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(54) Title: IMPROVED SKIN SUBSTITUTE MANUFACTURING METHOD

(57) Abstract: An improved skin substitute production method is presented that minimizes destruction of the nylon weave netting that comprises the skin substitute at the pore holes of the skin substitute membrane, The skin substitute is comprised of non-biological materials produced with a series of regularly-spaced pores and a nylon weave netting. The top component is a thin (approximately.001 " thick) silicone elastomer in which pore holes have been vacuum-pulled; physically attached to the silicone elastomer is a fine knitted nylon fabric (12/1, 15/1 denier).

Improved Skin Substitute Manufacturing Method

RELATED APPLICATIONS

This is a Continuation-in-Part of US Pat. App. 12/326,373, currently co-pending, which is a Continuation-In-Part of US Pat. App. 12/049,321, currently co-pending.

FIELD OF THE INVENTION

This invention relates to the field of artificial skin substitutes used for wound and burn dressings, and other purposes.

BACKGROUND OF THE INVENTION

A number of skin substitutes exist in the current market that address the wound dressing and burn dressing problem. There is is currently no perfect product and there are still gaps in the capabilities of state-of-the-art artificial skin substitutes.

The present invention provides a precision, porous, stretchable membrane that fosters an ideal three-dimensional environment for the protection of existing cells and growth of new skin cells. The present invention promotes rapid adhesion to the wound as well as large sheet coverage (up to 24" by 24"), not offered by the state-of-the-art.

The present invention is made stretchable and tear resistant by

using a fine knit nylon fabric. Additionally, the porosity of the overlying membrane is greater in terms of placement and area of pores, compared to the state-of-the-art. The membrane is semi-permeable, allowing water vapor transmission and preventing fluid accumulation between the dressing and the wound surface.

As a consequence, the porosity of the membrane enhances the healing process, making it faster and safer. The three-dimensional membrane structure is also made capable of holding a biological agent that further increases the healing abilities of the covered area. These agents include biological agents such as chondrotin 6 sulfate, and others.

The present invention is easy to handle, flexible and stretchable, can be stored at room temperature, and is safe and sterile. Packaging and sterilizing of the invention is crucial. From a production and laboratory standpoint, manufacturing the invention is efficient in terms of time and materials. After manufacture, the product will be ready for immediate
sterilization and shipping for use on patients.

Technical Background

Some ideal properties of a skin substitute from (Rusczak, 2006)

and Properties from (Robert H. Demling)

a. Rapid and sustained adherence to wound surface and Inner surface structure that permits cell migration, proliferation and in growth of new tissue

(The most important criterion is adherence)

b. Absence of antigenicity

c. Tissue compatible

d. Absence of local or systemic toxicity

e. Impermeable to exogenous microorganisms

f. Water vapor transmission similar to normal skin

g. Rapid and sustained adherence to wound surface

h. Conformal to surface irregularities

i. Elastic to permit motion of underlying tissue

j. Resistant to linear and shear stresses

k. Tensile strength to resist fragmentation (when removed)

l. Inhibition of wound surface flora and bacteria

m. Long shelf life, minimal storage requirements

n. Low cost

o. Minimize nursing care of wound

p. Minimize patient discomfort

q. Translucent properties to allow direct observation of healing

r. Reduce heal-time

s. Patient acceptance

Prior Art

Tissue Based Skin Substitutes

Alloderm by LifeCell, Inc - AlloDerm is human tissue and is processed from donated human skin. The tissue goes through a cell removal process while retaining the important biochemical and structural components. AlloDerm is, thus, acellular human dermis. US Patent Number 6,933,326 - Particulate acellular tissue matrix.

