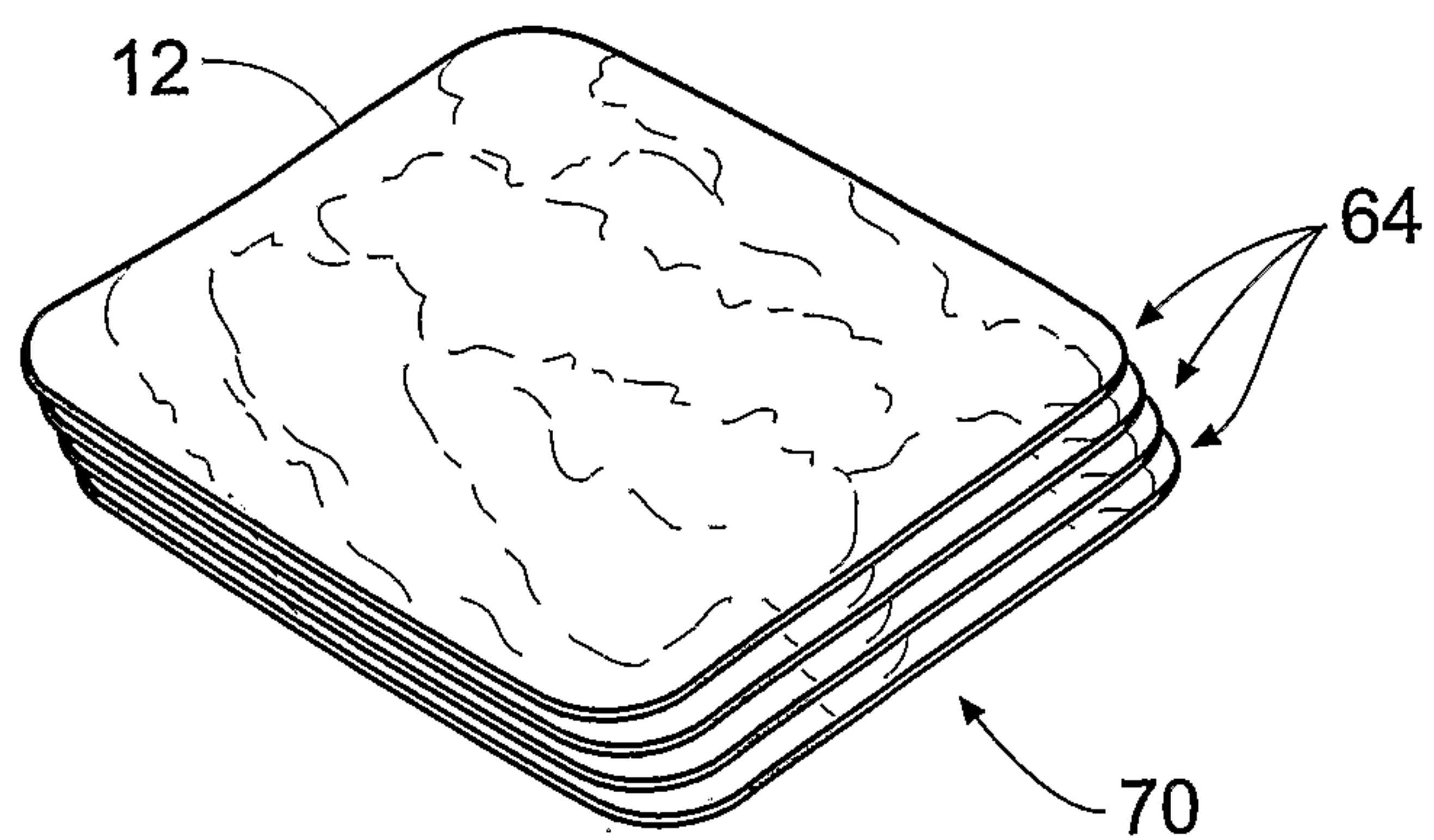
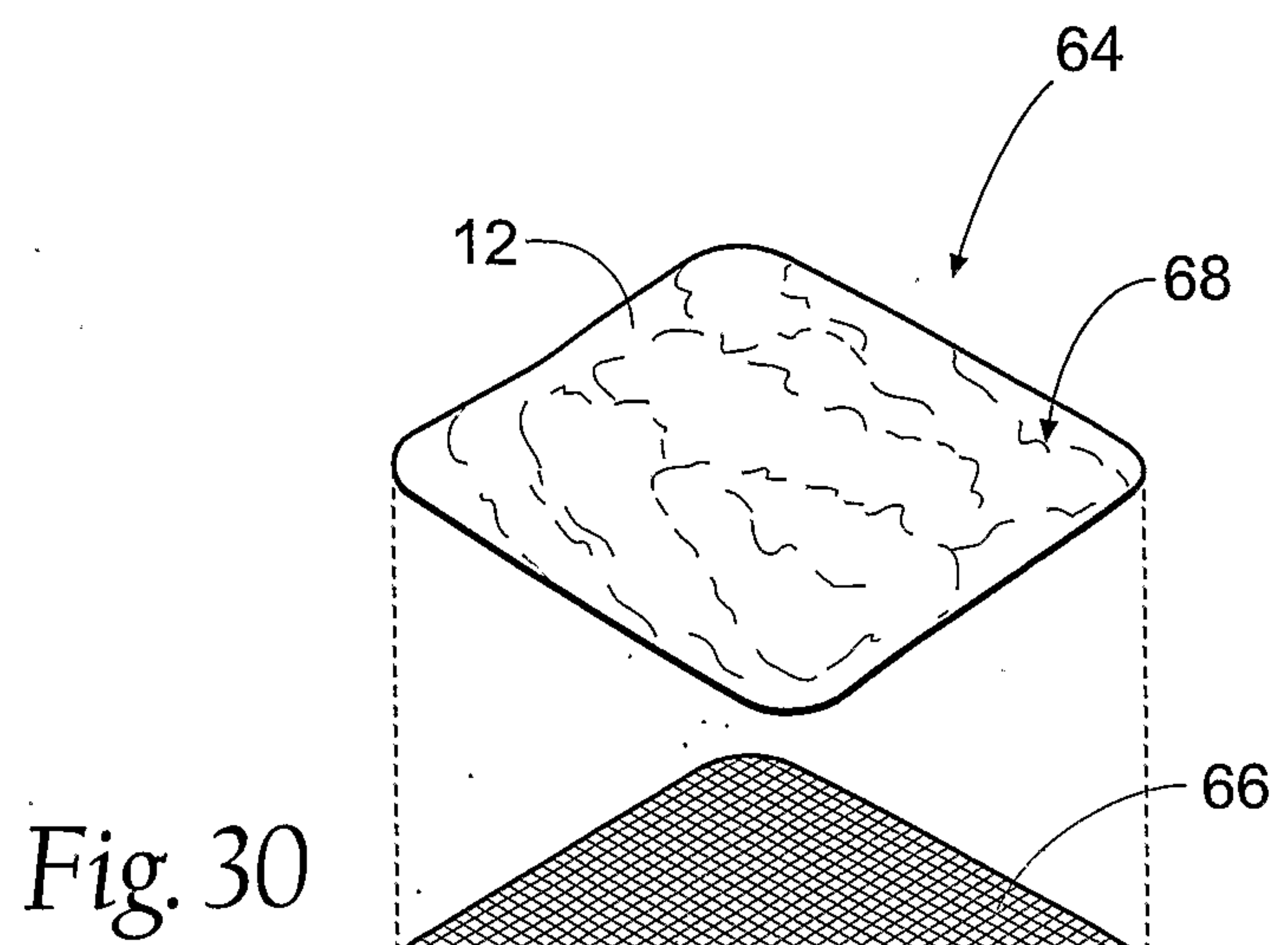
