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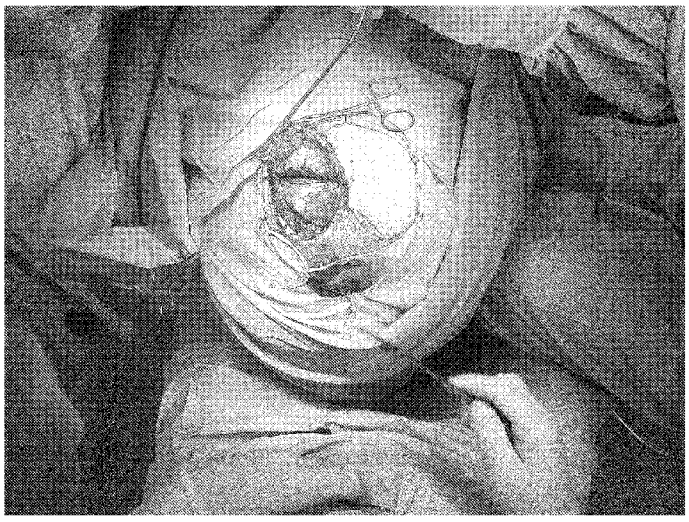

FIG. 1

(57) Abstract: The present invention is directed to a tissue separation barrier system for preventing the abnormal union of two or more tissues, as well as related methods of use. These tissue separation barrier systems offer the balance of strength and flexibility to allow the tissues, such as skin, to move in a smooth and natural manner while affording a barrier between two or more tissues. Furthermore, particular embodiments of the present invention include the methods of manufacturing the tissue separation barrier systems of the present invention.

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NOVEL TISSUE SEPARATION BARRIER SYSTEMS AND RELATED METHODS OF USE

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 62/268,610, filed on December 17, 2015, under Attorney Docket No. DME-003-1; the entirety of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

A common complication of many different types of surgery is the formation of adhesions, otherwise known as adherences. Adhesions are considered abnormal fibrous tissue entities which form between tissues, thus abnormally adhering tissues to one another, particularly those tissues damaged from and/or during surgery. In fact, in some instances, additional surgery or surgeries are necessary to separate these joined tissues. Moreover, adhesions make any repeat surgeries difficult and hazardous to the subject.

Certain imperfect solutions currently exist for external wound protection, yet do not offer a suitable solution to prevent the formation of these adhesions between tissues. However, the films, gels, and multi-tier products useful for wound protection lack true anti-adhesion properties. In reality, most of these wound protection solutions relate to materials which adhere to tissues and can become an integral part of the adhesions. Removal of these materials is difficult and may simply continue the cycle of tissue damage, adhesion formation, and surgery to remedy the adhesions. Moreover, these products, which may offer strength, do not offer the combined flexibility necessary for use internally

Accordingly, there remains a need for implantable systems that are useful for tissue separation that are capable of serving as a barrier with sufficient strength, flexibility and reduced adhesion properties to allow for ease of implantation, prevention of adhesions, and ease of removal without tissue damage.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to a tissue separation barrier system for preventing the abnormal union of two or more tissues, as well as related methods of use. These tissue separation barrier systems offer a balance of strength and flexibility to allow the tissues, such as skin and the subdermal tissues, to move in a smooth and natural manner while affording a barrier between two or more tissues. Furthermore, particular embodiments of the present invention include the methods of manufacturing the tissue separation barrier systems of the present invention.

As such, one aspect of the present invention provides a tissue separation barrier system for preventing the abnormal union of two or more tissues. The tissue separation barrier comprises a single layer anti-adhesion silicone polymer wherein the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues and with sufficient flexibility to allow for ease of movement of said tissues.

In another aspect, the present invention provides a reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a homogenized mixture of a Part A siloxane with a Part B siloxane and about 20% reinforcing material, *e.g.*, silica. The Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and the Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane.

In yet another aspect, the present invention provides a method of separating two or more tissues. The method comprises the implantation of a single layer anti-adhesion silicone polymer of any tissue separation barrier system of the present invention between two or more tissues. The single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that said tissues remain separated until removal of said single layer anti-adhesion silicone polymer.

Another aspect of the present invention provides a method of preventing the abnormal union of any two or more tissues. The method comprises implantation of a single layer anti-adhesion silicone polymer of any tissue

separation barrier system of the present invention between two or more tissues. The single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that the abnormal union of said tissues is prevented until removal of said single layer anti-adhesion silicone polymer.

Another aspect of the present invention provides a method of protecting a sub-epidermal wound comprising implantation of a single layer anti-adhesion silicone polymer any tissue separation barrier system of the present invention between two or more tissues, wherein at least one of said tissues requires protection as a result of a wound, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that said sub-epidermal wound remains protected until removal of said single layer anti-adhesion silicone polymer.

An additional aspect of the present invention provides a method of manufacturing a single layer anti-adhesion silicone polymer of any tissue separation barrier system of the present invention. The method comprises the steps of: placing a mixture of a Part A siloxane and a Part B siloxane into a container, *e.g.*, a cartridge, wherein the Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and the Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane, and combined comprise about 20% reinforcing material, *e.g.*, silica; subjecting the mixture to a pre-injection homogenization process; injecting the pre-injection processed mixture into a mold; curing the molded mixture in an oven; cooling the molded mixture to room temperature; and demolding the cured mixture, thus forming a single layer anti-adhesion silicone polymer of any tissue separation barrier system of the present invention.

Another aspect of the present invention provides any tissue separation barrier system of the present invention manufactured according to any method of manufacturing of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Advantages of the present apparatus will be apparent from the following detailed description, which description should be considered in combination with the accompanying drawings, which are not intended to limit the scope of the invention in any way.

Figure 1 is a photographic image that depicts a top down perspective view of the opening of an incision after a first surgical craniectomy, wherein the skin flap is observed as intact. One embodiment of the tissue separation barrier systems of the present invention may be seen inside the brain cavity, which allows the skin flap to be easily separated.

Figure 2 is a photographic image that depicts the retrieved tissue separation barrier system seen in Figure 1, which further shows no tissue adhered to it whatsoever.

Figure 3 is a photographic image that depicts the flap of Figure 1 completely opened. It was achieved in a surprisingly fast manner, *i.e.*, just 2 minutes, with no need to do any type of coagulation with a perfectly preserved periosteum in the skin flap (*i.e.*, in known surgeries of similar nature the skin flap must be coagulated with a bipolar bayonet), and the bone margin is completely exposed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a tissue separation barrier system for preventing the abnormal union of two or more tissues, as well as related methods of use. The tissue separation barrier systems of the present invention comprise single layer anti-adhesion silicone polymers which offer a balance of strength and flexibility to allow the tissues, such as skin and the subdermal tissues, to move in

a smooth and natural manner while affording a barrier between the two or more tissues.

Silicones, or siloxanes, which have had a long and complex history of use in the medical field, have found use as scaffolds or supports for tissue growth, and paradoxically have also been used to manufacture "inert" forms and shapes, such as surgically-implantable facial or breast implants. Such inert silicone implants are far from perfect in that these forms often require periodic removal and replacement. In some instances, particularly with relatively inflexible facial implants, skin may actually slip from and expose the implant.

The single layer anti-adhesion silicone polymers of the present invention are engineered to be implantable between two or more tissues and with sufficient flexibility to allow for ease of movement of said tissues. The ease of movement of said tissues relates to the increased ease of movement with respect to non-flexible alternative materials known in the art for external wound protection. As such, the tissue separation barrier systems of the present invention not only reduce possible complications in dozens of different types of surgical procedures, but it will also effectively reduce surgical times and in surgery consumptions, improving the efficiency of the surgical services. In certain embodiments, the tissue separation barrier systems afford comparatively less bleeding, and less risks of infection than would otherwise occur.

The present invention, including tissue separation barrier systems and related methods will be described with reference to the following definitions that, for convenience, are set forth below. Unless otherwise specified, the below terms used herein are defined as follows:

I. Definitions

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be

construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

The term "abnormal union" is used herein to refer to a sticking together of substances which are not normally connected, joined or adhered to or with one another. In the context of the present invention, the substances are tissues which are not normally connected, joined or adhered to or with one another. The abnormal union of tissues, *e.g.*, adhesions, often occurs when damage to one or more tissues initiates an inflammatory process in which the tissues, *e.g.*, damaged tissues, form a new, fibrous tissue which connects, joins or adheres the tissues, *e.g.*, damaged tissues. Abnormal unions of tissue may occur between two or more damaged or undamaged tissues, or any combination thereof, *e.g.,* a damaged tissue may abnormally unite with an undamaged tissue.

The term “about” is used herein in reference to the degree or extent of the term which it modifies, and that such extent is near but not exactly 100%, and industry accepted standards will assist in defining the quantitative aspects of how “near” 100% is defined. In certain embodiment, the term “about” may indicate a variability of ± 1% surrounding the designated value.

The term "adhesion" is art recognized and is used herein to describe the new, fibrous tissue that abnormally unites one or more tissues which are not normally connected, joined or adhered to or with one another. Adhesions are often formed when damage to one or more tissues initiates an inflammatory process in which tissue, *e.g.*, damaged tissues, form a new fibrous tissue which connects or joins tissues, *e.g.*, damaged tissues. Adhesions may form between any two or more tissues of the same type, *e.g.*, two normally spatially-distinct intestinal tissues may be joined by an adhesion following abdominal injury or surgery, or of different types, *e.g.*, adhesions may join a bladder to an intestine after a hysterectomy. Adhesions may form between two or more damaged or undamaged tissues, or any combination thereof, *e.g.,* a damaged tissue may form an adhesion with an undamaged tissue.

The term "anti-adhesion" is used hereinto describe the feature or ability of a material or substance to prevent the abnormal union of one or more tissues,

e.g., damaged tissues. In certain embodiments, an anti-adhesion material or substance may operate by means of a physical barrier. The anti-adhesion materials of the present invention are comprised of a silicone polymer, *e.g.*, a single layer silicone polymer.

The term "barrier" is used herein to describe a material or substance, *e.g.*, a silicone polymer, which blocks, prevents, or hinders the abnormal union of tissues, *e.g.*, damaged tissues. .

The term “C1-3alkyl” is art recognized and used to describe lower linear or branched carbon chain functional groups on a molecular structure, including but are not limited to, for example, methyl, ethyl, propyl, or isopropyl.

The terms "comfort" or "comfortable" are used herein to describe the feature or ability of a material or substance to ease pain or constraint, or to prevent a physically unpleasant feeling to a user/subject, *i.e.*, when implanted between two or more tissues, or otherwise associated to or with the user, the comfort of the materials described herein as useful in the tissue separation barriers of the present invention produce less of, *e.g.*, do not produce, a feeling of physical discomfort based on the underlying flexibility engineered into the material.