Apligraf by Organogenesis Inc. - Apligraf is supplied as a living, bi-layered skin substitute: the epidermal layer is formed by human keratinocytes and has a well-differentiated stratum corneum; the dermal layer is composed of human fibroblasts in a bovine Type I collagen lattice. US Patent Numbers: 4,485,096 5,106,949 5,536,656

Dermagraft by Smith & Nephew Inc - Dermagraft is a cryopreserved human fibroblast-derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold. US Patent Numbers: 4,963,489: Three-dimensional cell

and tissue culture system

Epicel by GenzymeBiosurgery - Epicel grafts are sheets of skin cells ranging from 2 to 8 cell layers thick. The grafts are grown or cultured from a postage stamp sized sample of patient's own healthy skin, which is sent to GenzymeBiosurgery for processing. The cells within the epidermis of the skin sample are separated and grown by a process called "tissue culture", which involves feeding the cells with specific nutrients and maintaining strict climate controls so that the cells multiply to form sheets of skin. During this process, irradiated mouse cells, also referred to as 3T3 cells, are used to promote cell growth and to ensure that there will be a sufficient number of grafts available as soon as possible for treatment. US Patent Numbers: 6,964,869: Method and composition for skin grafts.

EZ Derm by Brennen Medical, Inc - A modified pigskin impregnated with a soluble silver compound intended for treatment of burns. Originally developed by Genetic Laboratories. US Patent Numbers: Stabilized silver-ion amine complex compositions and methods 6,923,990. This is not a patent for EZ Derm but it is related to the silver that EZ-Derm uses

OrCel by Ortec International Inc. - A bilayered cellular matrix in

which normal human allogeneic skin cells (epidermal keratinocytes and dermal fibroblasts) are cultured in two separate layers into a Type I bovine collagen sponge. Donor dermal fibroblasts are cultured on and within the porous sponge side of the collagen matrix while keratinocytes, from the same donor, are cultured on the coated, non-porous side of the collagen matrix.

TransCyte by Smith and Nephew, Inc - Consists of a polymer membrane and newborn human fibroblast cells cultured under aseptic conditions in vitro on a nylon weave. Prior to cell growth, this nylon weave is coated with porcine dermal collagen and bonded to a polymer membrane (silicone). This membrane provides a transparent synthetic epidermis when the product is applied to the burn.

As fibroblasts proliferate within the nylon weave during the manufacturing process, they secrete human dermal collagen, matrix proteins and growth factors. Following freezing, no cellular metabolic activity remains; however, the tissue matrix and bound growth factors are left intact. The human fibroblast-derived temporary skin substitute provides a temporary protective barrier. TransCyte is transparent and allows direct visual monitoring of the wound bed.

Silver Based Skin Substitutes

Aquacell Ag

Silver powered antimicrobial dressing

ActiCoat

Using unique silver technology:

SILCRYST Nanocrystalline

Other Synthetic/Similar to our membrane Skin Substitutes

Biobrane, Biobrane-L by Bertek Pharmaceuticals - BiobraneÆ is a biocomposite temporary wound dressing constructed of an ultrathin, semipermeable silicone film with a nylon fabric partially imbedded into the film. The fabric presents to the wound bed a complex 3-D structure of trifilament thread to which porcine dermal collagen has been chemically bound. Blood/sera clot in the nylon matrix, thereby firmly adhering the dressing to the wound until epithelialization occurs. Patent Numbers: 4,725,279.

Integra Bilayer Matrix Wound Dressing by Integra LifeSciences Corp. - an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer.

Laserskin by Fidia Advanced Biopolymers - Lam, P. K. et al; "Development and evaluation of a new composite Laserskin graft", J

of Trauma: Injury, Infection and Critical Care. 47, 1999.pp. 918-922.

Oasis Wound Matrix by Healthpoint - A biologically derived extracellular matrix-based wound product that is compatible with human tissue. Unlike other collagen-based wound care materials, OASIS is unique because it is a complex scaffold that provides an optimal environment for a favorable host tissue response, a response characterized by restoration of tissue structure and function.

Glucan II - A smooth gas permeable polymeric layer attached to the mesh matrix.

A highly advanced carbohydrate dressing with Beta-Glucan.

SUMMARY OF THE INVENTION

The present silicone/nylon membrane has been developed for applications on wounds or burns. These applications include, but are not limited to superficial wounds, excised deep and full thickness wounds, donor sites, meshed autograph sites, and specialized wound locations such as the hands, face, and feet.

