

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
2 March 2006 (02.03.2006)

PCT

(10) International Publication Number  
**WO 2006/023444 A2**

(51) International Patent Classification:  
A61F 13/00 (2006.01)

(21) International Application Number:  
PCT/US2005/028985

(22) International Filing Date: 16 August 2005 (16.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/602,225 17 August 2004 (17.08.2004) US

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

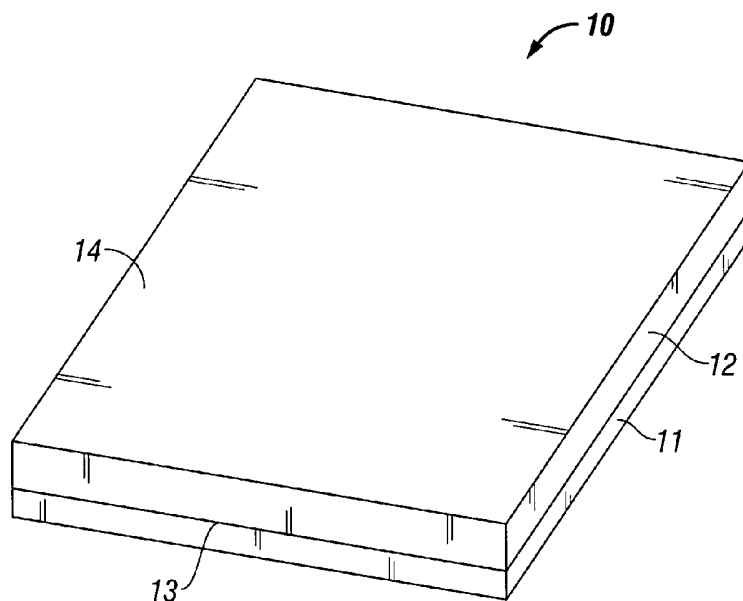
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— without international search report and to be republished upon receipt of that report

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

(54) Title: ANTI-ADHESION BARRIER



(57) Abstract: The present disclosure relates to medical devices comprising at least a first film layer and at least a second gel layer and to methods for preparing such devices.

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ANTI-ADHESION BARRIERCROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of and priority to U.S. Provisional  
10 Application Serial No. 60/602,225, filed on August 17, 2004, the entire disclosure of  
which is incorporated herein by reference.

BACKGROUND15 Technical Field

This disclosure relates to multi-layer devices for preventing tissue adhesion and  
promoting tissue growth.

Background of Related Art

In the field of internal medical care, such as internal surgery, there is a need for  
20 tissue regeneration devices which may prevent complications such as adhesions in the  
post-operative healing period. Adhesions which may be formed include the adhesion of  
tissue to tissue or of tissue to bone. It has been known to separate adjacent internal  
bodily surfaces by interposing a mesh or film so that during tissue regeneration following  
surgery no contact exists between the surfaces. One material which has been employed  
25 to prevent adhesions is an expanded polytetrafluoroethylene material known as Gore-  
Tex<sup>®</sup>. This material, however, is not hemostatic and is non-degradable by the human  
body. Thus the implant remains in the body, and, if necessary, must be removed  
surgically following the healing process. Another material is a mesh barrier of

carboxymethylcellulose known as Interceed<sup>®</sup>. This material, however, may not be applied in a blood-rich environment as under such circumstances the material quickly loses its barrier function. Films formed from poly(ethyleneoxide) and polyethylene terephthalate have also been proposed as barrier materials to prevent surgical adhesions.

5           It would be advantageous to provide a device for preventing the binding of tissue to tissue or of tissue to bone wherein the device prevents such binding while being sufficiently pliable as well as providing for growth of tissue, such as fibrous tissue, into the device.