The term "damage" as used herein with respect to tissues, is used herein to describe any injury or harm to a cell, tissue, organ, or subject. The damage may be visible to the naked eye, such as an incision in the skin, or may be invisible to the naked eye, such as damage to individual cells at the site of an incision or wound.

The term "encircle” is art recognized, and is used herein to describe the feature and ability of a material or substance (*e.g.*, a single layer silicone polymer tissue separation barrier system of the present invention) to form a partial or complete circle around an object, *e.g.*, a tissue or an organ in need of a protective barrier to prevent the formation of adhesions following surgery.

The terms "flexible” or “flexibility” are used herein to describe the fluidity or lack of stiffness of a material or substance, *e.g.*, a silicone polymer. A flexible material is one that is supple, and can be easily folded, rolled, bent, draped,

crushed, or the like. In particular, the silicone polymers useful in the present invention are sufficiently supple and flexible to allow for sufficient ease of movement of tissues when worn, used or otherwise associated to or with a user/subject. In certain embodiments, this sufficient flexibility affords enhanced comfort control.

The term "force" is art recognized, and used herein to describe the push, pull or torsion upon an object resulting from the object's interaction with another object. The force may be actively applied to the objects, for example, during implantation tissue is moved or "forced" in place relative to a single layer silicone polymer tissue separation barrier system of the present invention; or, for example, a user rubs, touches, twists, or otherwise moves or "forces" a tissue relative to an implanted single layer silicone polymer tissue separation barrier system of the present invention. The force also may be passively applied to the objects, for example gravity is a force which, given ample time, causes motion or a change of position of one object to another.

The term "homogenize" is art recognized, and used herein to describe the blending or disbursement of elements of a mixture into a uniform mixture. A mixture that is homogenized is often said to be "homogenous"; the components of the mixture are substantially uniformly and evenly distributed.

The language "in need of" is art recognized to describe a property where a pre-condition or diagnosis suggests that the subject or situation would be benefited.

The term "organ" is art recognized and is used herein to describe a part of a body, *e.g.*, a mammalian body, that has a differentiated structure consisting of cells and tissues which function and/or cooperate in a coordinated manner to perform some specific function in an organism, *e.g.*, a heart or a kidney.

The language "reinforcing material" is art recognized with respect to siloxane polymers to describe the material/composition that may be added during or before the formation of the polymer to alter the properties of the ultimate polymeric form, *e.g.*, related to strength and flexibility. For example, the term "reinforced dimethyl methylvinyl siloxane" is used herein to describe dimethyl

methylvinyl siloxane with reinforcing material added into the component, *e.g.*, silica, *e.g.*, fumed silica.

The term "silica" is art recognized to describe silicon dioxide, (*i.e.*, SiO_2). Silica may exist in crystalline or amorphous forms. "Fumed silica," is an amorphous silica that have been fused, *e.g.*, fused in a flame or fire; and it exhibits a high surface area and extremely low bulk density which impart viscosity-increasing, time-dependent shear thinning properties. Fumed silica powder is used as a thickener or reinforcing filler in the manufacture of materials of the present invention, *e.g.*, a single layer silicone polymers used in the tissue separation barrier systems of the present invention.

The terms "silicone" and "siloxane" are art recognized and used interchangeable herein to describe a compound having a molecular structure based on a chain of alternate silicon and oxygen atoms with organic groups (*e.g.*, methyl, ethyl, propyl, vinyl, and phenyl) attached to the silicon atoms. The polymers of silicone are generally described by their monomeric units which may be incorporated by combination thereof, *e.g.*, catalytic combination. The resulting polymers of silicone may afford a variety of properties, which may be modified by the addition of additives or reinforcing material during the combination process.

The term "single layer" is used herein to describe a homogenous material or substance of any depth, thickness, height, width or shape, *e.g.*, independent of initial or final shape. A single layer of material or substance is of the same composition on the interior as on any outside surface of the material.

The terms "subject" and "patient" refer to an animal (*e.g.*, a bird such as a chicken, quail or turkey) or a mammal including non-primates (*e.g.*, a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and primates (*e.g.*, a monkey, chimpanzee and a human). In a particular embodiment, the subject is a human. A subject may or may not be experiencing a disease, disorder, wound or other ailment. In certain embodiments, the subject is a subject in need of treatment with the tissue separation barrier systems of the present invention

based on a prior understanding of the presence of the disease, disorder, wound or other ailment.

The term "tissue" is art recognized and is used herein to describe a group or aggregate of cells and their surrounding intercellular substances that form a structure or structural material within a subject. The cells may be classified as a particular kind or type of cell, for example, connective tissue, epithelium, muscle tissue, or nerve tissue, and the like.

The term " wound" is art recognized, and is used herein to describe a physical injury to a body, *e.g.*, a mammal, by which an opening, laceration or break is made to living tissue. The wound may be epidermal, *e.g.*, a wound to the skin or sub-epidermal, *e.g.*, a wound to the membrane covering a kidney. In certain embodiments, for example, the physical injury resulting in a wound may be from violence, an accident or from a surgery.

II. Tissue Separation Barrier Systems of the Invention

One embodiment of the present invention provides a tissue separation barrier system for preventing the abnormal union of two or more tissues comprising a single layer anti-adhesion silicone polymer wherein the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues and with sufficient flexibility to allow for ease of movement of said tissues. In certain embodiments the tissue separation barrier system may further comprise additional components selected from the group consisting of instructions, packaging, a coloring additive, a radiopacity additive (*e.g.*, barium), an embedded sensor for communication of information from the implanted single layer anti-adhesion silicone polymer (*e.g.*, for communicating pressure, temperature, or electrical signal at the implanted single layer anti-adhesion silicone polymer), a digital marker (*e.g.*, micro-transponder, such as digital marker for RFID), NFC technology, an antibiotic, and any combination thereof, *i.e.*, without affecting the ability of the tissue separation barrier system to perform

its intended function. In certain embodiments, the tissue separation barrier system may further comprise a coating, such as, an antibiotic coating or an active coating, *e.g.*, color changing coating in the presence of certain antigens or similar reactions, without affecting the ability of the tissue separation barrier system to perform its intended function. In particular embodiments, the tissue separation barrier system comprises one or more antibiotics dispersed within the single layer anti-adhesion silicone polymer, without affecting the ability of the tissue separation barrier system to perform its intended function. In certain embodiments, the tissue separation barrier system may further comprise minimum invasive delivery technology.

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues in a subject, *e.g.*, a human or animal. In particular embodiments, the single layer anti-adhesion silicone polymer is engineered for enhanced comfort control. The enhanced comfort control may be engineered into the single layer silicone polymer tissue separation barrier systems of the present invention to afford a substantial reduction in the physical discomfort possible, *e.g.,* a reduction in the physically unpleasant feeling. It is the sufficient flexibility of these materials that allow for the sufficient ease of movement of tissues such that, when worn, used or otherwise associated to or with a user, the material affords/controls comfort in an enhanced manner, *e.g.*, produces less of or does not produce a feeling of physical discomfort, and is thus comfortable, *e.g.*, relatively comfortable, to a user/subject.

In certain embodiments of the present invention, the movement of said tissues is caused by the application of force on said tissues (*e.g.*, external or internal pressure or torsion). Moreover, the engineered flexibility of the system, *e.g.*, single layer anti-adhesion silicone polymer, affords the system the unique ability to sufficiently adjust to the application of force.

In certain embodiments of the present invention, the anti-adhesion silicone polymer comprises a reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a

homogenized mixture of a Part A siloxane with a Part B siloxane and about 20% reinforcing material, *e.g.*, silica; and wherein:

Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and

Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane.

In certain embodiments, Part A and Part B are combined in a ratio of about 10 to 13 of Part A siloxane to 1 Part B siloxane in a weight/weight ratio to form the RSF composite. In particular embodiments, Part A and Part B are combined in a ratio of about 11.5 Part A siloxane to 1 Part B siloxane in a weight/weight ratio to form the RSF composite. In specific embodiments, the reinforcing material is silica, *e.g.*, fumed silica.

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer is engineered to be functionally characterized by exhibiting

a hardness of about 27 to about 33 on Shore A durometer;

a tensile strength of greater than or equal to about 600 psi;

a tear strength of about 100 ppi;

an elongation limit of greater than or equal to about 350%; and

a linear shrinkage of about 2%.

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer may be constructed (*e.g.*, shapeable via mold, or transformable via shear or cutting processes) into any form. In particular embodiments, the shear or cutting process is performed during the manufacture, *e.g.*, before packaging. In particular embodiments, the user, *e.g.*, surgeon, may further engage in a shear or cutting process, *e.g.*, during surgery, to better suit clinical need.

In particular embodiments, the shape of the single layer anti-adhesion silicone polymer is any three dimensional form of a size, shape and thickness sufficient to separate tissues. In a specific embodiment, the shape of the single layer anti-adhesion silicone polymer is a sheet having a thickness of at least about 0.3 mm. (*e.g.*, at least about 0.4 mm, *e.g.*, at least about 0.5 mm, *e.g.*, at

least about 0.6 mm, *e.g.*, at least about 0.7 mm, *e.g.*, at least about 0.8 mm, *e.g.*, at least about 0.9 mm, *e.g.*, at least about 1 mm)

In particular, the single layer anti-adhesion silicone polymer may be shaped through the molding process. Alternatively, the single layer anti-adhesion silicone polymer may be divided, trimmed, pared, penetrated or otherwise modified in shape by another object, *e.g.*, a sharp object, *e.g.*, through cutting.

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer may be constructed (*e.g.*, shapeable via mold, or transformable via shear or cutting processes) into rectangular (*e.g.*, square shapes), such as 12 cm x 12 cm, 3 cm x 6 cm, or 242 cm x 24 cm, and in a variety of thicknesses (*e.g.*, 0.5mm to 1 mm), such that the single layer anti-adhesion silicone polymer achieves the intended functions as described herein. In particular embodiments, the shape is a square shape of 12 cm by 12 cm and 0.8 mm of thickness.

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer is engineered for the separation of tissue selected from the group consisting of connective tissue, muscle tissue, nervous tissue, epithelial tissue, and any combination thereof. For example, connective tissue may be selected from the group consisting of blood, bone, tendon, ligament, adipose, and areolar; muscle tissue may be selected from the group consisting of smooth (*e.g.*, lining an organ), skeletal, and cardiac; nervous tissue may be selected from the group consisting of central (*e.g.*, brain, spinal cord), and peripheral (*e.g.*, cranial nerves, spinal nerves, motor neurons); and epithelial tissue may be selected from the group consisting of cells that cover the surface of an organ (*e.g.*, skin, airway, reproductive tract, and inner lining of the digestive tract).

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer is removable (*e.g.*, without damaging said separated tissues, without damaging tissues surrounding said separated tissues, inducing bleeding, forming adhesions, or other complications).

