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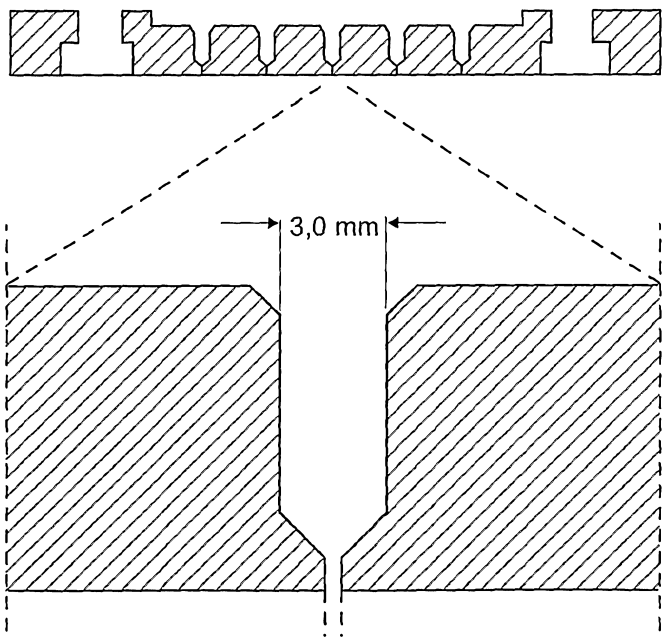
(54) **Title:** SHORTENED WOUND HEALING PROCESSES BY MEANS OF NOVEL FIBER NON-WOVENS

(54) **Bezeichnung:** VERKÜRZTE WUNDHEILUNGSPROZESSE MITTELS NEUARTIGER FASERVLIESE



(57) **Abstract:** A multilayered dressing having at least the following structure: a non-woven (1) which enters into contact with the wound, and a membrane (3) which is watertight and contains at least one water-insoluble polymer.

(57) **Zusammenfassung:** Multilagen-Verband, der wenigstens den folgenden Aufbau hat: ein Vlies 1, das mit der Wunde in Berührung kommen soll, und eine Membran 3, die wasserdicht ist und mindestens ein in Wasser unlösliches Polymer aufweist.

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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Shortened would healing processes by means of novel fiber non-wovens

The present patent application relates to a multilayer dressing based on a spunbonded or fibrous nonwoven.

Moist wound closure is known in the art (see, for example, Blank, Ingo, Wundversorgung und Verbandwechsel, Kohlhammer-Verlag, Stuttgart, 2001, 142, ISBN 3-17-016219-5; Stalick L., Managing and caring for a patient with a complicated wound. Br J Nurs. 2004 Oct 14-27; 13(18):1107-9; Metzger S., Clinical and financial advantages of moist wound management. Home Health Nurse. 2004 Sep; 22(9):586-90). The problem with this type of wound treatment is that the wound-contact medium, e.g. absorbent gauze, plaster etc., may become adherent to the wound during healing. When the contact medium is subsequently to be removed, the wound is often torn open again, whereby tissue which has just been newly formed is destroyed again and removed. It is obvious that wound healing is unnecessarily delayed thereby. On use of wound dressings which do not adhere to the wound, thus preventing the wound dressing becoming adherent to the wound, the wound defect lacks a supporting and lead structure on which the newly formed tissue can orient itself and grow. This circumstance leads to a substance defect developing in particular with deeper wounds. There is additionally unnecessary and unwanted scarring. This problem relates in clinical practice to all wounds which relate not just to the epidermis but also to the corium and, where appropriate, the subcutis (so-called "deep" wounds) and require reconstitution not only of the epidermal layers but also of the corium and, where appropriate, of the subcutis.

The thickness of the epidermis is normally variable and may, depending on the site, be from 0.03 to 4 mm thick. Age and gender also have an influence on the thickness of the epidermis. The epidermis has no blood vessels. It is formed of keratinocytes. Keratinocytes are corneocytes which have a cell nucleus and produce keratin. Keratin is water-repellent and confers strength on the skin.