The present invention produces thin silicone/nylon membranes on flat Teflon™ surfaces. In the previous instantiation, vacuum suction was used to produce pores in the membrane by pulling silicone through the Teflon surface. This method has been

abandoned, and the present invention uses a method of creating pores through gravity and friction.

Silicone Technology - The present invention uses a Silicone Dispersion mixed with a 15% Solution of Xylene: Heat Cured Mfg. Part Number V40000. It is a custom mixed product for this use and specifically requested for this application. The preferred supplier is Applied Silicones .

Knitting Technology - The present invention uses a knitting machine with a 13 inch cylinder with 1152 needles. It can knit varying length of tubes.

The boarding process follows the knitting of the tube and controls the final width (and length) of the nylon. The form size used in the boarding process is important. The current form is 15 3/4 inches wide by 32 inches long. The top of the form is tapered for approximately 2 inches. The boarding chamber is larger and can accommodate a form up to 19 inches wide and 32 inches long. There is a significant advantage over competing technologies with a larger final knitted product, allowing for larger final silicone/nylon membranes.

Fabric can be knitted in custom weaves. The preferred weaves

and settings for the machine are detailed in a series of technical guides. The different weaves give the final product varying characteristics and are critical in producing the proper end result.

Thin Film Technology

A process to cure a precision membrane after combining it with nylon on a thin, flat, chemically etched, Teflon™ coated "thin film" plate has been developed and is included below. The plate used to cure the membrane is formed out of a thin (.004" thick), flexible metal that has been chemically etched to produce the desired thickness and hole pattern.

The plate is coated with a low adhesion Teflon™ coat (Silverstone™). The coating is critical as the membrane will not release properly without it. As noted in the prior art, the Silverstone™ coating is superior to its alternates (White virgin Teflon™ and a standard Teflon™ coating). The plates are cleaned between uses so that no residue is left behind on the final silicone/nylon membrane.

The thin plate design allows for numerous benefits over the prior invention. First, issues with metal plates warping in extreme heat have been eliminated, as the process for developing the new plate does not require such high cure temperatures. Secondly, when

placed on the vacuum sub panel as described below, the thin plate can be held extremely flat. As in the prior art, it is absolutely critical that the surface is as flat as possible so as to allow for the silicone dispersion to be layered consistently, flat, and level, with minimal variations in thickness. These two additions in the current invention are superior to prior inventions.

The thin nature of the plate allows for ease of cleaning over prior inventions. The layering process is similar to the process in US Pat. App. 12/326,373. Differences in process are described below.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Typical Thin Film Panel

Figure 2. Sample Sub Panel Layout

Figure 3. Process Outline

DETAILED SPECIFICATION

The skin substitute100 is comprised of two layers of material, a membrane layer 101 and a nylon weave 102. The membrane layer 101 is fixedly attached to the nylon weave102 during manufacture. The two layers of the invention are made from non-organic material.

The membrane layer101 possesses a plurality of pores 103 arranged across its surface in a regular pattern. The pores103 can be produced in its surface during manufacture by several means, including penetration of the membrane by needles and by means of vacuum suction. The preferred mode is the method described below.

The nylon weave 102 is a produced by a knitting machine with a 13 inch cylinder with 1152 needles. It can knit varying length of tubes of the nylon weave102.

The nylon weave102 can be knitted in custom weaves. The preferred weaves and settings for the machine are detailed in an industry standard specification sheet. The different weaves give the skin substitute100 varying characteristics and are critical in producing the proper end result.

The preferred process to produce the skin substitute 100 is to

cure the membrane layer 101 after combining it with nylon weave102 on a flat surface. The plate 105 used to cure the membrane layer101 and nylon weave 102 is formed out of an aluminum honey-comb structure with a low density. The low density of the plate105 gives it low heat sinking properties. The honey-comb like structure allows for a very strong and rigid design, while remaining extremely flat. It is critical that the surface is flat in order to allow the membrane layer 101 to be layered consistently flat, and level, with no variations in thickness.

The preferred embodiment method for making pore holes in the membrane layer 101 involves the use of a thin Teflon™ coated plate, the thin plate 110 as in Fig. 1, with etched holes in combination with a vacuum sub panel 111, as in Fig. 2, to create a thin membrane layer 101.