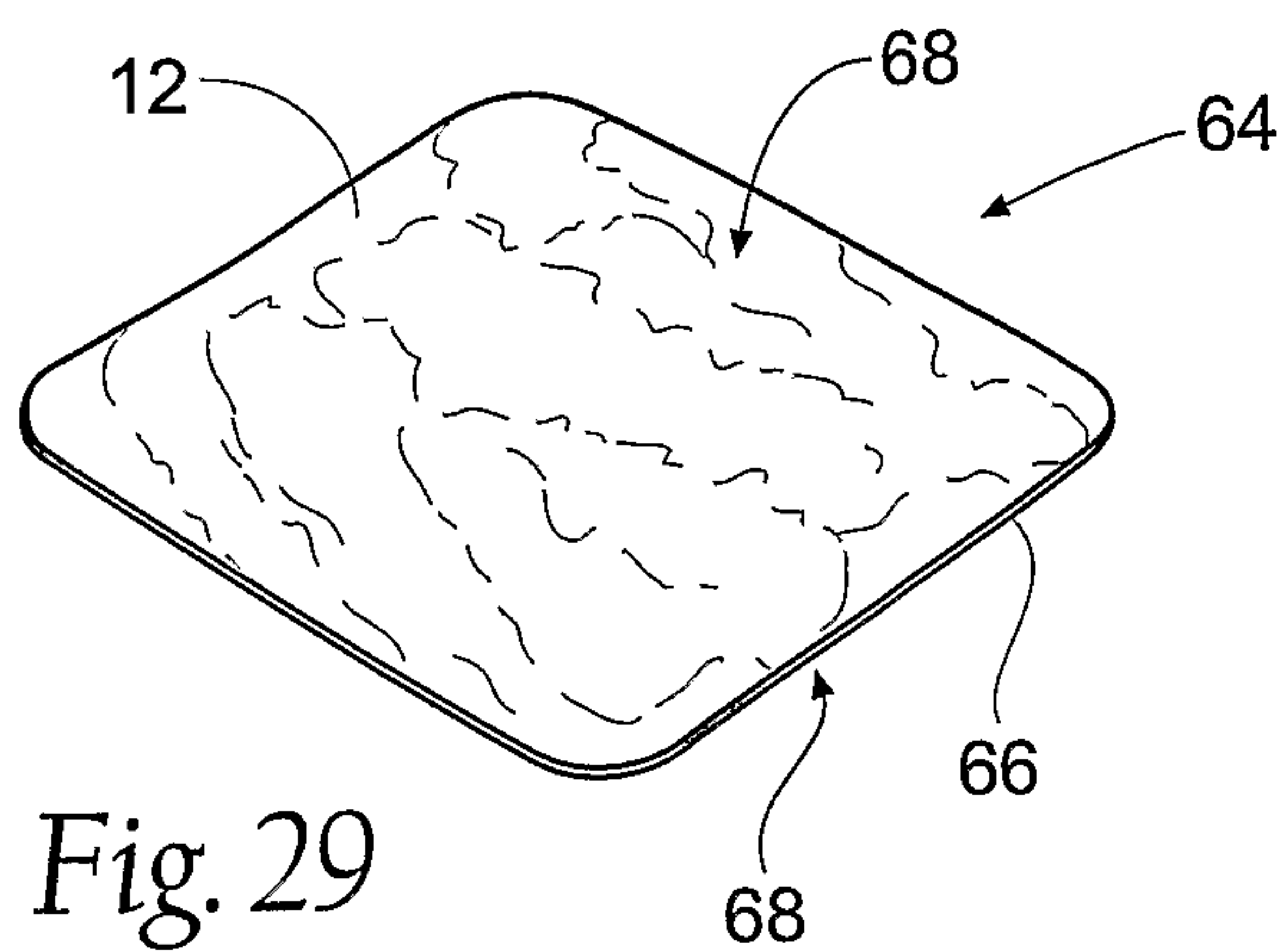