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer is suitable for permanent implantation. (*e.g.*, implanted by any suitable mechanical or surgically acceptable method of securing an implant)

In certain embodiments of the present invention, the single layer anti-adhesion silicone polymer exhibits non-reactive biocompatibility, *e.g.*, as determined by ISO standards (*e.g.*, non-inflammatory and non-allergenic). The bio-compatibility of a material or substance with a living organism, *e.g.*, a mammal, may be measured by many parameters such as, but not limited to, cytotoxicity, acute or subacute toxicity, systemic or subsystemic toxicity, chronic toxicity, sensitization, irritation, intracutaneous reactivity, genotoxicity, hemocompatibility, carcinogenicity, allergenicity, immunogenicity, comfort, implantability, durability, leaching of components, and the like.

In certain embodiments of the present invention, the tissue separation barrier system is permanently implantable. In this way, the tissue separation barrier system materials remain strong and in good condition over a long period of time and are suitable for existing as placed between two or more tissues for a long period of time without significant deterioration or loss of properties for use as a single layer silicone polymer tissue separation barrier system of the present invention.

In certain embodiments of the present invention, the silicone polymer is opaque, not opaque, or translucent.

Another embodiment of the present invention provides a tissue separation barrier system of the present invention manufactured according to any method of manufacturing as described herein.

A. Reinforced Silicone Flex (RSF) Composite

Another embodiment of the present invention provides a reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a homogenized mixture of a Part A

siloxane with a Part B siloxane and about 20% reinforcing material, *e.g.*, silica; and wherein:

Part A siloxane comprises reinforced di(C1-3alkyl) (C1-3alkyl)vinyl siloxane, *e.g.*, dimethyl methylvinyl siloxane, and

Part B siloxane comprises reinforced di(C1-3alkyl) (C1-3alkyl)hydrogen siloxane, *e.g.*, dimethyl methylhydrogen siloxane. This RSF composite serves as the anti-adhesion silicone polymer in certain embodiments of the systems of the invention.

In certain embodiments, part A and/or B may be modified with additional polymeric units that do not affect the ability of the material to perform its intended function. For example, in a particular embodiment, the Part B siloxane may comprise reinforced (C1-3alkyl) vinyl di(C1-3alkyl) (C1-3alkyl)hydrogen siloxane, *e.g.*, methyl vinyl dimethyl methylhydrogen siloxane.

In yet another embodiment of the present invention provides a reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a homogenized mixture of a Part A siloxane with a Part B siloxane and about 20% reinforcing material, *e.g.*, silica; and wherein:

Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and

Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane. This RSF composite serves as the anti-adhesion silicone polymer in certain embodiments of the systems of the invention.

In certain embodiments of the present invention, the Part A and Part B are combined in a ratio of about 10 to 13 of Part A siloxane to 1 Part B siloxane in a weight/weight ratio to form the RSF composite. In particular embodiments, Part A siloxane and Part B siloxane are combined in a ratio of about 11.5 Part A siloxane to 1 Part B siloxane in a weight/weight ratio to form the RSF composite.

In certain embodiments of the present invention, the reinforcing material is silica, *e.g.*, fumed silica.

The types and ratios of silicon monomers, *i.e.*, siloxanes, along with the reinforcing material components may be adjusted to manipulate the properties of

the composite (*e.g.*, the softness, hardness, flexibility, biocompatibility, inertness, lifespan, leachability, elastic properties, and durability, and the like) solely to produce composites with the parameters described herein for the intended purposes described herein.

In certain embodiments of the present invention, the RSF exhibits a low transparency.

III. Method of Use of Tissue Separation Barrier Systems of the Invention

Another embodiment of the present invention provides a method of preventing the abnormal union of any two or more tissues comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier systems of the present invention between two or more tissues, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that the abnormal union of said tissues is prevented until removal of said single layer anti-adhesion silicone polymer. In particular, in this embodiment, the tissue separation barrier system is used to prevent the abnormal union of two or more tissues, *e.g.*, the formation of adhesions, by implantation in a manner that keeps the two or more tissues from being physically connected.

An additional embodiment of the present invention provides a method of separating two or more tissues comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier systems of the present invention between two or more tissues, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that said tissues remain separated until removal of said single layer anti-adhesion silicone polymer. In particular, in this embodiment, the tissue separation barrier system is used as physical spacer unit to keep two or more distinct masses of tissues in separate spaces, *i.e.*, not

physically connected. While adhesion prevention may also occur, the tissue separation barrier systems are useful for their structural aspects as well.

In another embodiment, the present invention provides a method of protecting a sub-epidermal wound comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier systems of the present invention between two or more tissues, wherein at least one of said tissues requires protection as a result of a wound, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that said sub-epidermal wound remains protected until removal of said single layer anti-adhesion silicone polymer. In particular embodiments, the implantation protects a sub-epidermal wound from tissues selected from the group consisting of connective tissue, muscle tissue, nervous tissue, epithelial tissue, and any combination thereof.

In certain embodiments of the methods of use of present invention, the method prevents the formation of adhesions between said tissues.

In certain embodiments of the methods of use of present invention, the tissues are in need of separation.

In certain embodiments of the methods of use of present invention, the tissues are in a subject, *e.g.*, in a subject in need thereof.

In certain embodiments of the methods of use of present invention, the separated tissues are different types of tissues, *e.g.*, where the method would prevent adhesions that might join a bladder to an intestine after a hysterectomy.

In certain embodiments of the methods of use of present invention, the separated tissues are of the same type of tissue, *e.g.*, implanted within one type of tissue so that the same type of tissue is separated by the tissue separation barrier system, *e.g.*, where two normally spatially-distinct intestinal tissues could be joined by an adhesion following abdominal injury or surgery.

In certain embodiments of the methods of use of present invention, at least one of said tissues surrounds part or all of an organ and said implanted single layer anti-adhesion silicone polymer partially or fully encircles said organ.

In certain embodiments of the methods of use of present invention, at least one of said tissues is the tissue of an organ.

In certain embodiments of the methods of use of present invention, the abnormal union is in need of being prevented, *e.g.*, in need of remaining non-adhered to neighboring tissues, *e.g.*, to achieve proper healing.

IV. Method of Manufacture of Tissue Separation Barrier Systems of the Invention

Another embodiment of the present invention provides a method of manufacturing a single layer anti-adhesion silicone polymer of the present invention comprising the steps of:

placing a mixture of a Part A siloxane and a Part B siloxane into a container, *e.g.*, a cartridge, wherein the Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and the Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane, and combined comprise about 20% reinforcing material, *e.g.*, silica;

subjecting the mixture to a pre-injection homogenization process;

injecting the pre-injection processed mixture into a mold;

curing the molded mixture in an oven (*e.g.*, controlled oven, *e.g.*, 40 to 150 ^{o}C, *e.g.*, 120 ^{o}C);

cooling the molded mixture to room temperature (*e.g.*, 4-40 ^{o}C, *e.g.*, 15-25 ^{o}C, *e.g.*, 20 ^{o}C); and

demolding the cured mixture,

thus forming a single layer anti-adhesion silicone polymer of the tissue separation barrier system of the present invention.

In certain embodiments of the method of manufacturing of the present invention, the timing of the steps may be simultaneous where appropriate, *e.g.*, pre-injection homogenization may occur when placing in the container.

In certain embodiments of the method of manufacturing of the present invention, the method further comprises subjecting the demolded cured mixture to a mechanical transformation process (*e.g.*, cutting/shaping of the cured mixture, sterilization and/or non-damaging mechanical testing).

In certain embodiments of the method of manufacturing of the present invention, the Part A and Part B are combined in a weight/weight ratio of about 10 to 13 of Part A siloxane to 1 Part B siloxane. In particular embodiments of the method of manufacturing of the present invention, the Part A siloxane and the Part B siloxane are combined in a weight/weight ratio of about 11.5 Part A siloxane to 1 Part B siloxane.

In certain embodiments of the method of manufacturing of the present invention, the reinforcing material is silica, *e.g.*, fumed silica.

In certain embodiments of the method of manufacturing of the present invention, the pre-injection homogenization process within the container, *e.g.*, cartridge, comprises mechanical mixing, including for example, agitation or stirring. In certain embodiments, the pre-injection homogenization process within the container, *e.g.*, cartridge, further comprises the step of degassing said mixture. In specific embodiments, the pre-injection homogenization process further includes contaminant inspection, *e.g.*, visualization to ensure no particulate contaminant is present in the mix.

In certain embodiments of the method of manufacturing of the present invention, the oven temperatures range from about 40°C to about 150°C. In a particular embodiment the oven temperature is about 120°C. In certain embodiments, the cure period may range from 30 minutes to an hour, *e.g.*, 45 minutes.

In certain embodiments of the method of manufacturing of the present invention, the anti-adhesion silicone membrane is subjected to a sterilization process. In particular embodiments, the sterilization process is selected from the group consisting of autoclaving (*e.g.*, autoclaving in an ISO certified methodology), exposure to ultraviolet light and chemical sterilization.

In certain embodiments of the method of manufacturing of the present invention, the method is performed in a controlled environment suitable for producing a sterile, contaminant-free and defect-free single layer anti-adhesion silicone polymer suitable for surgical use. In particular embodiments of the invention, the present invention provides a device that affords the controlled environment characterized by the properties selected from the group consisting of dried and filtered air quality used for injection, increased compactness as compared with existing devices, compatible with ISO 6 type clean room, a homogenization system included which is under vacuum and sterile, certified to not use any contaminant or pyrogenetic material that could damage humans if implanted or in contact with blood and tissue, and any combination thereof.

EXEMPLIFICATION

Having thus described the invention in general terms, reference will now be made to the accompanying figures and exemplary embodiments, which are not intended to be limiting in any way.

In this respect, it is to be understood that the invention is not limited in its application to the details of construction and to the arrangements of the components set forth in the following description or illustrated in the figures. The invention is capable of other embodiments and of being practiced and carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein are for the purpose of description and should not be regarded as limiting.

Example 1

Preparation of Reinforced Silicone Flex (RSF) Composite

The reinforced silicone flex (RSF) composite described herein, *e.g.*, as useful in the tissue separation barrier systems of the present invention is a two part composite system formed by the curing of a homogenized mixture of a Part

A siloxane with a Part B siloxane and about 20% reinforcing material. In one embodiment, the Part A siloxane comprises reinforced dimethyl methylvinyl siloxane (Applied Silicone Corporation, PN40029 Part A), and the Part B siloxane (Applied Silicone Corporation, PN40029 Part B) comprises reinforced dimethyl methylhydrogen siloxane.