This method allows removal of portions of the membrane layer 101 at the pore holes in a manner that does not disturb the three-dimensional structure of the knitted nylon attached to the membrane layer 101.

Vacuum Sub Panel

The thin plate 110 is placed over a vacuum subpanel system.

The vacuum subpanel system consists of a vacuum box 106 the size of the subpanel plate 113 and the thin plate 110. The vacuum box 106 is sized such that when the subpanel plate 113 is placed on top of it, an airtight seal is created. The side of the vacuum box 106 has an opening where a vacuum or airflow system can be attached. The subpanel plate 113 contains numerous holes in a regular pattern, in the preferred embodiment roughly in the size and position of the holes in the thin plate 110 , with larger holes around the border. When the thin plate 110 is placed on top of the subpanel plate 113, it is placed off center, such that the holes in the thin plate 110 and the holes in the subpanel plate 113 do not line up.

When the vacuum system is activated, the thin plate 110 is pulled onto the subpanel plate 113 by air pressure and is not easily moved until the layering process is completed, the silicone membrane 101 is completed on top of the thin plate 110 and the vacuum system is deactivated.

Excess silicone is removed from the upper surface of the silicone membrane 101 via absorbent material. Nylon fabric is applied without wrinkles to the silicone membrane 101. The thin plate 110 with the silicone/nylon membrane on top of it is then lifted and placed

on a sheet of absorbent material, in the preferred embodiment parchment paper. The parchment paper is moved under the plate and the excess silicone membrane 101 extruded through the holes in the thin plate 110 rubs off, leaving clear holes in the silicone/nylon membrane. Finally, the thin plate 110 with the nylon and silicone layer is allowed to cure before removal of the porous silicone/nylon membrane.

Results: Over previous technology, the thin plate technology consistently produces higher quality membranes and drastically reduces cleaning time for the thin plate 110 and subpanel plate 113. It generates no debris and allows for greater flexibility in customizing hole/void patterns.

The apparatus and methods described are the preferred and alternate embodiments of this invention, but other methods are possible and are within the contemplation of this patent.

CLAIMS

What is claimed is

1. a skin substitute production means,

the skin substitute comprised of two layers of material, a membrane layer and a nylon weave,

the membrane layer fixedly attached to the nylon weave during manufacture of the skin substitute, the membrane layer and nylon weave made from non-organic material,

the membrane layer possessing a plurality of pores arranged across its surface in a pattern,

the skin substitute production means further comprised of a thin plate, a subplate, and a vacuum box,

the thin plate a rectangular, flat, rigid surface comprised of a low-density material with low heat sinking properties, with a plurality of vacuum holes, the vacuum holes drilled through the plate in a characteristic shape, the vacuum holes scattered about the plate in a random or regular pattern, the thin plate covered with a low adhesion coating,

the subplate a rectangular, flat, rigid surface comprised of a

low-density material with low heat sinking properties, with a plurality of vacuum holes, the vacuum holes drilled through the plate in a characteristic shape, the vacuum holes scattered about the plate in a random or regular pattern that does not overlap the pattern of the holes in the thin plate,

the low adhesion coating a thin coating that covers the upper surface of the thin plate, the low adhesion coating comprised of a spray-on liquid that reduces the physical adhesion between the plate and any plastic material placed on it,

the vacuum box a hollow box that when mated with the subplate makes a vacuum seal.

2. The skin substitute production means as in Claim 1 where the low adhesion coating is comprised of a substance selected from SilverstoneTM, White Virgin TeflonTM, and standard TeflonTM.