Fig. 25B

*Fig. 26A**Fig. 26B**Fig. 27**Fig. 28*



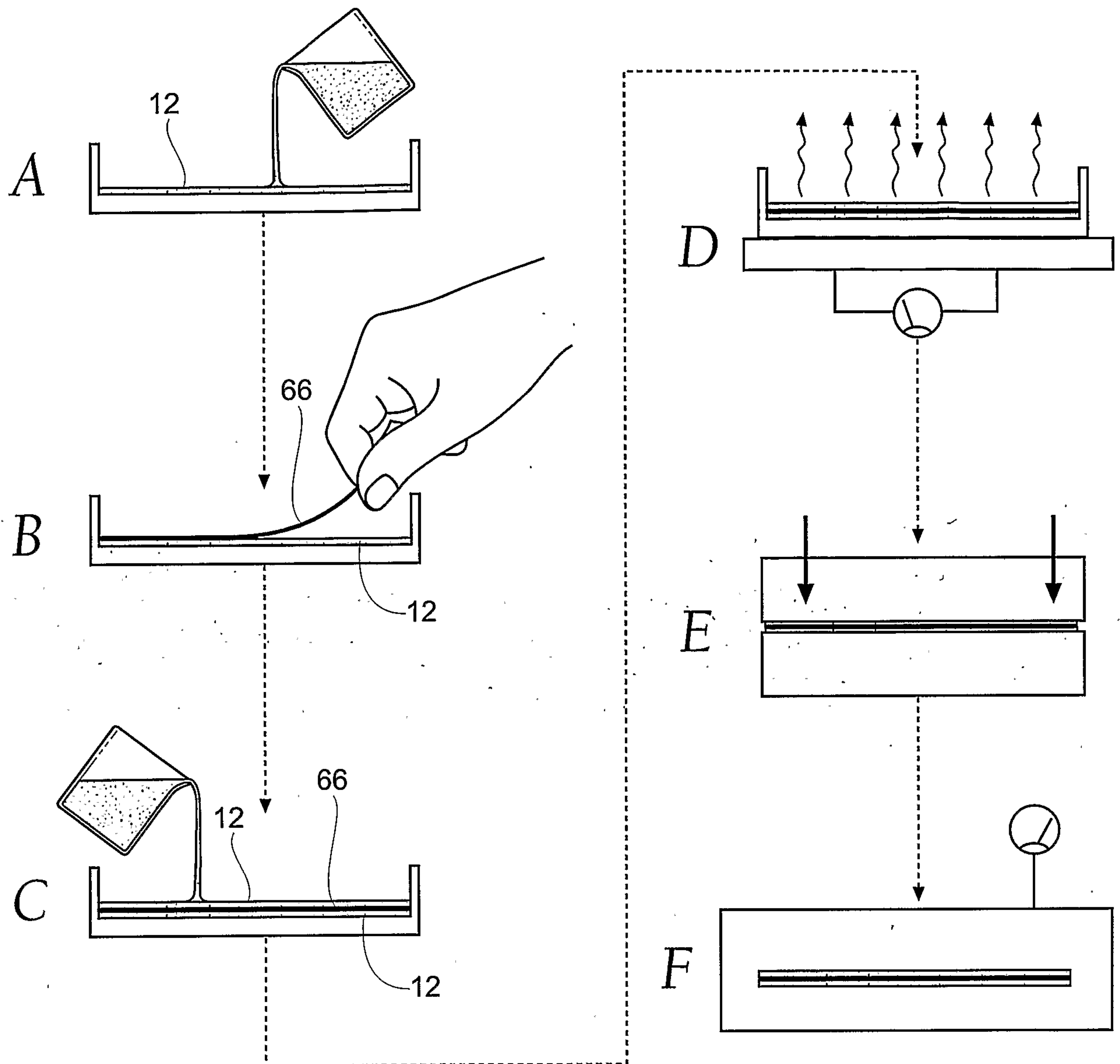