## 10    **SUMMARY**

          Anti-adhesion devices in accordance with this disclosure have a first, film layer, and a second, gel layer. The film side inhibits the formation of post-operative adhesions and scarring, and the gel side acts as a tissue scaffold and promotes wound healing, cellular infiltration, angiogenesis, etc. The first layer, acting as a barrier layer, has a water content of  
15   less than about 30%. The second layer, acting as a tissue growth promoter, has a water content of greater than about 40%.

## **BRIEF DESCRIPTION OF DRAWINGS**

          FIG. 1 is a schematic perspective view of an anti-adhesion device in accordance with  
20   is disclosure.

          FIG. 2 is a schematic flow sheet showing the steps of one exemplary process for making an anti-adhesion device in accordance with is disclosure.

**DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

As seen in FIG. 1, an anti-adhesion device (generally denoted by the numeral 10) in accordance with this disclosure have a first, relatively smooth thin film layer 11, and a second  
5 gel layer 12. The film side inhibits the formation of post-operative adhesions and scarring, and the gel side acts as a tissue scaffold and promotes wound healing, cellular infiltration, angiogenesis, etc.

The layers of the present anti-adhesion devices are made from a hydrophilic biomaterial. Examples of suitable hydrophilic biomaterials include polymers formed  
10 from one or more of the following monomers: methacrylic acid, acrylic acid, n-vinyl pyrrolidone, potassium sulfopropylacrylate, potassium sulfopropylmethacrylate, acrylamide, dimethylacrylamide, 2-methacryloyloxyethyl phosphorylcholine, hydroxyethylmethacrylate or similar biocompatible water-soluble vinyl monomers. In a particularly useful embodiment, at least one of the layers is formed from a solution  
15 containing hydroxyethylmethacrylate.

The present devices are prepared using techniques within the purview of those skilled in the art. FIG. 2 schematically shows one exemplary preparation process. As seen therein, the first, film side of the device can be formed by filling a mold 5 with a composition 6 containing the monomer(s) and, if desired or necessary, initiator,  
20 crosslinker, plasticizer and/or biological agent, and polymerizing the composition within the mold to form the film layer 11. The choice of particular initiators, crosslinkers, etc. will be determined by the specific choice of monomer(s).

The equilibrium water content (EWC), swelling, and mechanical properties of the film layer can be controlled by crosslink density (radiation conditions or crosslinker

concentration). The thickness of the film side can be controlled by the volume of the monomer composition polymerized in the mold. Suitable thickness for the film side can be is in the range of about 0.1 to about 5 mm.

5 The second, gel side can be prepared in situ upon the first, film side by exposing the previously prepared layer 11 to an aqueous solution 8 containing one or more of the above-mentioned monomers suitable for making hydrophilic polymers. This will cause the original film to swell. The swollen film, while resting in the second biodegradable monomer or comonomer solution, can be incubated to further enhance film swelling prior to polymerization. The second monomer solution 7 is then polymerized in the  
10 presence of the swollen film 11 using low dose gamma radiation or conventional chemical initiated free radical polymerization or any other polymerization method within the purview of those skilled in the art to form the gel layer 12. The resulting structure is a composite containing two-layers; namely, a first film layer 11 of relatively low water content and a second gel layer 12 having a relatively high water  
15 content.

The equilibrium water content (EWC), swelling, and mechanical properties of the gel side can be controlled by crosslink density (radiation conditions or DEOGMA concentration). The thickness of the second, gel layer polymerized on top of the first, film layer, is controlled by varying the volume of monomer solution. As the volume  
20 of the second monomer solution increases, the thickness of the gels layer increases as well. Typically, the thickness of the second, gel layer will be in the range of about 0.1 to about 5 mm.

In the resulting composite, the gel layer is intimately associated with the relatively smooth thin film at the interface 13 between the two layers (see FIG. 1). During polymerization, the gel may form an interpenetrating network (IPN) of gel monomer/comonomers within the attached thin film and/or covalent interactions, i.e. grafting of gel monomers to the thin film during *in situ* polymerization. In addition, the water content of the resulting composite increases as you move from the interface 13 towards the outer surface 14 of the second layer.