3. A method of production using the skin substitute production means of Claim 1, comprised of the steps of

assembling a skin substitute production means and producing a skin substitute,

the step of assembling a skin substitute production means comprised of the sub-steps of

selecting the thin plate material,

selecting the subplate material,

drilling the thin plate with vacuum holes,

drilling the subplate with vacuum holes offset from the pattern of vacuum holes for the thin plate,

spraying the upper surface of the thin plate with a low adhesion coating,

bake the coating at 800 degrees Fahrenheit for 15 minutes,

mate the subplate to the vacuum box,

placing the thin plate on top of the subplate,

The step of producing a skin substitute comprised of the sub steps of

layering the thin plate upper surface with .010 inch thick silicone membrane,

turn off vacuum in vacuum box,

remove thin plate with membrane on upper surface and place thin plate lower surface on absorbent material,

slide absorbent material out from under thin plate, pulling bits of membrane extending through holes in thin plate with it,

lay a section of nylon weave over the layer of silicone,

place thin plate with membrane and weave on layer of

absorbent material,

bake the composite on the plate at 190 degrees Fahrenheit for 25 minutes,

let the membrane and weave cool on the plate for 10 minutes, then carefully remove it.

4. A method of production using the skin substitute production method of Claim 3 where the absorbent material is parchment.