Fig. 33

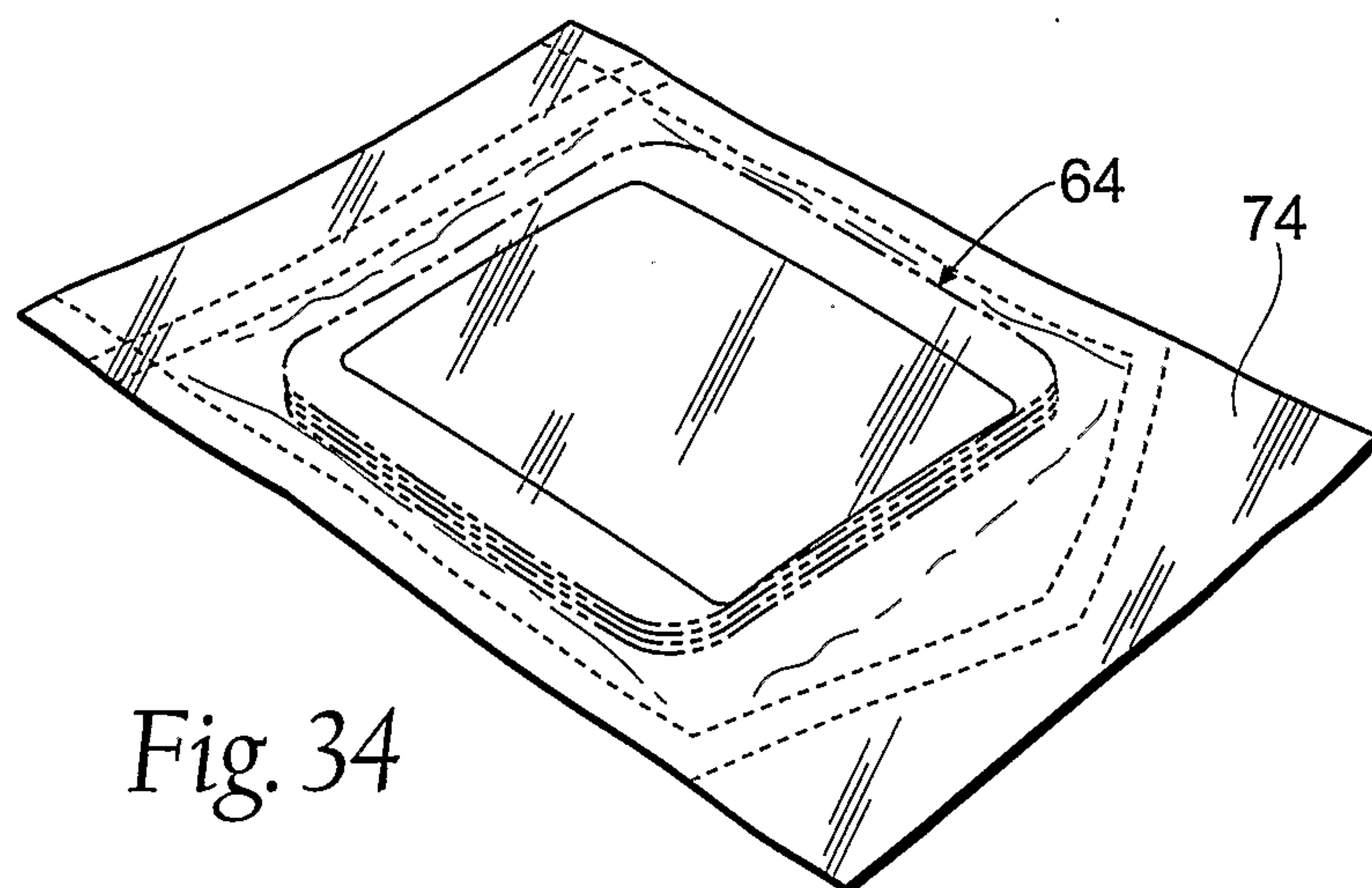


Fig. 34