The size, structure, and morphology of the gel can be controlled through monomer selection and concentration, reaction conditions (i.e. gamma dose and dose rate), solvents (water, buffered saline, media, etc.), agents incorporated (proteins, drugs, AM agents, etc.), and other parameters. The composites can also be lyophilized to produce a sponge-like morphology, on the second layer side, to assist in cell or tissue infiltration and wound healing, while retaining a smooth laminar surface on the film side.

In embodiments where the relatively smooth thin film side of the present anti-adhesion devices is made of poly-(hydroxyethyl methacrylate) (PHEMA), such films can be synthesized using  $^{60}\text{Co}$  gamma radiation, UV radiation, or conventional chemical initiated (AIBN, BPO, redox, etc.) free radical polymerization. In a typical preparation method, a composition containing HEMA monomer, AIBN as an initiator and diethyleneglycol dimethacrylate (DEGDMA) as a crosslinker is poured into a glass mold and polymerized at approximately  $65^{\circ}\text{C}$  for 1.5 hours. Resulting films are washed repeatedly with water and dried *in vacuo*. In another preparation method, PHEMA the first side of the device can be prepared using radiation polymerization (600 mC source,

295 - 1180 rad/min, 0.05 - 1 Mrad) without the need of chemical initiator or crosslinker, and using the same washing/drying regiment.

The present anti-adhesion devices can be any shape, and will normally be in the form of a sheet. The devices can be made to size or prepared as a large sheet from which  
5 desired shapes are cut or punched. The present anti-adhesion devices can advantageously be provided as six inch square sheets which can be cut to any desired size or shape by the surgeon prior to application to tissue.

The present anti-adhesion devices can also be surface modified following film formation. For example, a PHEMA anti-adhesion device can be surface modified with  
10 polymeric phospholipids for improved hemocompatibility and tissue interaction using gamma radiation grafting.

In another embodiment, the surface of the anti-adhesion devices can be patterned or templated in the nano-meso-micro scale to accommodate preferential tissue interaction at the tissue/buttrass interface. Such architecture or patterns can prevent or minimize  
15 post-operative tissue adhesions and superfluous collagen deposition, but afford desired mechanical and biophysical support for wound healing.

The composition from which each side of the anti-adhesion device is made may also contain one or more medically and/or surgically useful substances such as drugs, enzymes, growth factors, peptides, proteins, dyes, diagnostic agents or hemostasis agents  
20 or any other pharmaceutical used in the prevention of stenosis. Non-limiting examples of suitable medically and/or surgically useful substances include: antimicrobials, antibiotics, anti-fungals, anti-virals, monoclonal antibodies, polyclonal antibodies, antimicrobial proteins/peptides (whole and fragments), enzymes, gene therapy, viral particles,

chemotherapeutics, anti-inflammatories, NSAIDS, steroids, telomerase inhibitors, growth factors (TGF family, interleukin superfamily, fibroblast derived GFs, macrophage derived GFs, etc.), extracellular matrix molecules (laminin, thrombospondin, collagen, fibronectin, synthetic ECM, etc.), cell adhesion molecules, polysaccharides (hyaluronic acid, carboxymethyl cellulose, alginate, sulfonated dextran, heparin sulfate, chitosan, etc.) and others. These agents can be incorporated *in situ* into the composition used to make each side of the anti-adhesion device or post loaded onto either or each polymerized side of the anti-adhesion device using techniques within the purview of those skilled in the art. For example, the medically and/or surgically useful substances can be freely mixed or loaded, electronically or ionically bound, covalently immobilized, chelated, or encapsulated in particles, micelles, aggregates, or any nano-meso-micro solids of varied dimension, shape morphology and dispersion/suspension ability.