The underlying corium is an elastic layer of skin which contains a high proportion of loosely interwoven and connective tissue. It may also vary in thickness depending on the site. It is thin on the penis and on the eyelids at only 0.3 mm, whereas the thickness of the corium on the soles of the hands and the feet is up to 2.4 mm.

The abovementioned problems relate not only to wounds with delayed healing or no healing at all, such as the chronic diabetic-neuropathic ulcer, leg ulcer, pressure sores and infected wounds healing by second intention, but also wounds healing normally by first intention (e.g. ablative lacerations or abrasions (where tissue has been excoriated and thus removed from the wound) and split skin donor sites).

Starting from the previously described prior art, the inventors have addressed the problem of providing a contact medium in the widest sense (e.g. dressing, gauze, plaster) which can be brought into contact with the wound without the need to accept the abovementioned disadvantages (contact medium becoming adherent to the wound; destruction of tissue which has just formed, unnecessary delay in wound healing, excessive scarring, defect (healing) formation). It was therefore the inventors' aim to develop a structure with which it is possible in moist wound closure to leave the structure in the tissue and, even after healing of the wound, not remove it, in order thus not to interfere with the healing process, to give a lead structure to the newly forming tissue and in order ultimately to avoid scarring.

DE-C 196 09 551 discloses biodegradable and/or -absorbable fibrous structures (silica gel fibers or fibrous structures). These can be obtained by drawing threads from a spinning dope, which are dried where appropriate. The spinning dope comprises one or more partially or completely hydrolytically condensed compounds of silicon which are derived by hydrolytic condensation from monomers of the general formula SiX_4 in which the X radicals are identical or different and are hydroxy, hydrogen, halogen, amino, alkoxy, alkyloxy, alkylcarbonyl or alkoxycarbonyl or are derived from alkyl radicals and may be interrupted by oxygen or sulfur atoms or by amino groups.

Also known are the methods described in WO 01/42428 and EP-A 01 262 542 for producing a skin implant, and cells, tissues and organs, respectively, which make use of the aforementioned fibrous structures. WO 01/42428 describes a method for producing a skin implant, where skin cells are put onto the surface of a nutrient solution, and the cells then grow, characterized in that a sheetlike element composed of the abovementioned biocompatible, or biodegradable and/or –absorbable fibers is laid on the nutrient solution. The fibers of the sheetlike element have a diameter of from 5 to 20 µm. EP-A 01 262 542 describes by contrast a method for the *in vitro* production of cells, tissues and organs, where said fibrous matrix (see DE-C 196 09 551) serves as cell-supporting substance and/or lead structure for the extracellular matrix formed by the cells, and makes it possible for the cells to find a spatial arrangement which permits the cells to multiply and/or achieve their genetically determined differentiation.

The solution offered by the inventors to the problem described above forms one aspect of the present invention and consists of the use of the fibers disclosed in DE-C 196 09 551 for producing a multilayer dressing according to claim 1. This entails processing said fibers to a nonwoven which can then be combined with all conventional dressing means, in particular with dressing means which are introduced directly onto or into the wound. This combination is referred to here and hereinafter as multilayer dressing, even if it is not a typical dressing, but is a plaster, a compress, or the like. One aspect of the present invention thus relates to a multilayer dressing which has at least the following structure: a nonwoven 1, which is intended to come into contact with the wound, and a membrane 3, which is water-impermeable and includes at least one water-insoluble polymer.