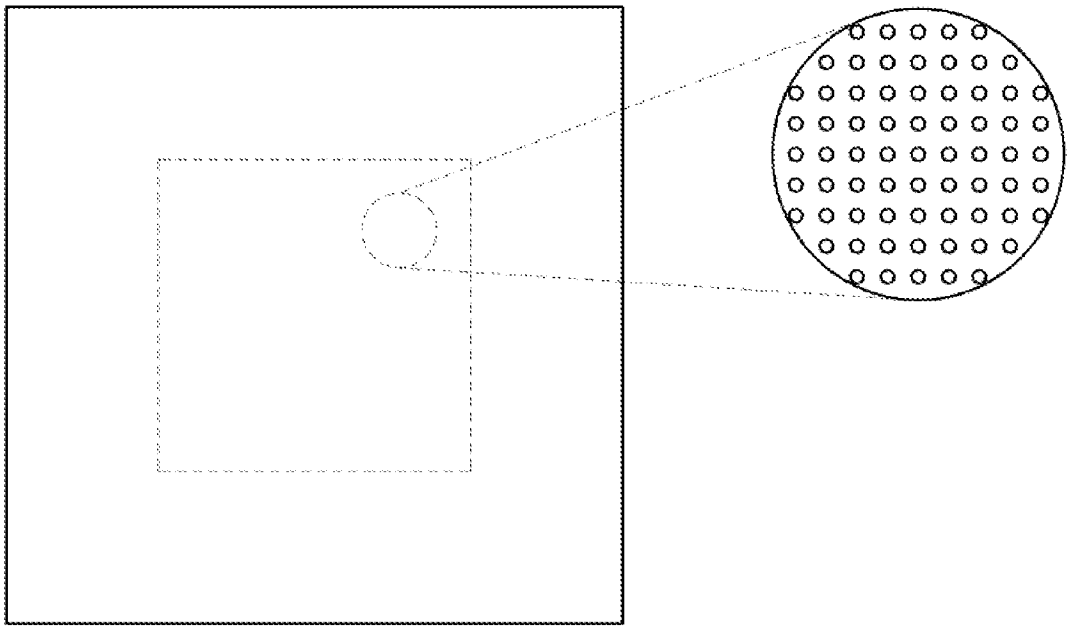


FIG. 1

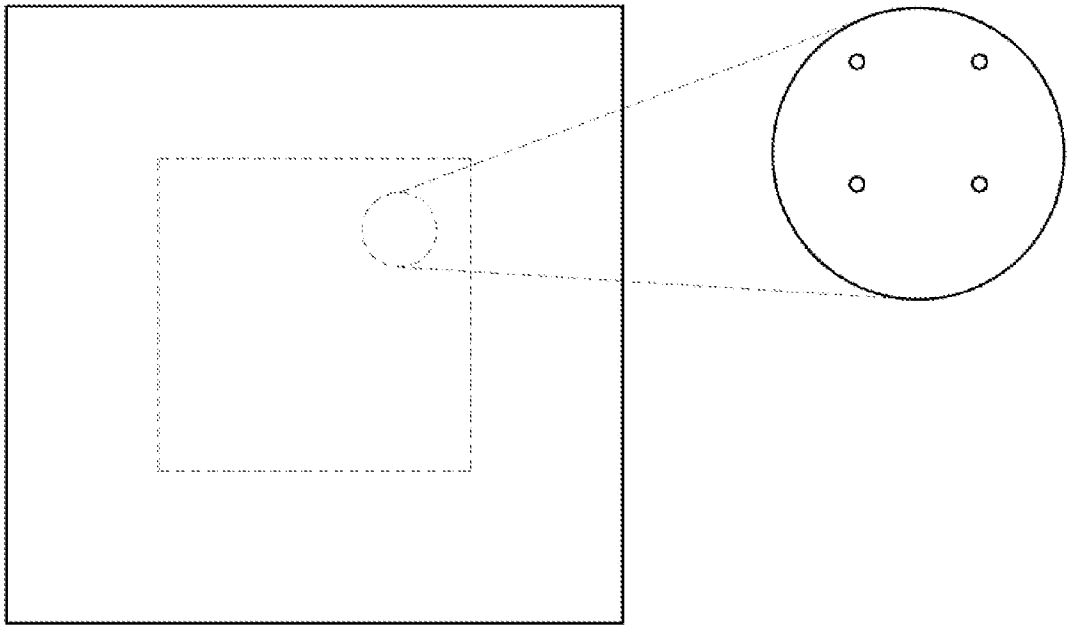
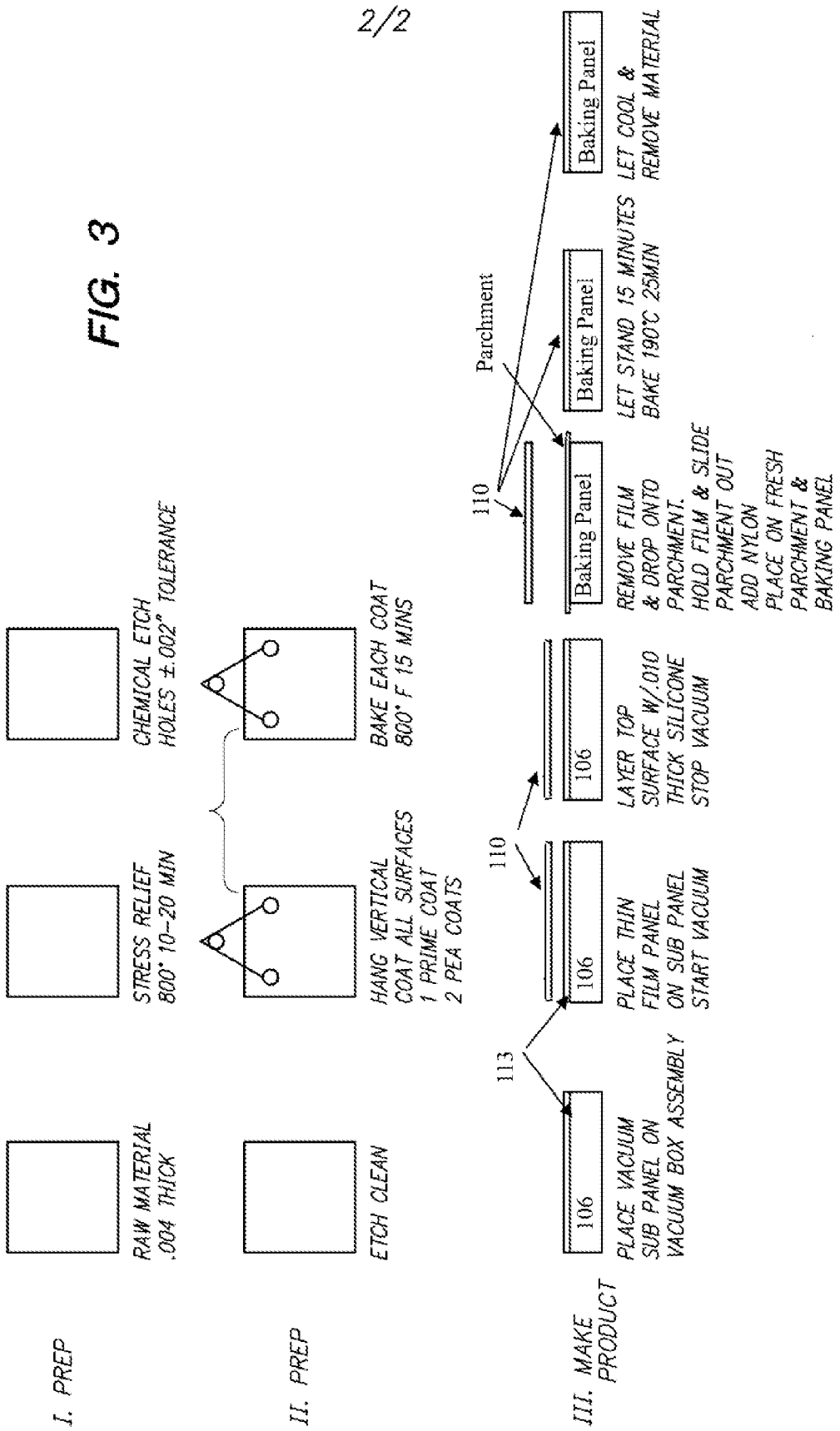