It should be understood that the composition of the first and second layers can be the same or different, depending on the composition of the monomer solutions employed in making each layer and the presence of any medically and/or surgically useful substances or optional ingredients. Useful optional ingredients include, but are not limited to, plasticizers, emulsifiers, solvents, foaming agents, blowing agents, surfactants, radio-opaque markers, colors, dyes, fragrances, etc.. These optional ingredients, when present, may be present in an amount of up to about 5 wt. % of the first layer and/or the second layer.

In another embodiment, the second layer may be coated with an adhesive such as, but not limited to, cellulose (such as carboxymethyl cellulose, or CMC, and hydroxypropyl methyl cellulose, or PIPMC); mucoadhesives, such as, but not limited to,

mucin, mucopolysaccharides, polycarbophil, tragacanth, sodium alginate, gelatin, pectin, acacia, and providone; acrylates (such as polyacrylic acid and methyl methacrylate); polyoxyethylene glycol having a molecular weight of from about 100,000 to about 4,000,000; mixtures of zinc oxide and eugenol; a fibrin-glue layer; a chitosan layer; and  
5 glucosamine. Such a coating improves initial adhesion of the second layer of the device to tissue, such as the peritoneum.

It is also contemplated that a fibrous reinforcing element (not shown), such as a surgical grade mesh, can be incorporated into the anti-adhesion devices in accordance with the present disclosure. Suitable fibrous reinforcing elements can be made from a  
10 biocompatible non-absorbable (i.e., permanent) material, such as, for example “TEFLON” which is a registered trademark owned by DuPont de Nemours & Co., or a biocompatible absorbable material. The biocompatible materials can be woven, knit or non-woven. Bio-absorbable materials include those fabricated from homopolymers, copolymers or blends obtained from one or more monomers selected from the group  
15 consisting of glycolide; glycolic acid, lactide, lactic acid, p-dioxanone,  $\epsilon$ -caprolactone and trimethylene carbonate. Non-absorbable materials include those that are fabricated from such polymers as polyethylene, polypropylene, nylon, polyethylene terephthalate, polytetrafluoroethylene, polyvinylidene fluoride, and the like. Further non-absorbable materials include and are not limited to stainless steel, titanium and the like. To  
20 incorporate a fibrous reinforcing element into the present anti-adhesion devices, the reinforcing element can be added to the mold prior to addition of the monomer solution used to form the film layer. Alternatively, the reinforcing element can be placed on top of the film layer after it is formed, with the subsequent addition of the solution used to

form the second, gel layer. Polymerization of the second solution will result in incorporation of the reinforcing element at or near the interface of the two layers.

The devices of the present disclosure may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of  
5 tissue to bone. Examples of uses of the devices of the present disclosure include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, Fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for used during laparoscopy; barriers between periodontal tissue; barriers between cartilages or between cartilage and bone; barriers between digestive  
10 organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between muscle tissue and bone; barriers between the esophagus and mediasternum; barriers between the gall bladder or  
15 pancreas and the peritoneum; and barriers for scrotal surgery, i.e., hernias.

The devices of the present disclosure may also be used for guided tissue regeneration. For example, the devices may be used to cover internal perforations, such as, for example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce  
20 areas prone to, or showing scar formation, such as, for example, inguinal hernias. The device therefore acts as a patch for covering the perforation until complete healing, followed by monomer absorption, is achieved. It is also contemplated that the devices

may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The devices of the present disclosure may be employed as a scaffolding to treat ulcers. The second, growth promoting layer stimulates the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The devices of the present disclosure may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The devices may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The devices may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The devices may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

Since the resulting composites of the present disclosure are easily moldable, malleable and bendable, these devices may also be used with a wide variety of different medical devices, such as sutures, anchors, implants, scaffolds, staples, etc.