According to a first aspect of the invention there is provided a multilayer dressing comprising:

a nonwoven, which is intended to come into contact with a wound, and

a water-impermeable membrane comprising at least one water-insoluble polymer, wherein the membrane is an adhesive plaster comprising an adhesive portion that adheres to the skin surrounding the wound, or comprises no adhesive portion and adheres to the skin surrounding the wound only when an adhesive has been applied to the skin surrounding the wound,

wherein the nonwoven includes biodegradable and/or -absorbable fibrous structures obtained by drawing threads from a spinning dope, wherein the spinning dope comprises one or more partially or completely hydrolytically condensed compounds of silicon which are derived by hydrolytic condensation from monomers of the general formula SiX_4 in which the X radicals are identical or different and are hydroxy, hydrogen, halogen, amino, alkoxy, alkyloxy, alkylcarbonyl or alkoxycarbonyl or are derived from alkyl radicals and may be interrupted by oxygen or sulfur atoms or by amino groups,

and wherein the bonding between the membrane and the nonwoven is loose and easily broken or non-existent.

The abovementioned multilayer dressing has the following structure:

a nonwoven 1, which is intended to come into contact with the wound, and

a membrane 3, which is water-impermeable and includes at least one water-insoluble polymer, wherein the membrane 3 is wither an adhesive plaster 3 and includes an adhesive portion which adheres to the skin surrounding the wound, or includes no adhesive portion and adheres to the skin surrounding

the wound only when an adhesive has been applied to the skin surrounding the wound,

and where the bonding between membrane 3 and nonwoven 1 is loose and easily broken or non-existent.

and where the bonding between membrane 3 and nonwoven 1 is loose and easily broken or non-existent.

The multilayer dressing is in particular a multilayer dressing whose membrane 3 is as described and whose nonwoven 1 includes biodegradable and/or –absorbable fibrous structures which can be obtained by drawing threads from a spinning dope, where the spinning dope comprises one or more partially or completely hydrolytically condensed compounds of silicon which are derived by hydrolytic condensation from monomers of the general formula SiX_4 in which the X radicals are identical or different and are hydroxy, hydrogen, halogen, amino, alkoxy, alkyloxy, alkylcarbonyl or alkoxycarbonyl or are derived from alkyl radicals and may be interrupted by oxygen or sulfur atoms or by amino groups.

A multilayer dressing as described in the previous paragraph where the X radicals are identical and ethyl is particularly preferred.

Further preferred is a multilayer dressing as described in the penultimate paragraph, where the hydrolytic condensation takes place in the presence of one (or a plurality of) amino acids and/or of one (or a plurality of) peptides and/or of one (or a plurality of) DNA molecule(s) or fragments. In this case, the X radicals in the formula SiX_4 of the silane are optionally identical and are optionally ethyl. The presence of the amino acid(s) and/or peptides and/or DNA/DNA fragments brings about their incorporation into the fibers, by either covalent or non-covalent linkage. The amino acids/peptides/DNA/DNA fragments are released from the fibers, corresponding to the degradation thereof, after the multilayer dressing has been introduced into the wound. In this case, on the one hand the amount of material released (amino acids/peptides/DNA/DNA fragments) is determined by the amount of material incorporated into the fibers (amino acids/peptides/DNA/DNA fragments), but on the

other hand the rate of release from the fibers is also determined by the rate of degradation of the fibers. The fiber property (1) cell adhesion, which is described hereinafter (page 14), makes it possible for the amino acids/peptides/DNA or DNA fragments to be incorporated into the proliferating cells to a particular extent, whereby in particular also a direct influence of the information encoded in the DNA/DNA fragments on the cells is ensured. This circumstance proves to be particularly important and helpful for wounds with reduced regional or even systemic metabolic capacity, because an external supply of the wound region with the amino acids necessary for cellular metabolism is ensured thereby, and wound healing is made possible for the first time thereby.