Reinforced dimethyl methylvinyl siloxane (reinforced with about 20% fumed silica) was homogenized with reinforced dimethyl methylhydrogen siloxane (reinforced with about 19.8-20% fumed silica and comprising a catalytic amount of platinum suitable for catalytic hydrosilylation) at a ratio of 11.5 to 1 weight/weight in a controlled environment in a clean room ISO class 6. The pre-injection homogenized mixture, comprising about 20% reinforcing material, was then submitted to a mechanical treatment for complete homogenization, with extraction of air from the mix via degassing, followed by contaminant inspection.

The degassed mixture was then placed into a cartridge/container for use on an injection machine which injects the mix into a mold, all of which was done with the mix completely protected from the environment and only using sterilized and cleaned instruments with the support of air pressure with certified filtered air and the sterile and clean containers.

The injection process, which was supervised to avoid spills and contaminants, positioned the mixture inside a mold that was then cured at 120 degrees Celsius in a controlled oven for 45 minutes. The mold was then cooled at 20 degrees Celsius until the temperature was the same as the room, forming a single layer anti-adhesion silicone polymer. The single layer anti-adhesion silicone polymer was then demolded and checked for contaminants and physical imperfections that could affect the correct function of the material as used in the tissue separation barrier systems of the present invention as described herein.

The single layer anti-adhesion silicone polymer may be then cut into any shape depending on the specific use. Subsequently, a second supervision for contaminants and physical defects may then be performed.

The shaped material was then cleansed in a controlled environment, folded as necessary, and packed in a sterilization bag for sterilization in steam.

A final check for possible damage was performed, followed by packaging in a final package before being shipped to the operating room for use.

Implant tests used to assess the local effects of material on living tissue at both the macroscopic and microscopic levels according to ISO standards are shown in Examples 3, 4 and 5. Further, the use of the RSF composite in a tissue separation barrier system of the present invention is demonstrated in Example 2.

Example 2

Surgical Use of Tissue Separation Barrier System

A. Craniectomy with bi-coronal incision of a skin flap

The single layer anti-adhesion silicone polymer of Example 1, as used as a tissue separation barrier system of the present invention, was used to protect one tissue from an adjacent one during a decompressive craniectomy over the open dura directly on the brain tissue.

In this respect, the tissue separation barrier system of the present invention was placed over the open dura directly on the brain tissue in the decompressive craniectomy.

Figure 1 is a photographic image that depicts a top down perspective view of the opening of an incision after a first surgical craniectomy, wherein the skin flap is observed as intact. The tissue separation barrier system of the present invention may be seen inside the brain cavity, which allows the skin flap to be easily separated, *i.e.*, when the skin flap is closed the dermis will not adhere to either the single layer anti-adhesion silicone polymer or the tissue under it. As such, during the chronical reintervention of the cranioplasty, the skin flap will be separated from all the tissue, avoiding having to make the incisions to find the field between periosteum and dura or brain tissue. It reduced time (*i.e.*, only 5

minutes was necessary for a bi-coronal incision of the skin flap), reduced bleeding, reduced risk of producing a CFR fistula and reduced similar risks related to the procedure of separating such tissues, and that way reducing the morbidity of the patient and increasing productivity of the surgery.

Further, Figure 2 is a photographic image that depicts the retrieved tissue separation barrier system seen in Figure 1, which further shows no tissue adhered to it whatsoever. And Figure 3 is a photographic image that depicts the flap of Figure 1 completely opened. It was achieved in a surprisingly fast manner, *i.e.*, just 2 minutes, with no need to do any type of coagulation with a perfectly preserved periosteum in the skin flap (*i.e.*, in known surgeries of similar nature the skin flap must be coagulated with a bipolar bayonet), and the bone margin is completely exposed.

B. Additional Examples

Another example where the tissue separation barrier systems of the present invention would be similarly useful would be to protect surgical sites with aggressive fibrotic outcomes, *e.g.*, to avoid adhesions between the organs, *e.g.*, for life. For example, protections of the dura after a laminectomy or similar intervention, avoiding the fibrosis caused adherence to the medula's dura, for life. In fact, the device can be implanted for the duration of the life of the subject, without losing any of its characteristics.

In yet another example, the tissue separation barrier systems of the present invention would be similarly useful to position after making an eventration intervention with a mesh. The tissue separation barrier system may be placed over the intestines to avoid the adherence of them to the mesh, reducing the complications related with such adhesions.

Example 3

Cytotoxicity Analysis (ISO 10993-5)

The toxicity of the reinforced silicone flex (RSF) composite described herein and used in the tissue separation barrier systems of the present invention, was evaluated *in vitro*.

Materials and supplies:

Material/Supply	Lot number	Manufacturer
Single Strength Minimum Essential Medium with Earle's Salts (1XMEM)	1535328	LIFE TECHNOLOGIES ®
Horse Serum	61373986	ATCC
Fungizone (amphotericin B solubilized)	1392647	LIFE TECHNOLOGIES ®
Penicillin-streptomycin	1411482	LIFE TECHNOLOGIES ®
Dulbecco's Phosphate Buffered Saline (PBS)	61443818	ATCC

Multiple cultures of L-929 mammalian (mouse) fibroblast cells (ATCC cell line CCL 1, NCTC clone 929) were prepared according to methods known in the art. The cell were grown in 10 cm^2 wells in a 5% serum supplemented cell culture medium and incubated at 37 ± 1°C in a humidified incubator with 5 ± 1% CO_2. The cell cultures were plated 24 - 48 hours prior to use in order to allow for a cell monolayer with greater than 80% confluence to form.

An extract of the reinforced silicone flex (RSF) composite described herein was prepared by incubating the RSF composite with Minimum Essential Medium (MEM). MEM was a 5% serum supplemented cell culture medium comprised of 93% single strength minimum essential medium with Earle's salts (1XMEM), 5% horse serum, 1% penicillin-streptomycin, and 1% fungizone (amphotericin B solubilized).

An ethylene-oxide sterilized sheet of RSF composite having a total surface area of 136.0 cm^2 was used for the extraction at a ratio of 60 cm^2/20 ml

(thickness was equal to or greater than 0.05 cm), yielding a volume of 45.3 mL. The sheet of RSF composite was cut into small pieces and placed in a sterile glass container. To prepare the test extract, MEM extraction medium was added and the pieces of RSF composite were completely immersed. In a similar fashion, control extracts lacking the RSF composite were also prepared; the negative control extract was prepared using an autoclave-sterilized USP high-density polyethylene reference standard plastic (USP) and the positive control extract was prepared using non-sterile Tygon AF4040 plastic (Saint-Gobain Performance Plastics). The test and control extract solutions were incubated for 24 ± 2 hours at 37 ± 1°C with agitation. Tables 1 and 2 show the duration and conditions used to prepare the test and control extracts. Before extraction, all solutions appeared clear and free of particulates.

Table 1: Extraction of RSF composite

Total surface area (cm^2)	Extraction ratio (cm^2/mL)	Total volume extracted (mL)	Extraction		
			Extraction medium	Temperature (^{0}C)	Duration (hrs)
136.0	60/20	45.3	1XMEM	37 ± 1	24 ± 2

Table 2: Extraction of positive, negative, and reagent only controls

Extract	Surface areas		Total volume (mL)	Extraction		
	Area (cm^2)	Extraction ratio (cm^2/mL)		Extraction medium	Temperature (^{0}C)	Duration (hrs)
Positive control	31.2	60/20	10.4	1XMEM	37 ± 1	24 ± 2
Negative control	33.8	60/20	11.3			
Reagent control	NA	NA	20			

NA = not applicable

Test Procedure

Following the extraction period, each solution was visually inspected. The RSF composite extract appeared slightly opaque and small, wispy particulates were observed in the solution; the color of the RSF composite extract did not change during the incubation period. Particulate matter was absent from all control extracts and the color of the control extracts did not change during the incubation period. The extractions were not diluted, filtered, and/or manipulated in any way prior to dosing and were applied to the cultured cells within 24 hours of the completion of the extraction process.

For each solution tested, the growth medium was decanted from three wells, each containing a monolayer of L-929 mouse fibroblast cells (ATCC Cell Line CCL1, NCTC Clone 929), and rinsed with 2 mL of 1x Dulbecco's PBS. Following removal of the PBS, 2 mL of the RSF composite test or control solutions were flooded onto the cells. The cells were incubated for 48 ± 2 hours at 37 ± 1°C in a humidified incubator with 5 ± 1% CO_2.

At 24 and 48 ± 2 hours following dosing, the cells were examined under an inverted light microscope using 100X magnification. The conditions of the cell cultures were graded according to the criteria in Table 3. The average score for the triplicate test wells at the 48-hour point was used to determine the final cytotoxic response of the cells to the RSF composite and control extracts.

Table 3: Qualitative morphological criteria used to grade the cell cultures

Grade	Reactivity	Description of criteria
0	None	Discrete intracytoplasmatic granules, no cell lysis, no reduction of cell growth
1	Slight	Not more than 20% of the cells are round, loosely attached and without intracytoplasmatic granules, or show changes in morphology; occasional lysed cells are present; only slight growth inhibition observed
2	Mild	Not more than 50% of the cells are round, devoid of intracytoplasmatic granules, no extensive cell lysis; not more than 50% growth inhibition observed

3	Moderate	Not more than 70% of the cell layers contain rounded cells or are lysed; cell layers not completely destroyed, but more than 50% growth inhibition observed
4	Severe	Nearly complete or complete destruction of the cell layers

Results

Test results for the RSF composite, positive, negative, and reagent controls are presented in Table 4.

Table 4: Test Results

Replicate number	Reactivity 24 hrs	Grade 24 hrs	Reactivity 48 hrs	Grade 48 hrs
RSF composite extract #1	None	0	None	0
RSF composite extract #2	None	0	None	0
RSF composite extract #3	None	0	None	0
Controls				
Positive #1	Moderate	3	Severe	4
Positive #2	Moderate	3	Severe	4
Positive #3	Moderate	3	Severe	4
Negative #1	None	0	None	0
Negative #2	None	0	None	0
Negative #3	None	0	None	0
Reagent #1	None	0	None	0
Reagent #2	None	0	None	0
Reagent #3	None	0	None	0

0 = none (no reactivity); 1 = slight reactivity; 2 = mild reactivity; 3 = moderate reactivity; 4 = severe reactivity.
ISO Standard Interpretation: cytotoxicity is attributed to an extract exhibiting a score of greater than 2.

Cells treated with the RSF composite extract exhibited a response grade of 0, that is, no reactivity was observed at the 24 and 48 hour time points. Cells treated with the negative and reagent control extracts also exhibited a response grade of 0, that is, no reactivity was observed at the 24 and 48 hour time points. Cells treated with positive control extract exhibited a response grade of 3, that is, the cells were moderately affected, at the 24 hour time point; the severity of the cellular reaction increased to a response grade of 4, that is, the cells were severely affected, at the 48 hour time point.