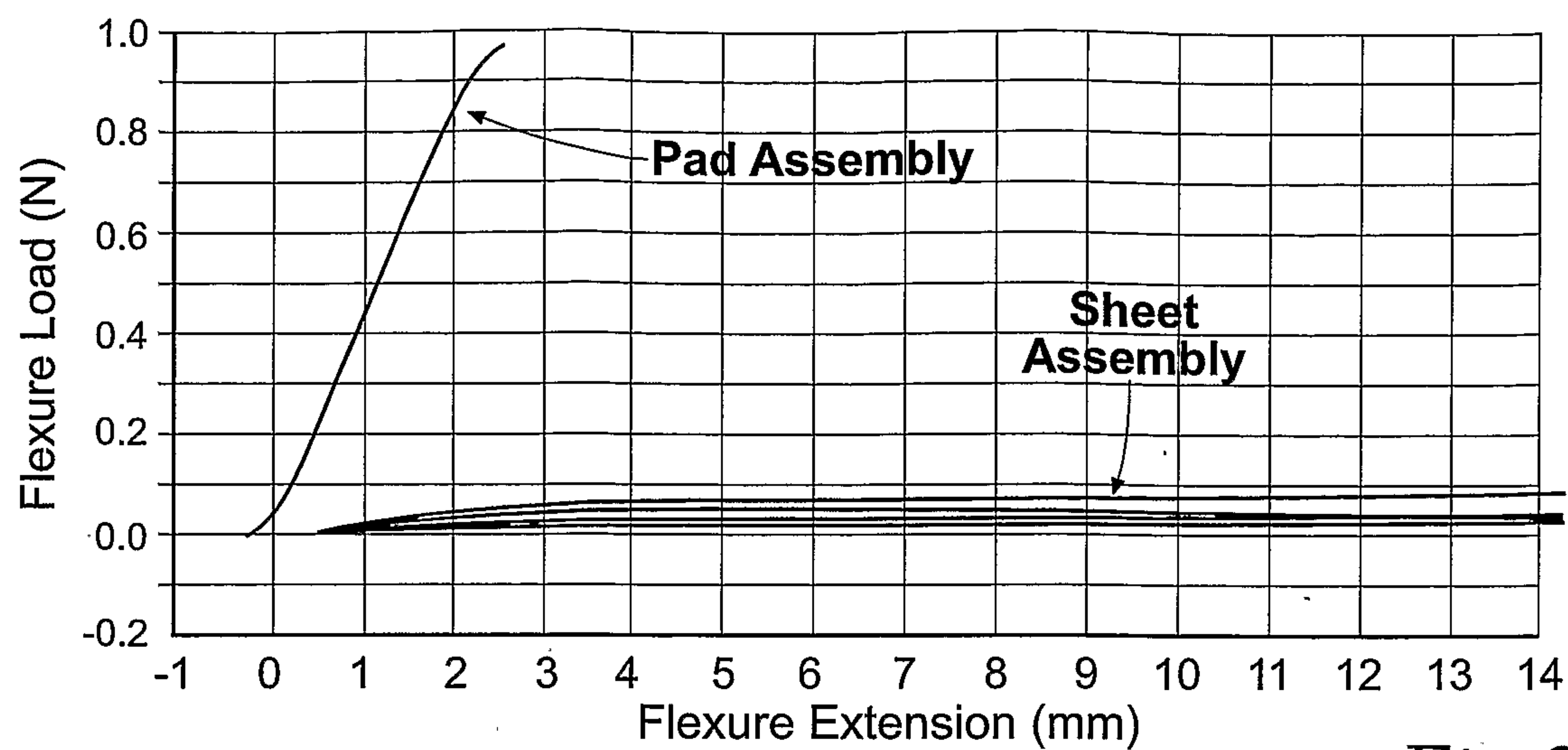


Fig. 35

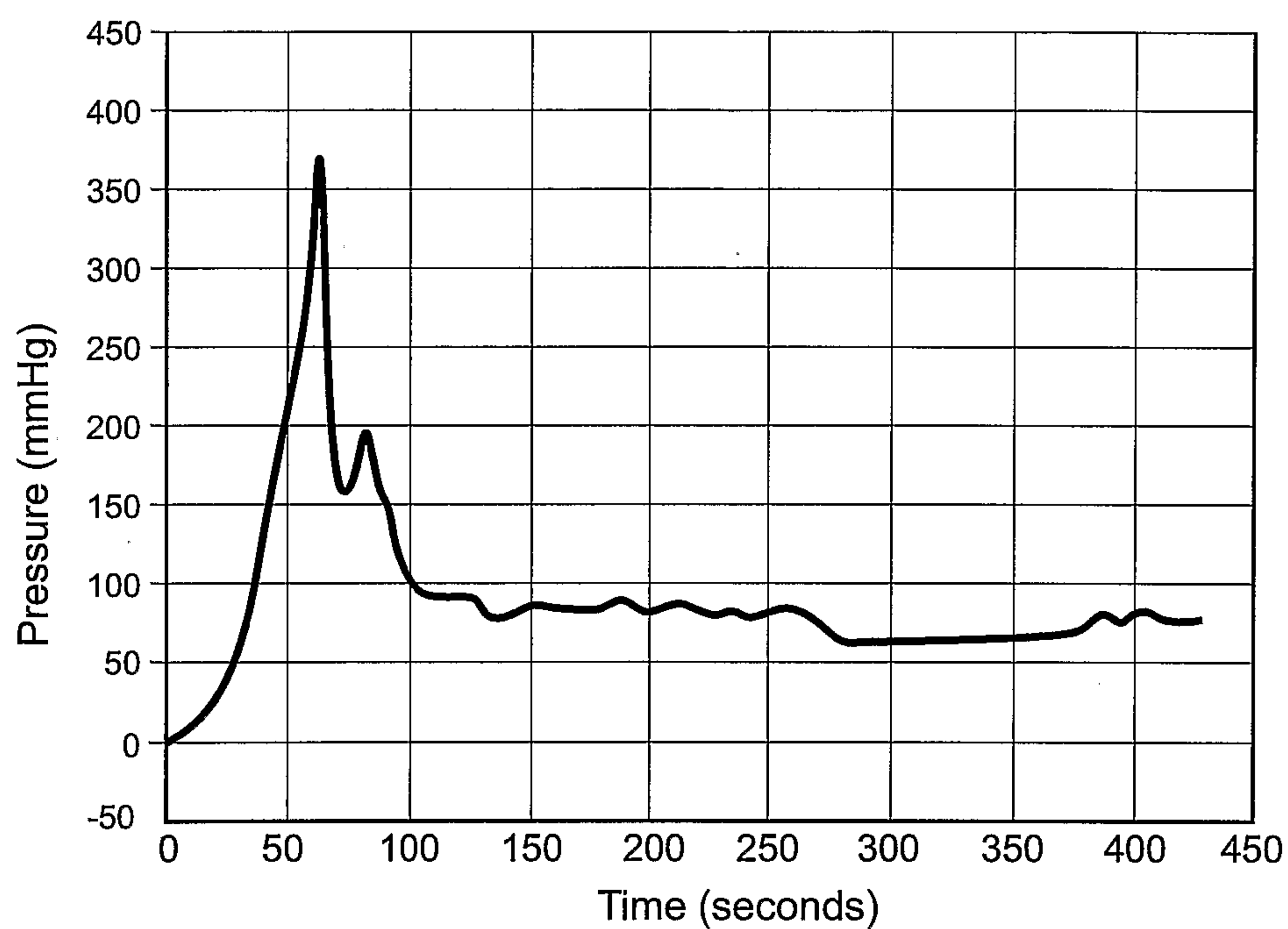