Figures 1 to 6 are briefly explained here. These figures show

- the diagrammatic structure of a multilayer dressing of the invention (fig. 1);
- the sketch of a perforated die in a die plate (fig. 2);
- a diagrammatic representation of a godet system and of an air-conditioning unit (fig. 3);
- the adhesion of cells to the fiber surface visual by means of SEM (fig. 4), where fig. 4A and B show the SiX_4 fibers used according to the invention without cells, fig. 4C and D show the SiX_4 fibers with cells and their excellent adhesion and distribution and fig. 4E and F show a collagen fiber with cells whose morphology can be ascertained only with difficulty as a result of the rough nature of the collagen matrix;
- the dimensional stability and shrinkage resistance of the SiX_4 fibers used according to the invention compared with collagen fibers and PGA fibers, where the left-hand column shows, from top to bottom, a collagen fiber, a PGA fiber and an SiX_4 fiber according to the invention before cell culturing starts, and where the right-hand column shows, from top to bottom, a collagen fiber, a PGA fiber and an SiX_4 fiber according to the invention four weeks after the start of cell culturing (fig. 5); and
- the metabolic activity of cells (dermal fibroblasts) measured as fluorescence by means of the Alamar blue assay after they have been cultured for 1, 2 and

4 weeks with a collagen fiber, PGA fiber, the SiX_4 (SIX) fiber according to the invention and without fiber for comparison (fig. 6).

As already mentioned, moist nonwovens can be produced from the silica gel fibers or fibrous structures described in DE-C 196 09 551 (of the chemical formula, based on the monomer unit, $SiO_{2-x}OH_x$ or, based on the polymer, $Si_n(OH)_{2x}O_{2n-x}$, with x = 0-1), which are introduced according to the invention as supporting and lead structure into the wound and thus are brought into direct contact with the tissue. The nonwovens are differentiated into fibrous nonwovens and spunbonded nonwovens. The spunbonded nonwovens which are produced from continuous single fibers or filaments are particularly advantageous for 3D applications, while the fibrous nonwovens are particularly suitable for 2D applications.

The method for producing the single fibers/filaments can be taken from the patent DE-C 196 09 551. In this connection, a person skilled in the art will take into account and know that numerous parameters such as temperature, pressure, molar ratio of the individual components, chemical nature of the precursors, of the solvent or of the catalyst can be varied in order to produce where appropriate particularly suitable fibers and nonwovens (with high or lower biodegradability and bioabsorbability).

The method described in DE-C 196 09 551 is to be described here once again, where appropriate in somewhat more detail. It is preferred according to the invention to use TEOS (tetraethoxysilane) as silane in a sol-gel process, although all the silanes mentioned in DE-C 196 09 551, or mixtures of at least two of them, can likewise be used. A condensation product with a suitable degree of condensation is prepared in the presence of hydroalcoholic solution (preferably an ethanol/water mixture according to the invention) which serves on the one hand (ethanol or ethanol/water) as solvent, but on the other hand (water) also as reactant for the hydrolytic condensation, at room temperature or else slightly reduced temperature (12-15°C). A preferred catalyst for the condensation is an organic acid such as citric, succinic or tartaric acid. These acids adjust the pH of the reaction mixture to about 3-4. The pH must always be 7 or below, because particles are formed or the reaction mixture undergoes gellation when alkaline.

The product of the condensation is adjusted where appropriate to a suitable viscosity by filtration and removal of solvent, as is also described in DE-C 196 09 551. It can be stored at temperatures below 0°C for a certain time (several hours to a few months) to obtain a so-called spinning sol (a spinning dope), because the condensation proceeds only very slowly at temperatures below 0°C. The spinning sol preferably has a solids content (solids mean (partial) condensation products, i.e. oligomers or oligomeric structures) of about 10% (i.e. the solvent content is about 90%). It is likewise preferred according to the invention for the period from the start of the condensation reaction to the obtaining of the spinning sol to be 2-3 days.

The spinning sol is finally put into a precooled (<0°C) pressurized vessel out of which it is forced through small dies under pressure in the form of long, non-breaking or breaking-resistant threads. The threads have, depending on the size of the dies, a diameter of about 10 to 100 µm and a length of several (e.g. 3-5) m. If the threads are wound up, they can be further extended and their diameter further reduced where appropriate by drawing (stretching) during the winding up (where appropriate in a hydroalcoholic atmosphere). The winding up of the threads takes place with spinning speeds of 100-1000 m/min, preferably with speeds of about 200 m/min. The threads spun in this way can be intermingled over a roll on a carrier belt. The threads on the carrier belt can then be exposed to various temperatures by the carrier belt traveling at a speed of 1-10 cm/min through various temperature zones so that, through a condensation reaction proceeding further, the number of OH groups remaining in the fibers (i.e. the biodegradability and bioabsorbability of the fibers) can be adjusted as desired (it is preferred according to the invention to cool the threads in the form of gel filaments on the carrier belt instantaneously to -35°C).