Based upon the results of these experiments, the reinforced silicone flex (RSF) composite described herein and used in the tissue separation barrier systems of the present invention, does not elicit cytotoxicity or a cytotoxic response, that is, the RSF composite described herein, and thus the tissue separation barrier systems of the present invention utilizing the RSF composite, can be considered to be non-cytotoxic.

Example 4

Acute Systemic Toxicity Test (ISO 10993-11)

The acute systemic toxicity of the reinforced silicone flex (RSF) composite described herein and used in the tissue separation barrier systems of the present invention, was evaluated *in vivo*.

Materials and supplies:

Reagents	Lot number	Manufacturer
0.9% Sodium Chloride Injection, USP (SCI)	38-041-JT	Hospira
Cottonseed Oil (OIL)	1CH0076	Spectrum

Twenty young, albino, adult male CD-1 mice (Charles River, Hollister, CA; initial weight 17-21 grams) were used to evaluate the *in vivo* effect of an extract

of RSF composite; five mice were used for each test or control group. The mice were housed in groups in polycarbonate cages in a controlled environment at a nominal temperature range of 20 to 26°C, a humidity range of 50 ± 20%, and a light/dark cycle of 12 hours. The mice received fresh drinking water and Certified Laboratory Rodent Diet *ad libitum*. The mice were allowed to acclimate to the conditions for 5 days prior to use.

An extract of the reinforced silicone flex (RSF) composite described herein was prepared by incubating the RSF composite with either 0.9% sodium chloride injection USP (SCI) or cotton seed (OIL). Ethylene-oxide sterilized sheets of RSF composite, each having a total surface area of 136.0 cm^2, were used for the extractions at a ratio of 60 cm^2/20 ml (thickness was equal to or greater than 0.05 cm), yielding a volume of 45.3 mL. Each sheet of RSF composite was cut into small pieces and were completely immersed in the appropriate volume of either SCI or OIL. SCI and OIL control extracts lacking the RSF composite were also prepared. The test and control extract solutions were incubated for 1 ± 0.1 hours in an oven at 121 ± 2°C with agitation.

Test Procedure

Following extraction, the extracts were allowed to cool enough to be handled, shaken well and decanted into sterile vessels. The RSF composite sheet and the RSF composite extract were visually inspected after extraction and compared to control solutions. The RSF composite extracted in SCI and OIL appeared to be unaffected by the extraction process, remaining clear, with no change in color and no visible particulates. The cooled, inspected SCI and OIL extracts were administered to the mice within 24 hours of extraction; the extracts were administered undiluted and were not filtered.

A total of twenty (20) mice were used in this test, 10 mice each to the SCI and OIL groups. The 10 animals were further divided into five RSF composite test and five control groups for the SCI and OIL treatments. Five test mice from the SCI group were each injected intravenously, via tail vein, with 50 mL/kg of the RSF composite SCI extract at a slow, steady rate (approximately 100 uL/sec).

Five control mice were each injected intravenously, via tail vein, with 50 mL/kg of the corresponding SCI control. Five test mice from the OIL group were each injected intraperitoneally with 50 mL/kg of RSF composite OIL extract. Five control mice were each injected intraperitoneally with 50 mL/kg of the corresponding OIL control.

The animals were observed for signs of biological reactivity at several time points after administration of the extracts: a) immediately after dosing, b) 4 hours ± 15 minutes, c) 24 ± 2 hours, d) 48 ± 2 hours, and e) 72 ± 2 hours. The biological parameters observed included, but were not limited to, changes in skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous system, somatomotor activity, weight, and behavior patterns. The animals were weighed prior to dosing and at the 24, 48 and 72 hour time points.

Results

Table 5: Clinical observations

Group	Animal number	Immediately after dosing	4 hours	24 hours	48 hours	72 hours
SCI test	1	NBR	NBR	NBR	NBR	NBR
	2	NBR	NBR	NBR	NBR	NBR
	3	NBR	NBR	NBR	NBR	NBR
	4	NBR	NBR	NBR	NBR	NBR
	5	NBR	NBR	NBR	NBR	NBR
SCI control	6	NBR	NBR	NBR	NBR	NBR
	7	NBR	NBR	NBR	NBR	NBR
	8	NBR	NBR	NBR	NBR	NBR
	9	NBR	NBR	NBR	NBR	NBR
	10	NBR	NBR	NBR	NBR	NBR
OIL test	11	NBR	NBR	NBR	NBR	NBR
	12	NBR	NBR	NBR	NBR	NBR
	13	NBR	NBR	NBR	NBR	NBR
	14	NBR	NBR	NBR	NBR	NBR
	15	NBR	NBR	NBR	NBR	NBR

OIL control	16	NBR	NBR	NBR	NBR	NBR
	17	NBR	NBR	NBR	NBR	NBR
	18	NBR	NBR	NBR	NBR	NBR
	19	NBR	NBR	NBR	NBR	NBR
	20	NBR	NBR	NBR	NBR	NBK

NBR = no biological reactivity

Table 6: Dose volumes and animal weights

Group	Animal number	Dose (mL)	Pre-test weight (g)	24 hr weight (g)	48 hr weight (g)	72 hr weight (g)	Weight change (g)*
SCI test	1	1.0	20	21	22	25	+ 5
	2	1.1	21	22	24	26	+ 5
	3	1.0	19	21	23	26	+ 7
	4	1.0	20	21	23	25	+ 5
	5	1.0	20	23	25	27	+ 7
				■			
SCI control	6	1.0	20	22	24	26	+ 6
	7	1.0	19	21	23	24	+ 5
	8	1.0	19	21	23	25	+ 6
	9	1.0	20	21	22	24	+ 4
	10	1.0	19	21	23	24	+ 5
OIL test	11	1.0	19	21	22	24	+ 5
	12	0.9	18	19	22	24	+ 6
	13	0.9	18	21	23	24	+ 6
	14	1.0	19	21	23	25	+ 6
	15	0.9	18	20	21	23	+ 5
OIL control	16	1.0	19	21	22	24	+ 5
	17	1.0	19	21	22	24	+ 5
	18	0.9	18	19	21	23	+ 5
	19	0.9	18	19	20	22	+ 4
	20	0.9	17	18	20	21	+ 4

*Body weight change was calculated by subtracting the pre-test weight from the 72 hour weight

The biological observations are presented in Table 5, where it can be seen that all animals from all four SCI and OIL groups appeared healthy; no

abnormalities were observed at any of the specified time points during the three day observation period. Exposure of the mice to the RSF composite extracts, both in SCI and OIL, did not result in observable symptoms of acute systemic toxicity.

The animal body weights and dose volumes are presented in Table 6. All of the animals in the SCI groups gained weight by the end of the test. The animals dosed with the RSF composite SCI extract gained about 5 to 7 grams while the animals dosed with the SCI control extract gained about 4 to 6 grams. The animals dosed with the RSF composite OIL extract gained about 5 to 6 grams while the animals dosed with the OIL control extract gained about 4 to 5 grams.

Example 5

Intracutaneous (Intradermal) Reactivity Test (ISO 10993-10)

The local response of the reinforced silicone flex (RSF) composite described herein and used in the tissue separation barrier systems of the present invention, was evaluated *in vivo*.

Materials and supplies:

Reagents	Lot number	Manufacturer
0.9% Sodium Chloride Injection, USP (SCI)	38-041-JT	Hospira
Cottonseed Oil (OIL)	1CHD076	Spectrum

Three adult female New Zealand White rabbits (Western Oregon Rabbit Company, Philomath, OR; initial weight 2.6-2.9 kgs) were used to evaluate the localized *in vivo* effect of an extract of the RSF composite; each rabbit was used for both test and control injections. The animals were housed individually in

suspended cages and maintained in a controlled environment at a nominal temperature range of 16 to 22°C, a humidity range of 50 ± 20%, and a light/dark cycle of 12 hours. The rabbits received a Certified Laboratory Rabbit Diet (approximately 165 grams per day) and water *ad libitum*. The animals were acclimated to the testing facility for at least 7 days prior to initiation of the study. Health observations were performed prior to the study to ensure that the animals were acceptable for study use.

An extract of the reinforced silicone flex (RSF) composite described herein was prepared by incubating the RSF composite with either 0.9% sodium chloride injection USP (SCI) or cotton seed (OIL). Ethylene-oxide sterilized sheets of RSF composite, each having a total surface area of 136.0 cm^2, were used for the extractions at a ratio of 60 cm^2/20 ml (thickness was equal to or greater than 0.05 cm), yielding a volume of 45.3 mL. Each sheet of RSF composite was cut into small pieces and were completely immersed in the appropriate volume of either SCI or OIL. SCI and OIL control extracts lacking the RSF composite were also prepared. The test and control extract solutions were incubated for 1 ± 0.1 hours in an oven at 121 ± 2°C with agitation.

Test Procedure

Following extraction, the extracts were allowed to cool enough to be handled, shaken well and decanted into sterile vessels. The RSF composite sheet and the RSF composite extract were visually inspected after extraction and compared to control solutions. The RSF composite extracted in SCI and OIL appeared to be unaffected by the extraction process, remaining clear, with no change in color and no visible particulates. The cooled, inspected SCI and OIL extracts were administered to the rabbits within 24 hours of extraction; the extracts were administered undiluted and were not filtered.

Three animals were used in this study. On the day of the test, the fur on the back of each animal was clipped with electric clippers. Each extract was vigorously agitated prior to withdrawal of injection doses to ensure even distribution of extracted matter. A volume of 0.2 ml- of the RSF composite

extract in SCI was injected intracutaneously at five sites on one side of the spinal column, anterior to the midline, of each of three rabbits. A 0.2 mL portion of SCI control was injected intracutaneously at five sites on the opposite side of the spinal column of the same three rabbits (Fig. 1). This process was repeated on the same animals for the RSF composite extracted in OIL and OIL control but posterior to the dorsal midline. The dose sites were marked with permanent marker in order to aid in the identification of dose site locations.

The rabbits were observed daily for signs of ill health. The animals were also observed for signs of tissue reactivity, such as erythema, eschar formation and edema, at several time points after administration of the extracts: a) immediately after dosing, b) 24 ± 2 hours, c) 48 ± 2 hours, and d) 72 ± 2 hours (see Table 7 for grading criteria).

Table 7: Classification system for intracutaneous (intradermal) reactions

Erythema and eschar formation	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet-redness) to eschar formation preventing grading of erythema	4
Edema formation	Score
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised about 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Total Possible Score for Irritation	8

Table adopted from ISO 10993-10 Biological Evaluation of Medical Devices - Test for Irritation and Skin Sensitization.

After the 72 hour time point, all erythema grades plus edema grades (24. 48 and 72 his) were totaled separately for the test sites and control sites for each individual animal. For each individual animal, each of the totals was divided by 15 (3 scoring time points x 5 test and control injection sites). The overall mean scores for each test and corresponding control were calculated by adding the scores for all three animals and dividing by three (total number of animals). The final test score was obtained by subtracting the overall mean score of the control from the overall mean score of the test.