Fig. 36A

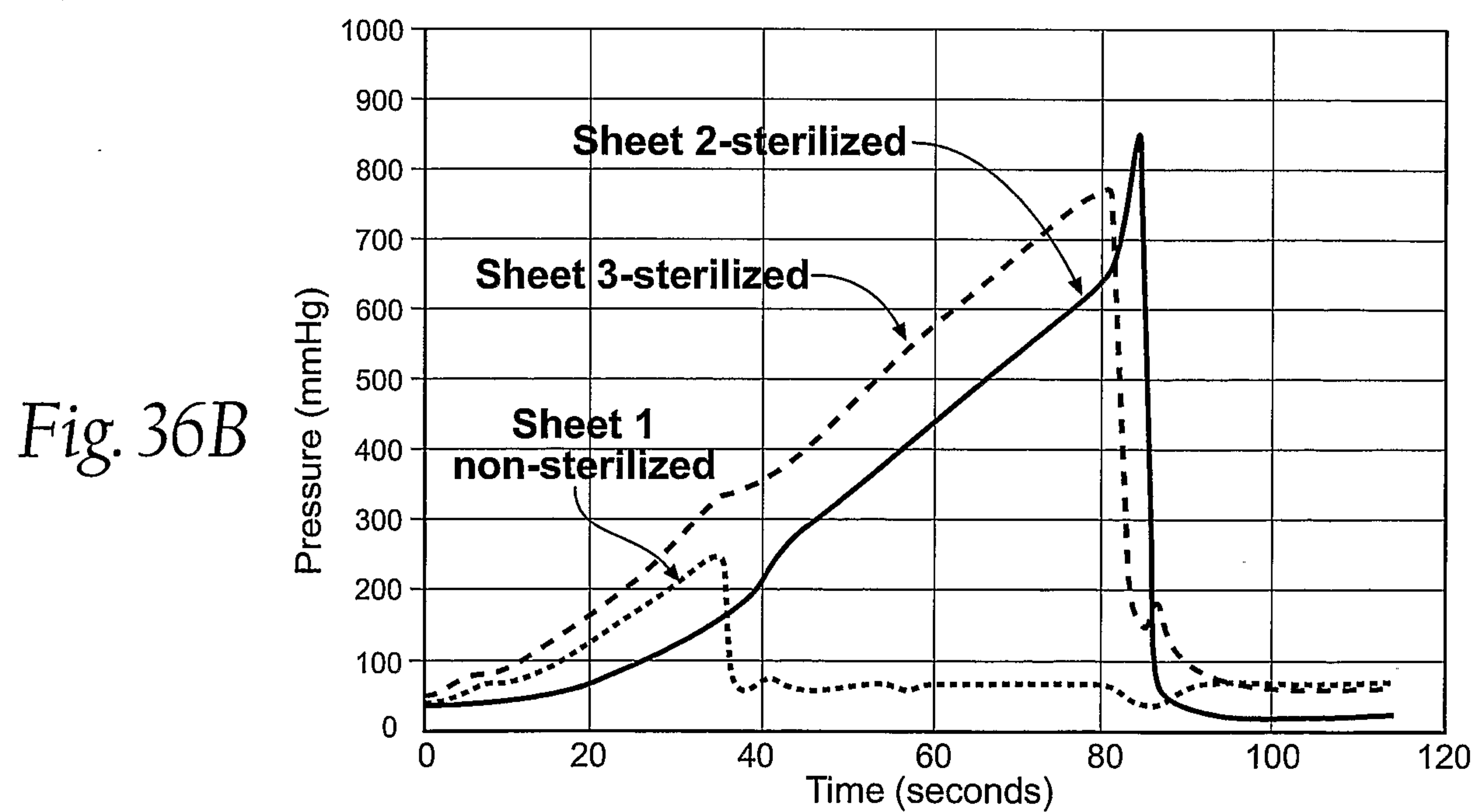


Fig. 36B