The intermingled threads (continuous fibers) are then compressed to give (spunbonded or fibrous) nonwovens. The compression is effected by a pressure roll. In this case, needle devices (pressure rolls with needles) are frequently also employed. The movement of the needles up and down results in a milling process which confers an additional strength on the nonwoven. The pressure of the roll with

and without needles can be adjusted without restriction. The pressure required according to the invention is typically 1-10 MPa. The nonwoven then undergoes a thermal treatment, with the temperatures varying in the range from -35°C to +65°C. A temperature below -5°C is preferred, and a temperature below -20°C is particularly preferred. This thermal treatment results in a structurally strong bonded fabric with a simultaneously sufficient number of silanol, i.e. non-condensed OH, groups in the nonwoven. The number of non-condensed OH groups controls the (bio)absorbability: more non-condensed OH groups present mean a greater (bio)absorbability. The number of OH groups can be adjusted specifically by varying the holdup times at various temperatures. The fibers of the nonwoven to be used according to the invention preferably have about one OH group per 5-10 Si atoms, meaning $SiO_{2-x}OH_x$ with x = 0.1-0.2 in the above formula for the monomer unit.

The nonwoven is subsequently where appropriate brought to a temperature of 50°C or to a temperature above 50°C in order to remove any water and ethanol still present (e.g. from the solvent, but also from the residues of the initial silane, in particular when TEOS is initial silane) to the desired extent, but usually not completely. This is because it is desirable according to the invention for the (e.g. spunbonded) nonwovens to retain a sufficient residual moisture in order to stabilize the thermodynamically unfavored gel state (fibers with non-condensed OH groups in the nonwoven) compared with the SiO_2 which is more favored at room temperature (fibers without non-condensed OH groups, i.e. glass fibers, in the nonwoven). Spunbonded nonwovens produced in this way can retain their gel state over several months in closed (airtight) packages. The presence of residual ethanol, but also that of water, proves to be particularly advantageous in this connection. This probably derives from the fact that, in a (saturated) ethanol atmosphere, condensation does not proceed in the direction of SiO_2. On the contrary, it may in some cases be reversed, ultimately determining the bioabsorbability of the fiber.

The described method is used to produce spunbonded nonwovens. However, fibrous nonwovens – often called needle-punched nonwovens – can also be produced in this way. In this case, the fibers are cut into pieces after the spinning process. These

staple fibers have lengths of 0.1-10 cm. The staple fibers are subsequently dropped onto a carrier belt, pressed, needled and subjected to a thermal treatment as described above. In contrast to spunbonded nonwovens, the fibrous nonwovens have no pronounced 3D structure. They are therefore frequently employed in 2D applications (superficial injuries in the upper epidermal level). The use of fibrous nonwovens is therefore particularly advantageous according to the invention in the management of superficial wounds (upper epidermal level). It can generally be stated that fibrous nonwovens have in general greater strengths in the plane of the fibers and are therefore better suited for places under mechanical stress, e.g. skin over muscles.

The above-described production of the fiber takes place in the sol-gel process on a machine with, for example, a length of about 5 m, a width of about 2 m and a height of about 6 m. The weight of the machine results in a pressure of from 850 to 1000 kg/m^2 in the region underneath the spinning tower. However, the dimensions of the machine may also differ considerably from the magnitudes mentioned here, depending on the fittings and capacity. For production, the machine requires a cooling water circulation with adequate water supply, and preferably a heavy-current connection.