Results

Table 8. Reaction scores (SCI extract)

Animal ID: 63104	TEST SITES			CONTROL SITES		
	24 ± 2hrs	48 ± 2hrs	72 ± 2 hrs	24 ± 2hrs	48 ± 2 hrs	72 ± 2 hrs
Erythema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Edema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	0	0	0	0	0	0
Total mean*	0			0		
Animal ID: 63045	TEST SITES			CONTROL SITES		
	24 ± 2 hrs	48 ± 2 hrs	72 ± 2hrs	24 ± 2hrs	48 ± 2 hrs	72 ± 2hrs
Erythema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Edema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	0	0	0	0	0	0
Total mean*	0			0		
Animal ID: 63106	TEST SITES			CONTROL SITES		
	24 ± 2 hrs	48 ± 2hrs	72 ± 2hrs	24 ± 2hrs	48 ± 2 hrs	72 ± 2 hrs
Erythema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Edema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0

Total reaction score/ observation	0	0	0	0	0	0
Total Mean*	0			0		

*Total mean = total reaction scores/15. Means are rounded to one decimal place.

Interpretation of results:
Test overall mean score (Total means for all three animals divided by three): 0/3 = 0
Control overall mean score (Total means for all animals divided by three): 0/3 = 0
Final test score (The difference between Test overall mean score and Control overall mean score): 0-0 = 0

Table 9. Reaction scores (OIL extract)

Animal ID: 63104	TEST SITES			CONTROL SITES		
	24 ± 2 hrs	48 ± 2 hrs	72 ± 2hrs	24 ± 2 hrs	48 ± 2 hrs	72 ± 2hrs
Erythema	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1
Edema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	5	5	5	5	5	5
Total Mean*	1.0			1.0		
Animal ID: 63045	TEST SITES			CONTROL SITES		
	24 ± 2hrs	48 ± 2 hrs	72 ± 2 hrs	24 ± 2 hrs	48 ± 2 hrs	72 ± 2 hrs
Erythema	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1	1 I 1 1 1	1 1 1 1 1
Edema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	5	5	5	5	5	5
Total Mean*	1.0			1.0		
Animal ID: 63106	TEST SITES			CONTROL SITES		
	24 ± 2 hrs	48 ± 2hrs	72 ± 2 hrs	24 ± 2hrs	48 ± 2 hrs	72 ± 2 hrs
Erythema	1 1 1 1 1	1 1 1 1 1	! 1 1 1 1	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1
Edema	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	5	5	5	5	5	5

Total Mean*	1.0	1.0

*Total mean = total reaction scores/15. Means are rounded to one decimal place.

Interpretation of results:
Test overall mean score (Total means for all three animals divided by three): 3.0/3 = 1.0
Control overall mean score (Total means for all animals divided by three): 3.0/3 = 1.0
Final test score (The difference between Test overall mean score and Control overall mean score): 1.0-1.0 = 0

Table 10: Positive control reaction scores (Freund's Complete Adjuvant in cottonseed oil)

	TEST SITES			CONTROL SITES		
Animal ID; 62632	24 ± 2 hrs	48 ± 2hrs	72 ± 2 hrs	24 ± 2 hrs	48 ± 2hrs	72 ± 2hrs
Erythema	3 3 3 3 3	3 3 3 3 3	3 3 3 3 3	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1
Edema	4 4 4 4 4	4 4 4 4 4	4 4 4 4 4	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	35	35	35	5	5	5
Total Mean*	7.0			1.0		
	TEST SITES			CONTROL SITES		
Animal ID: 62608	24 ± 2 hrs	48 ± 2 hrs	72 ± 2 hrs	24 ± 2 hrs	48 ± 2 hrs	72 ± 2hrs
Erythema	3 3 3 3 3	3 3 3 3 3	4 4 4 4 4	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1
Edema	4 4 4 4 4	4 4 4 4 4	4 4 4 4 4	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0
Total reaction score/ observation	35	35	40	5	5	5
Total Mean*	7.3			1.0		
Animal ID: 62614	TEST SITES			CONTROL SITES		
	24 ± 2hrs	48 ± 2 hrs	72 ± 2hrs	24 ± 2hrs	48 ± 2 hrs	72 ± 2hrs
Erythema	2 2 2 2 2	1 1 1 1 1	2 2 2 2 2	1 1 1 1 1	1 1 1 1 1	1 1 1 1 1
Edema	4 4 4 4 4	3 3 3 3 3	3 3 3 3 3	0 0 0 0 0	0 0 0 0 0	0 0 0 0 0

Total reaction score/ observation	30	20	25	5	5	5
Total Mean*	5.0			1.0		

*Total mean = total reaction scores/15. Means are rounded to one decimal place.

Interpretation of results:
Test overall mean score (Total means for all three animals divided by three): 19.3/3 = 6.4
Control overall mean score (Total means for all animals divided by three): 3.0/3 = 1.0
Final test score (The difference between Test overall mean score and Control overall mean score): 6.4-1.0 = 5.4

Table 11: Average reaction scores at each observation period

Extract	Observation period	Average test score	Average control score	Difference
SCI	24 Hr	0	0	0
	48 Hr	0	0	0
	72 Hr	0	0	0
OIL*	24 Hr	1.0	1.0	0
	48 Hr	1.0	1.0	o
	72 Hr	1.0	1.0	0
Positive control (Freund's adjuvant)	24 Hr	6.7	1.0	5.7
	48 Hr	6.0	1.0	5.0
	72 Hr	6.7	1.0	5.7

*Intradermal injection of oil frequently elicits some inflammatory response. Means are rounded to one decimal place.

All animals remained healthy throughout the test period. The individual irritation scores are presented in Tables 8 and 9. The differences between the overall mean scores for RSF composite and controls using SCI and OIL as extraction media were less than 1.0. Based on erythema and edema scores shown below, no irritation was noted when RSF composite extract injection sites were compared to the control injection sites. Injection of the rabbits with the RSF

composite extracts, both in SCI and OIL, did not result in observable negative intracutaneous (intradermal) reactions.

For the SCI extract, the overall mean score for the test was 0, the overall mean score for the control was 0, and the difference between the overall mean scores was 0. For the OIL extract, the overall mean score for the test was 1.0, the overall mean score for the control was 1.0, and the difference between the overall mean scores was 0. The average reaction scores at each observation period for both SCI and OIL are presented in Table 11. The differences between average test scores and average control scores were less than 1.0 at all observation time points.

The susceptibility of the rabbits to a known irritating agent (*i.e.,* the positive control, Freund's Complete Adjuvant in cottonseed oil) was established in a prior positive control study (see Table 10). In this study, the overall mean score for the positive control was 6.4, the overall mean score for the control was 1.0, and the difference between the overall mean scores was 5.4. The differences between average positive control scores and average control scores were greater than 1.0 at all observation periods thus confirming that the rabbits were able to demonstrate detectable skin irritation following injection of an irritating substance.

Incorporation by Reference

The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents were considered to be within the

scope of this invention and are covered by the following claims. Moreover, any numerical or alphabetical ranges provided herein are intended to include both the upper and lower value of those ranges. In addition, any listing or grouping is intended, at least in one embodiment, to represent a shorthand or convenient manner of listing independent embodiments; as such, each member of the list should be considered a separate embodiment.

CLAIMS

What is claimed is:

1. A tissue separation barrier system for preventing the abnormal union of two or more tissues comprising a single layer anti-adhesion silicone polymer wherein the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues and with sufficient flexibility to allow for ease of movement of said tissues.

2. The tissue separation barrier system of claim 1, wherein the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues in a subject.

3. The tissue separation barrier system of claim 2, wherein the single layer anti-adhesion silicone polymer is engineered for enhanced comfort control.

4. The tissue separation barrier system of any one of claims 1, 2 or 3, wherein the movement of said tissues is caused by the application of force on said tissues.

5. The tissue separation barrier system of claim 1, wherein the anti-adhesion silicone polymer comprises a reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a homogenized mixture of a Part A siloxane with a Part B siloxane and about 20% reinforcing material; and wherein:

Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and

Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane.

6. The tissue separation barrier system of claim 5, wherein Part A and Part B are combined in a ratio of about 11.5 Part A siloxane to 1 Part B siloxane in a weight/weight ratio to form the RSF composite.

7. The tissue separation barrier system of claim 5 or 6, wherein said reinforcing material is silica.

8. The tissue separation barrier system of claim 1, wherein the single layer anti-adhesion silicone polymer is engineered to be functionally characterized by exhibiting

a hardness of about 27 to about 33 on Shore A durometer;
a tensile strength of greater than or equal to about 600 psi;
a tear strength of about 100 ppi;
an elongation limit of greater than or equal to about 350%; and
a linear shrinkage of about 2%.

9. The tissue separation barrier system of claim 1, wherein the single layer anti-adhesion silicone polymer may be constructed into any form.

10. The tissue separation barrier system of claim 9, wherein the shape of the single layer anti-adhesion silicone polymer is any three dimensional form of a size, shape and thickness sufficient to separate tissues.

11. The tissue separation barrier system of claim 9 or 10, wherein the shape of the single layer anti-adhesion silicone polymer is a sheet having a thickness of at least about 0.3 mm.

12. The tissue separation barrier system of claim 1, wherein the single layer anti-adhesion silicone polymer is engineered for the separation of tissue selected from the group consisting of connective tissue, muscle tissue, nervous tissue, epithelial tissue, and any combination thereof.

13. The tissue separation barrier system of claim 1, wherein the single layer anti-adhesion silicone polymer is removable.

14. The tissue separation barrier system of claim 1, wherein the single layer anti-adhesion silicone polymer is suitable for permanent implantation.

15. A reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a homogenized mixture of a Part A siloxane with a Part B siloxane and about 20% reinforcing material; and wherein:

Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and

Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane.

16. The RSF composite of claim 15, wherein Part A siloxane and Part B siloxane are combined in a ratio of about 11.5 Part A siloxane to 1 Part B siloxane in a weight/weight ratio to form the RSF composite.

17. The RSF composite of claim 15 or 16, wherein said reinforcing material is silica.

18. A method of separating two or more tissues comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier system of claim 1 between two or more tissues, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues,

such that said tissues remain separated until removal of said single layer anti-adhesion silicone polymer.

19. The method of separating tissues of claim 18, wherein said tissues are in need of separation.

20. The method of separating tissues of claim 18, wherein said tissues are in a subject.

21. `The method of separating tissues of claim 20, wherein said subject is a subject in need thereof.

22. The method of separating tissues of claim 1, wherein said separated tissues are different types of tissues.

23. The method of separating tissues of claim 18, wherein said separated tissues are of the same type of tissue.

24. The method of separating tissues of claim 18, wherein at least one of said tissues surrounds part or all of an organ and said implanted single layer anti-adhesion silicone polymer partially or fully encircles said organ.