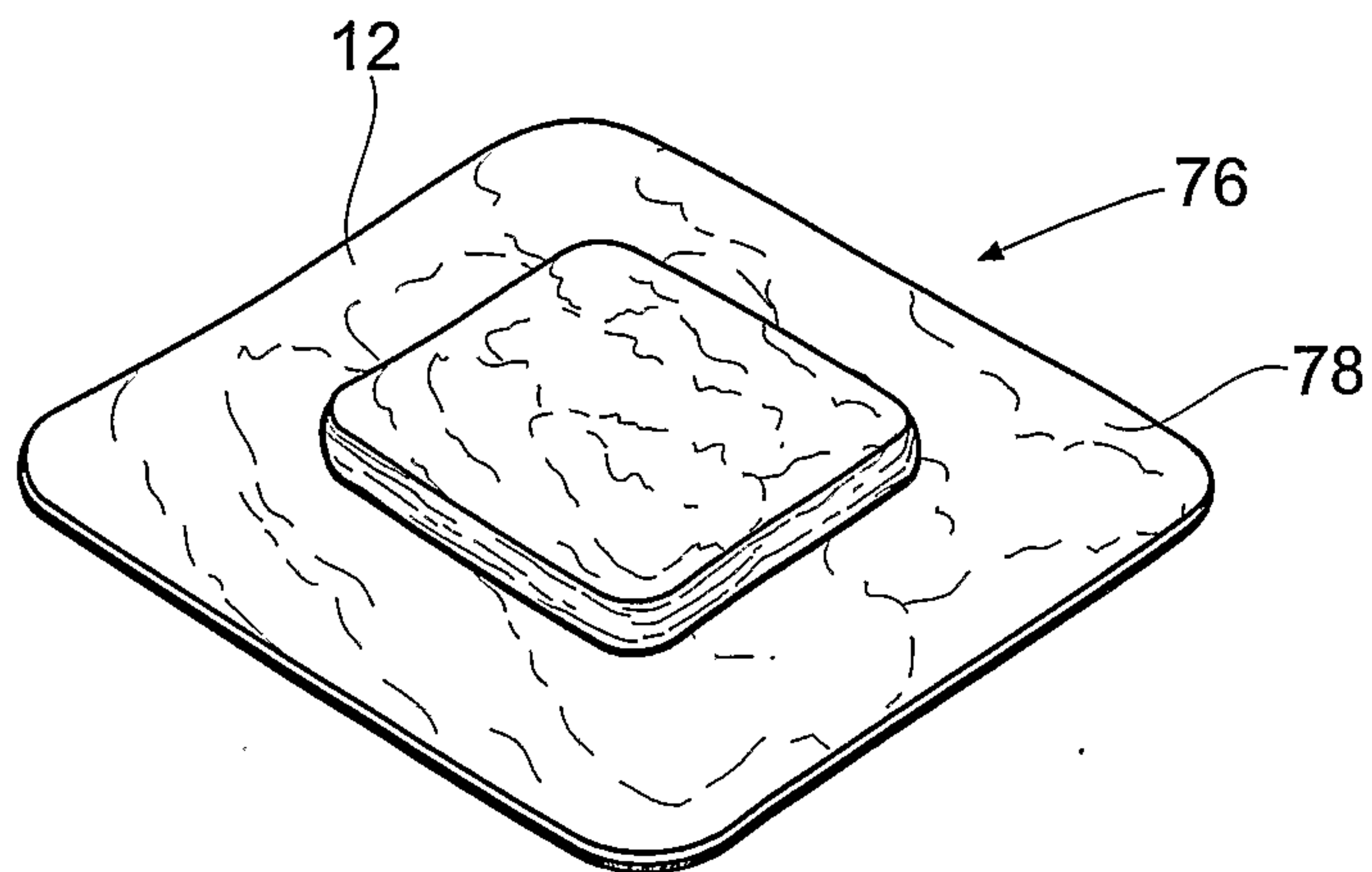


Fig. 37

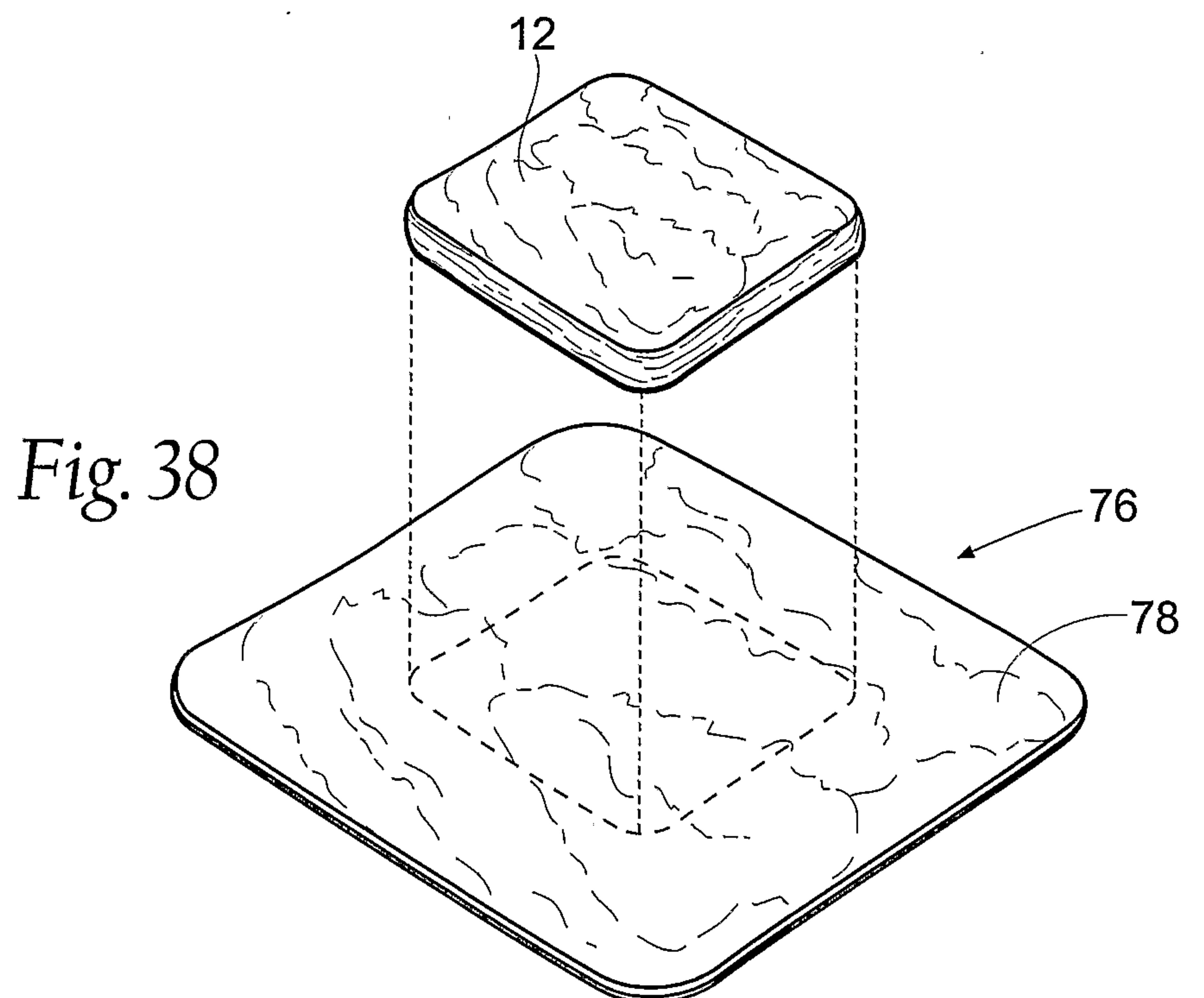