At the current time, the fiber is produced according to the invention on an air-conditioned spinning system. The air-conditioned spinning system is provided with entering air which has a defined temperature and humidity by an air-conditioning unit which is driven by circulating air. Temperatures in the range from 10 to 40°C are preferred, especially temperatures of about 20°C. The unit is an air-conditioned testing cabinet designated SB22/160/40-UKA supplied by Weiß Umwelttechnik GmbH. It was retrofitted for circulating air operation by Weiß. In an insulated spinning tower which is 2 m long and which has an external diameter of 680 mm, an inner pipe with a diameter of 300 mm and with 3 mm circular perforations is inserted to avoid interfering compression by the circulating air operation. The spinning tower is connected to a box in which the winding devices for the abovementioned continuous fibers or filaments are located. The panes of the box were made of window glass (thickness 24 mm) for sufficient insulation and have a K value of 1.1.

The air leaving the box is returned to the air-conditioning unit and processed there. The sensor for the air conditioning is in this case not the interior of the unit but an external probe in the spinning shaft. For actuation of the air-conditioning equipment, which is also possible manually, a PC provided with appropriate software by the manufacturer was attached. It is possible with the aid of the PCC_WIN, Version 1.05 program to preset temperature and humidity programs and all other necessary settings for the unit. When the spinning is in progress, a plotter can represent the temperature and humidity in the spinning shaft as a function of time. An additional temperature probe was attached to measure the external temperature, and this value is acquired digitally. For upgrading the spinning system with process control technology, all the essential measurement points are equipped with an analog output.

The connections for entering and leaving air between air-conditioning unit and spinning tower or box consist of flexible, doubly insulated tubing with an internal diameter of 100 mm (external diameter: 250 mm). The connections were in each case covered with Armaflex. Since ethanol is released where appropriate from the spinning dope during the spinning process and may accumulate in the closed circulation of air-conditioning unit, spinning tower and box, the system has been equipped with a gas-warning device from GfG Gesellschaft für Gerätebau. A sensor calibrated for ethanol and designated MWG 0238 EX was installed in each case in the box in the direct vicinity of the motors, and in the test chamber of the air-conditioning circulating air unit. An evaluation unit (GMA· 100-BG) gives a first alarm when the concentration of the ethanol in the chamber air has reached 25% of the lower explosive limit for ethanol, and a second alarm when 50% of the lower explosive limit is reached. An alarm is likewise triggered if the sensor breaks down or malfunctions.

A bellows gate valve and an adapter flange with three possibilities for connection is attached at the upper end of the spinning tower, onto which the jacketed spinning head which is insulated to the outside can be installed. According to the test report of the pressure testing, the spinning head is suitable for a pressure of up to 50 bar

(5×10^6 PA). With an internal diameter of 45 mm, the spinning head has a capacity of 0.33 liter of spinning dope.

The die plate is attached on the underside of the spinning head. The plate with a diameter of 89 mm has a recess 1.5 mm deep, into which a stainless steel fabric in an aluminum holder is inserted. The wire fabric has two layers, the first layer having a mesh width of 80 µm.

The second supporting layer has a mesh width of 315 µm. The aluminum holder of the wire fabric is designed so that it protrudes by 0.5 mm when the network is placed in the die plate. When the plate with the network is screwed with 15 Nm onto the spinning head, the compressed Al ring ensures the necessary seal between spinning head and plate. Die plates with 7 and 19 orifices were used. The approach bore of an orifice is 3.0 mm wide, and the orifice diameter is 0.15 mm. A capillary length of 0.45 mm results in an L/D ratio of 3. A sketch of a perforated die in a die plate is shown in fig. 2.

The temperature of the jacketed spinning head is controlled with the aid of a LAUDA thermostat (designation RE 112), the inlet and outlet tubing being covered with Armaflex for insulation.