25. A method of preventing the abnormal union of any two or more tissues comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier system of claim 1 between two or more tissues, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues,

such that the abnormal union of said tissues is prevented until removal of said single layer anti-adhesion silicone polymer.

26. The method of preventing the abnormal union of tissues of claim 25, wherein at least one of said tissues is the tissue of an organ.

27. The method of preventing the abnormal union of tissues of claim 25 or 26, wherein said abnormal union is in need of being prevented.

28. The method of preventing the abnormal union of tissues of claim 25, wherein said tissues are in a subject.

29. `The method of separating tissues of claim 28, wherein said subject is a subject in need thereof.

30. The method of preventing the abnormal union of tissues of claim 25, wherein said separated tissues are different types of tissues.

31. The method of preventing the abnormal union of tissues of claim 25, wherein said separated tissues are of the same type of tissue.

32. The method of preventing the abnormal union of tissues of claim 25, wherein at least one of said tissues surrounds part or all of an organ and said implanted single layer anti-adhesion silicone polymer partially or fully encircles said organ.

33. The method of preventing the abnormal union of tissues of claim 25, wherein the method prevents the formation of adhesions between said tissues.

34. A method of protecting a sub-epidermal wound comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier system of claim 1 between two or more tissues, wherein at least one of said tissues requires protection as a result of a wound, wherein said single layer anti-adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues,

such that said sub-epidermal wound remains protected until removal of said single layer anti-adhesion silicone polymer.

35. The method of protecting of claim 34, wherein the implantation protects a sub-epidermal wound from tissues selected from the group consisting of

connective tissue, muscle tissue, nervous tissue, epithelial tissue, and any combination thereof.

36. The method of protecting of claim 34 or 35, wherein said separated tissues are different types of tissues.

37. The method of protecting of claim 34 or 35, wherein said separated tissues are of the same type of tissue.

38. The method of protecting of claim 34, wherein at least one of said tissues surrounds part or all of an organ and said implanted single layer anti-adhesion silicone polymer partially or fully encircles said organ.

39. A method of manufacturing a single layer anti-adhesion silicone polymer of claim 1 comprising the steps of:

placing a mixture of a Part A siloxane and a Part B siloxane into a container, wherein the Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and the Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane, and combined comprise about 20% reinforcing material;

subjecting the mixture to a pre-injection homogenization process;

injecting the pre-injection processed mixture into a mold;

curing the molded mixture in an oven;

cooling the molded mixture to room temperature; and

demolding the cured mixture,

thus forming a single layer anti-adhesion silicone polymer of claim 1.

40. The manufacturing method of claim 39, further comprising subjecting the demolded cured mixture to a mechanical transformation process.

41. The manufacturing method of claim 39 or 40, wherein Part A siloxane and Part B siloxane are combined in a weight/weight ratio of about 11.5 Part A siloxane to 1 Part B siloxane.

42. The manufacturing method of claim 39, wherein said reinforcing material is silica.

43. The manufacturing method of claim 39 or 40, wherein said pre-injection homogenization process within the container further comprises, the step of degassing said mixture.

44. The manufacturing method of claim 39, wherein said oven temperatures range from about 40°C to about 150°C.

45. The manufacturing method of claim 39, wherein said anti-adhesion silicone membrane is subjected to a sterilization process.

46. The manufacturing method of claim 45, wherein said sterilization process is selected from the group consisting of autoclaving, exposure to ultraviolet light and chemical sterilization.

47.. The manufacturing method of claim 39, wherein said method is performed in a controlled environment suitable for producing a sterile, contaminant-free and defect-free single layer anti-adhesion silicone polymer suitable for surgical use.