The present anti-adhesion devices can be sterilized and package using techniques within the purview of those skilled in the art. The method of sterilization should be chosen to preserve the efficacy of any medically and/or surgically useful substances contained in the device. The device may be packaged in a pre-swollen or “wet” state  
5 which may lessen the devices shelf-life. Also, the device may be packaged in a “dry” or non-swollen state wherein the device could be pre-swollen prior to use or could swell in situ upon contact with natural bodily fluids.. Such a packaging may lengthen the shelf-life of the device.

While the above disclosure has related generally to specific embodiments of anti-  
10 adhesion devices and their use, it is to be understood, however, that the scope of the present disclosure is not to be limited to the specific embodiments described above. For example, rather than sheets, the present layered devices can be formed into tubular structures. As another example, the present devices are not limited to two layers, but rather more than two layers can be prepared, if desired using the presently described  
15 techniques. Therefore, the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the present disclosure.

**WHAT IS CLAIMED IS:**

1. An anti-adhesion device comprising:  
a composite of a first layer and a second layer, wherein the first layer comprises a first biodegradable monomer and the second layer comprises a second biodegradable monomer, and wherein the water content of the first layer is less than about 40% and the water content of the second layer is between about 40 and 90%.  
5
2. The anti-adhesion device of claim 1 wherein the first biodegradable monomer is selected from the group consisting of poly- (hydroxyethyl methacrylate), methacrylic acid, acrylic acid, n-vinyl pyrrolidone, potassium sulfopropylacrylate, potassium sulfopropylmethacrylate, hydroxyethyl methacrylate, acrylamide, dimethylacrylamide, 2-methacryloyloxyethyl phosphorylcholine and combinations thereof.  
10
3. The anti-adhesion device of claim 1 wherein the biodegradable monomer is poly (hydroxyethyl methacrylate).  
15
4. The anti-adhesion device of claim 1 wherein the second biodegradable monomer is selected from the group consisting of poly (hydroxyethyl methacrylate), methacrylic acid, acrylic acid, n-vinyl pyrrolidone, potassium sulfopropylacrylate, potassium sulfopropylmethacrylate, hydroxyethyl methacrylate, acrylamide, dimethylacrylamide, 2-methacryloyloxyethyl phosphorylcholine and combinations thereof.  
20

5. The anti-adhesion device of claim 1 wherein the second biodegradable monomer is poly (hydroxyethyl methacrylate).

6. The anti-adhesion device of claim 1 wherein the first layer of the  
5 composite is selected from the group consisting of a film, mesh or gel.

7. The anti-adhesion device of claim 1 wherein the second layer is selected from the group consisting of a film, mesh or gel.

10 8. The anti-adhesion device of claim 1 wherein the water content of the first layer is between about 5% and about 35%.

9. The anti-adhesion device of claim 1 wherein the water content of the second layer is between about 45% and about 85%.

15

10. The anti-adhesion device of claim 1 further comprising a biological agent selected from the group consisting of antimicrobials, antibiotics, antimetotics, anti-fungal, anti-viral, mono and polyclonal antibodies, antimicrobial proteins, whole antimicrobial peptides, fragmented antimicrobial peptides, enzymes, genetic therapy,  
20 viral particles, chemotherapeutics, anti-inflammatories, NSAIDS, steroids, telomerase inhibitors, growth factors, ECM molecules, cell adhesion molecules, polysaccharides, dyes, and combinations thereof.

11. A process for forming an anti-adhesion device comprising:  
polymerizing a first biodegradable monomer to form a first layer, swelling the first layer  
in a second biodegradable monomer, and polymerizing the swelling first layer in the  
second biodegradable monomer.

5

12. The process of claim 11 further comprising the step of incubating the  
swelling first layer in the second biodegradable monomer prior to polymerization.

13. A process for preventing the binding of tissue to tissue or of tissue to bone  
10 comprising:  
placing between two tissues or between tissue and bone a device comprising a composite  
of a first and second layer, wherein the first layer comprises a first biodegradable  
monomer and the second layer comprises a second biodegradable monomer, and wherein  
the water content of the first layer is less than about 40% and the water content of the  
15 second layer is between about 40 and 90%.