FIG. 2

FIG. 3


I. PREP
RAW MATERIAL .004 THICK
STRESS RELIEF 800° 10-20 MIN
CHEMICAL ETCH HOLES ±.002" TOLERANCE
II. PREP
ETCH CLEAN
HANG VERTICAL COAT ALL SURFACES 1 PRIME COAT 2 PEA COATS
BAKE EACH COAT 800° F 15 MINS
III. MAKE PRODUCT
106
PLACE VACUUM SUB PANEL ON VACUUM BOX ASSEMBLY
113
106
PLACE THIN FILM PANEL ON SUB PANEL START VACUUM
110
106
LAYER TOP SURFACE W/.010 THICK SILICONE STOP VACUUM
110
Parchment
Baking Panel
REMOVE FILM & DROP ONTO PARCHMENT.
Baking Panel
LET STAND 15 MINUTES BAKE 190°C 25MIN
Baking Panel
LET COOL & REMOVE MATERIAL
HOLD FILM & SLIDE PARCHMENT OUT
ADD NYLON
PLACE ON FRESH PARCHMENT & BAKING PANEL

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/48557

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - B29C 65/00 (2010.01)
USPC - 156/285
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - B29C 65/00 (2010.01)
USPC - 156/285

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Non-patent Literature; Patents (key word limited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB); Google (Google Scholar; Google Patents)
Search Terms Used: skin substitute, dressing, bandage, alternative skin tissue, graft, method, process, means, producing, manufacturing, preparing, making, vacuum, porthole, plates, teflon, support, sub-plate, substrate, silicone, nylon weave, nylon, woven

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,034,751 A (HUNG) 12 July 1977 (12.07.1977) col 1, ln 6-8; col 2, ln 7-12; col 5, ln 15-17; col 6, ln 39-44; col 7, ln 21-32; col 14, ln 21-33, 43-68; col 15, ln 1-4; col 16, ln 33-41; col 17, ln 7-30, 49-68; col 18, ln 1-12, 22-30; fig 5	1-4
Y	US 4,725,279 A (WOODROOF) 16 February 1988 (16.02.1988) col 1, ln 8-17; col 3, ln 43-52; col 8, ln 5-13; col 19, ln 44-59	1-4
Y	US 4,556,056 A (FISCHER, et al.) 03 December 1985 (03.12.1985) col 1, ln 10-14; col 4, ln 50-68 to col 5, ln 1-7	1-4
Y	US 2004/0078015 A1 (COPAT, et al.) 22 April 2004 (22.04.2004) para [0002], [0025], [0103]-[0105]	1-4
A	US 2004/0138604 A1 (SIGURJONSSON, et al.) 15 July 2004 (15.07.2004)	1-4
A	WOODROOF. The Search for an Ideal Temporary Skin Substitute: AWBAT. ePlasty, 12 February 2009, Vol 9, pp. 95-104.	1-4
A	US 2008/0125687 A1 (FLICK, et al.) 29 May 2008 (29.05.2008)	1-4

☐ 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
09 December 2010 (09.12.2010)	20 DEC 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)