48. A tissue separation barrier system according to claim 1 manufactured according to the method of claim 39.

FIG. 1

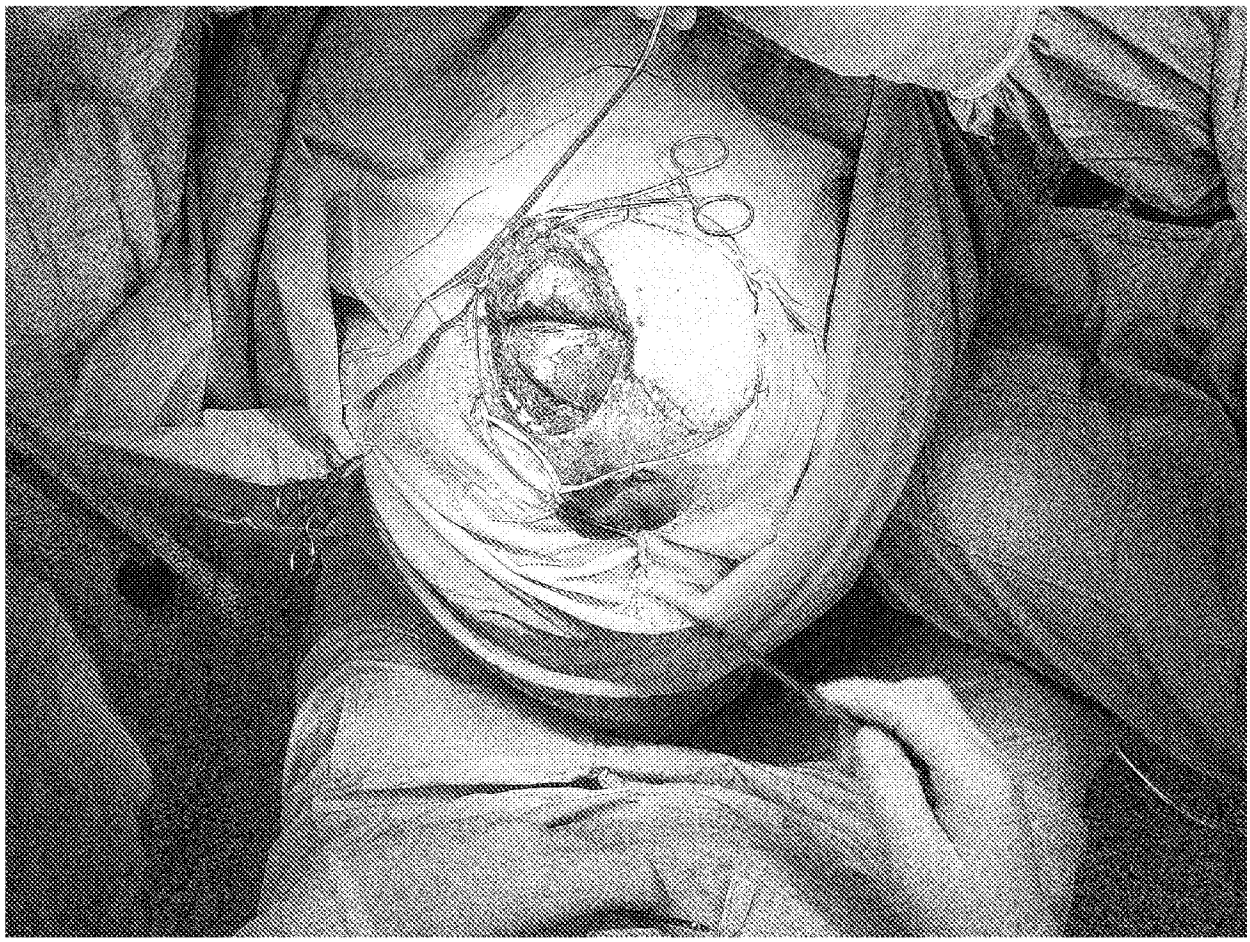


FIG. 2

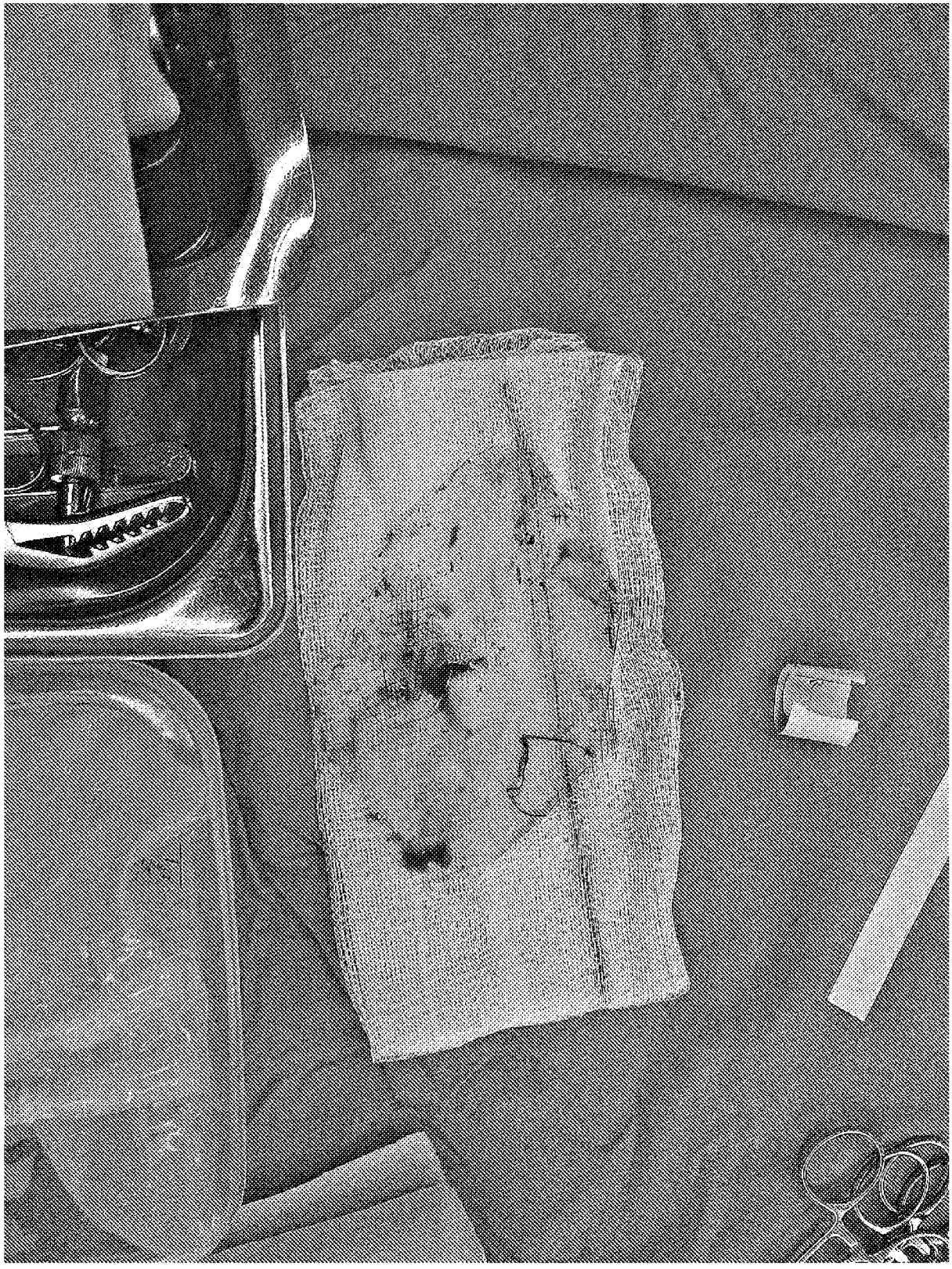
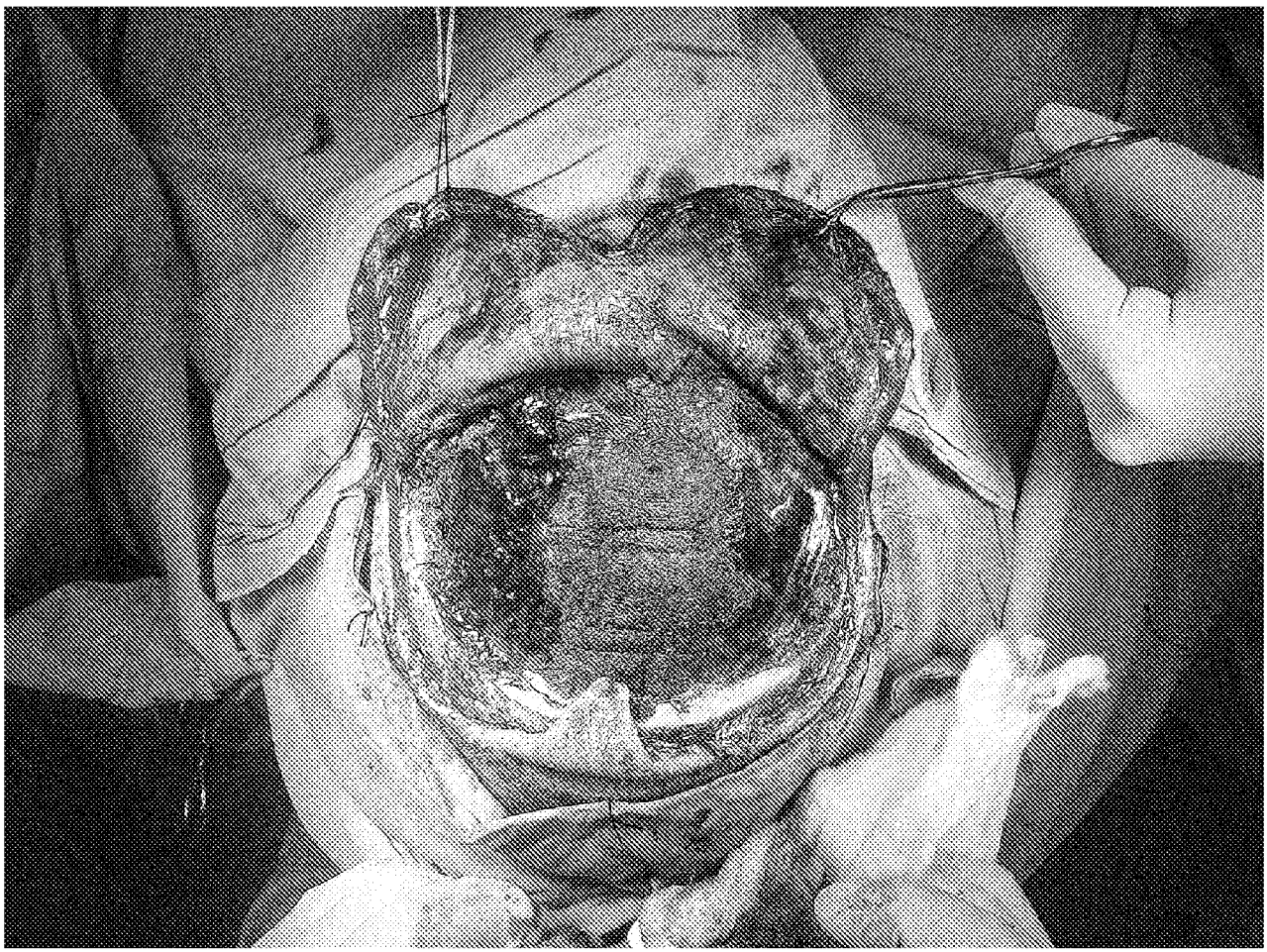


FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/67405

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12M 1/14, C12N 5/07, A61F 2/00(2017.01)
CPC - C12M 25/02, C12M 21/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,795,584 A (Totakura et al.) 18 August 1998 (18.08.1998) Col 3 ln 20-25; col 4 ln 55-60; col 5 ln 5-10; col 10 ln 50-55 and entire document	1-4,9-14 --- 5-8
X --- Y	US 2011/0224341 A1 (Davies et al.) 15 September 2011 (15.09.2011) Abstract, para [0047], para [0061]-[0063], Table 2; para [0052], para [0046]	15-17 --- 5-8
Y	US 2011/0230810 A1 (Raman et al.) 22 September 2011 (22.09.2011) Abstrcat, para [0012]-[0024]	1-17
Y	US 2009/0048684 A1 (Lesh) 19 February 2009 (19.02.2009) Abstrcat, para [0009]-[0077]	1-17
Y	US 2010/0174328 A1 (Seaton et al) 8 July 2010 (08.07.2010) Abstract, para [0013]-[0019]	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2017	28 APR 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/67405

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 48
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

----------see supplemental box ----------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-17

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/67405

----------contineud from Box III----------

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-17 is directed towards a tissue separation barrier system for preventing the abnormal union of two or more tissues comprising a single layer anti-adhesion silicone polymer wherein the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues and with sufficient flexibility to allow for ease of movement of said tissues.

Group II: Claims 18-38 is directed towards a method of separating two or more tissues comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier system between two or more tissues, wherein said single layer anti- adhesion silicone polymer is engineered with sufficient flexibility to allow for ease of movement of said tissues, such that said tissues remain separated until removal of said single layer anti-adhesion silicone polymer or such that the abnormal union of said tissues is prevented until removal of said single layer anti-adhesion silicone polymer or such that said sub-epidermal wound remains protected until removal of said single layer anti-adhesion silicone polymer.

Group III: Claims 39-47 is directed towards a method of manufacturing a single layer anti-adhesion silicone polymer comprising the steps of: placing a mixture of a Part A siloxane and a Part B siloxane into a container, wherein the Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and the Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane, and combined comprise about 20 percent reinforcing material; subjecting the mixture to a pre-injection homogenization process; injecting the pre-injection processed mixture into a mold curing the molded mixture in an oven; cooling the molded mixture to room temperature; and demolding the cured mixture, thus forming a single layer anti-adhesion silicone polymer.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group II requires a method of separating two or more tissues comprising implantation of a single layer anti-adhesion silicone polymer of the tissue separation barrier system between two or more tissues, such that said tissues remain separated until removal of said single layer anti-adhesion silicone polymer or such that the abnormal union of said tissues is prevented until removal of said single layer anti-adhesion silicone polymer or such that said sub-epidermal wound remains protected until removal of said single layer anti-adhesion silicone polymer not required by groups I and III.

Group III requires a method of manufacturing a single layer anti-adhesion silicone polymer comprising the steps of: placing a mixture of a Part A siloxane and a Part B siloxane into a container, wherein the Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and the Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane, and combined comprise about 20 percent reinforcing material; subjecting the mixture to a pre-injection homogenization process; injecting the pre-injection processed mixture into a mold curing the molded mixture in an oven; cooling the molded mixture to room temperature; and demolding the cured mixture, thus forming a single layer anti-adhesion silicone polymer, not required by groups I and II.

Shared Technical Features:

Groups I-III share the common feature of a tissue separation barrier system for preventing the abnormal union of two or more tissues comprising a single layer anti-adhesion silicone polymer wherein the single layer anti-adhesion silicone polymer is engineered to be implantable between two or more tissues and with sufficient flexibility to allow for ease of movement of said tissues. However, these shared technical features (claim 1) do not represent a contribution over prior art, because the shared technical feature is obvious over US 2011/0230810 A1 to Raman et al.(hereinafter Raman) in view of US 2009/0048684 A1 (Lesh). Raman discloses a tissue separation barrier system for preventing the abnormal union of two or more tissues (para [0001], present invention can be used generally as an anti -adhesion membrane or as a barrier to tissue reaction) comprising a silicone polymer (para [0018], anti-adhesion patch of a first silicone layer) wherein the layer is engineered to be implantable between two or more tissues (para [0022], biocompatible implantable patch) with sufficient flexibility to allow for ease of movement of said tissues (para [0040], present device is initially presented to the surgeon as a flattened, flexible device that is easy to handle). Raman does not specifically disclose a single layer patch. However, Lesh discloses a implantable device (para [0009], invention comprises an implantable tissue augmentation device) made of silicone polymers (para [0018], inner layer comprises silicone) that consists of a single layer (para [0018], the device comprises only a single layer). As both Raman and Lesh disclose implantable devices, it would have been obvious to a person having ordinary skill in the art to know the anti-adhesion silicone patch disclosed by Raman can be a single layer patch as disclosed by Lesh as making a single layer is easier to manufacture through routine experimentation.
Groups I and III share the technical feature of a reinforced silicone flex (RSF) composite, wherein said RSF composite is a two part composite system formed by the curing of a homogenized mixture of a Part A siloxane with a Part B siloxane and about 20 percent reinforcing material; and wherein: Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and Part B siloxane comprises reinforced dimethyl methylhydrogen siloxane. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is anticipated by US 2010/0174328 A1 to Seaton, Jr. et al.(hereinafter Seaton). Seaton discloses a reinforced silicone flex composite (para [0037], reinforced reinforced dimethyl methylvinyl siloxanes) which is a two part composite system formed by the curing of a homogenized mixture of a Part A siloxane with a Part B siloxanes (para [0037], comprises two highly viscous liquid components, namely reinforced dimethyl methylvinyl siloxanes and reinforced dimethyl methylhydrogen siloxanes, supplied in equal parts) and about 20 percent reinforcing material (para [0040], silica amorphous 21 percent) and wherein Part A siloxane comprises reinforced dimethyl methylvinyl siloxane, and Part B siloxane comprises reinforced dimethyl methylhydrogen siloxanes (para [0037], comprises two highly viscous liquid components, namely reinforced dimethyl methylvinyl siloxanes and reinforced dimethyl methylhydrogen siloxanes, supplied in equal parts).

As the shared technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups. Therefore, Groups I-III lack unity under PCT Rule 13.NOTE: Claim 22 is assumed to depend from claim 18 for the purposes of this opinion.