14. The process of claim 13 wherein the step of placing between two tissues  
or between tissue and bone a device comprising a composite of a first and second layer,  
wherein the first layer comprises a first biodegradable monomer selected from the group  
20 consisting of poly (hydroxyethyl methacrylate), methacrylic acid, acrylic acid, n-vinyl  
pyrrolidone, potassium sulfopropylacrylate, potassium sulfopropylmethacrylate,  
hydroxyethyl methacrylate, acrylamide, dimethylacrylamide, 2-methacryloyloxyethyl  
phosphorylcholine and combinations thereof.

15. The process of claim 13 wherein the step of placing between two tissues or between tissue and bone a device comprising a composite of a first and second layer, wherein the second layer comprises a second biodegradable monomer selected from the group consisting of poly (hydroxyethyl methacrylate), methacrylic acid, acrylic acid, n-  
5 vinyl pyrrolidone, potassium sulfopropylacrylate, potassium sulfopropylmethacrylate, hydroxyethyl methacrylate, acrylamide, dimethylacrylamide, 2-methacryloyloxyethyl phosphorylcholine and combinations thereof.

16. The process of claim 13 wherein the step of placing between two tissues  
10 or between tissue and bone a device comprising a composite of a first and second layer, wherein the first layer comprises poly (hydroxyethyl methacrylate).

17. The process of claim 13 wherein the step of placing between two tissues or between tissue and bone a device comprising a composite of a first and second layer,  
15 wherein the second layer comprises poly (hydroxyethyl methacrylate).

18. The process of claim 13 wherein the step of placing between two tissues or between tissue and bone a device comprising a composite of a first and second layer, wherein the water content of the first layer is between about 5% and about 35%.

20

19. The process of claim 13 wherein the step of placing between two tissues or between tissue and bone a device comprising a composite of a first and second layer, wherein the water content of the second layer is between about 45% and about 85%.

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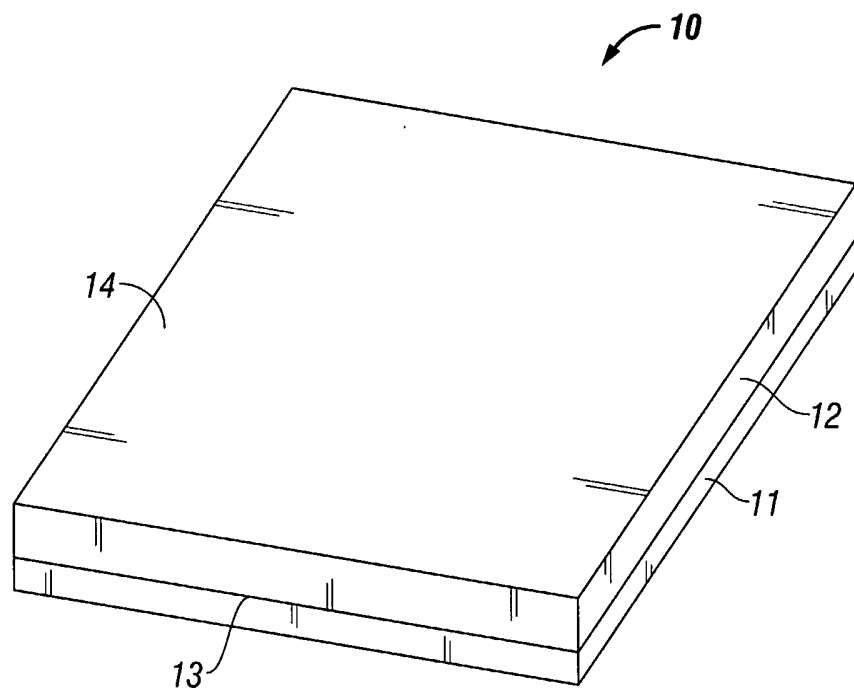