Fig. 38

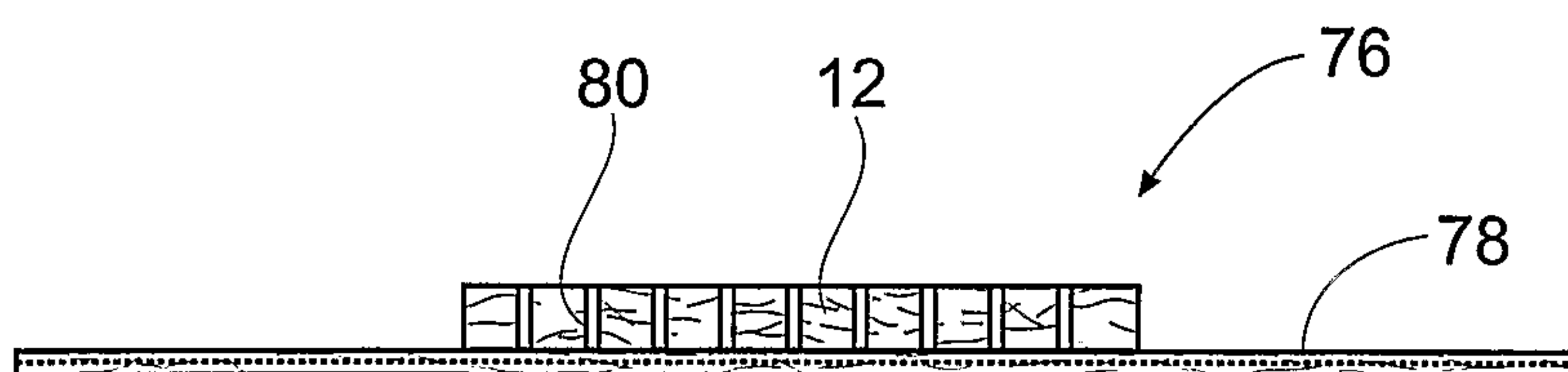


Fig. 39