FIG. 1

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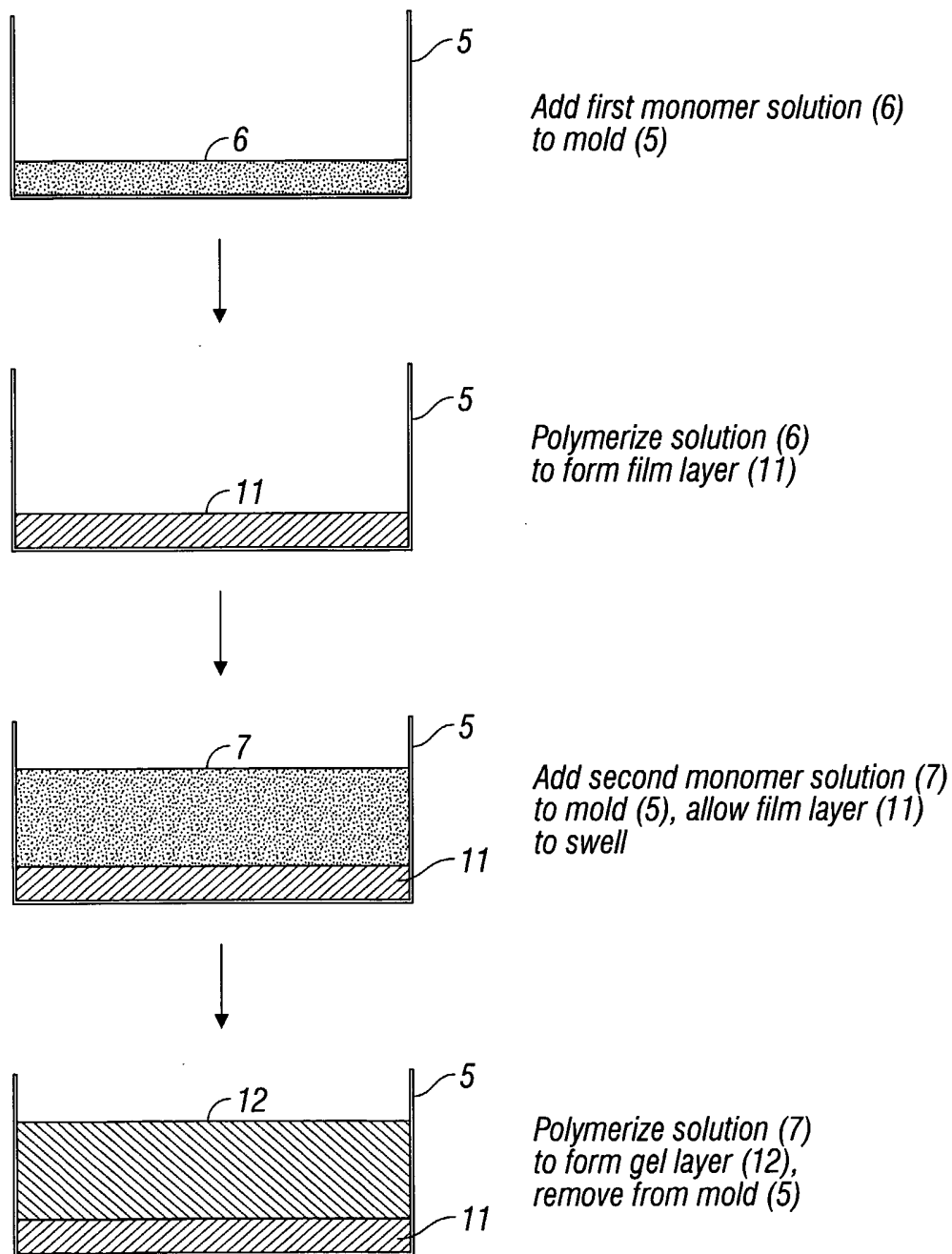


FIG. 2