Viewing glasses are inserted into the three connections of the adapter flange between spinning head and tower in such a way that the emergence of the threads from the dies can be observed during the spinning process. In the design of a filament-laying device, besides a winding unit, account was also taken of the possibility of fiber bailing via a gas-conveying nozzle. For this purpose, a system of two godets with a length of 159 mm and 220 mm was designed for the draft of the filaments, the rear godet being inclined by 8° relative to the one at the front. Drive takes place via a motor-tacho combination (designation S4.3 G 60) and transmission (designation 381, 3.71:1) from Faulhaber. The rotation rate of the first godet is automatically taken over by the second godet.

The second godet can be rotated up to 10% faster via a draft controller. A third godet serves as winder and can be operated independently of the draft unit. It consists of a mandrel which is likewise actuated by a motor-tacho combination from Faulhaber, and a cardboard roll can be gripped on the mandrel. This cardboard roll is composed of five separate circular segments which are connected by a spring construction to give a circle diameter of 159 mm. In the relaxed state, the diameter of the roll is reduced from 159 mm to 143 mm. The five segments are laminated on the outside with a Teflon sheet.

The third godet is installed on a charging unit from Isel-Automation. Using a stepping motor with the designation 160 MCM, the winding device can be charged over a length of 500 mm. The charging rate from the advance and return of the unit can be set at values from 2 to 16 min^{-1}, and the godet can be run manually with a second control unit. A control unit for the godet motors and the charging stepping motor was constructed from controllers (IT 142-C), a 1-axis stepping motor control with adapter card and a control card (UMS 6) from Isel-Automation. A diagrammatic representation of the godet system and of the air-conditioning unit is to be found in fig. 3.

It is advantageous according to the invention for the nonwovens (in the subsequent text, just the term nonwoven is used as synonymous with spunbonded nonwoven and fibrous nonwoven) to be placed in or on wounds which are provided with externally supplied physiological solutions such as physiological saline solution (0.9%) either by first intention without secretion or by second intention. The absorption of the nonwoven in the wound during the healing process makes it unnecessary to remove the nonwoven during or after the wound healing. The fiber thickness can be adjusted without restriction owing to the compaction process in the nonwoven and is varied according to the nature and depth of the wound. Typical areas of application are for wound depths of 1-20 mm, preferably 2-12 mm, substantially independently of the thickness of the epidermis.

In addition, it is possible by varying the production parameters for the continuous fibers and the nonwovens (choice of the groups X in SiX_4, choice of the reaction conditions for the hydrolytic condensation, and thus choice of the proportion of non-polymerized groups, etc., see DE-C 196 09 551) for the absorption time of the fibers and thus of the nonwoven to be adjusted and adapted to the conditions of the wound. Thus, depending on requirements, the absorption time can be adjusted to from 3 to 180 days, it being possible to extend the interval continuously upward as desired. In this connection, the inventors have found that it is possible by varying the number of OH groups in the fiber or the nonwoven, and by adding morphogenic factors (healing promoters) which are linked to the fibers (in the nonwoven) chemically via OH groups or physically by physisorption on the extremely large, highly hydrophilic surface, for the absorption time of the nonwoven to be adjusted and adapted to the moist wound conditions. It has proved to be advantageous for a functional OH group to be present every fifth to tenth Si atom. A functional OH group means in this connection a possible free reaction site in the form of an OH group where, for example, medicaments such as antibiotics, antimycotics, steroids and generally medicaments with local or systemic effect can be coupled by hydrogen bonds or condensation to the nonwoven and are then released gradually in the wound (drug release). The absorption times are then around about 30 days, and the degradation products (SiO_2 or SiO(OH) as nanoparticles) typically have a diameter of 0.5-1 nm. The structure is elucidated accurately in this case by Si solid-state NMR, in particular by Q4 mode measurement. Pressures preferred according to the invention are typically 1-10 bar (10^5-10^6 Pa), preferably 2-3 bar, and reaction times in the spinning process are preferably 20-60 s, while the temperatures (in the spinning process) are preferably kept at 15-23°C, in particular at about 20°C.

Owing to the geometry of the fibers, there is in fact observed to be a promotion of wound healing (tissue guiding). In this connection, the highly hydrophilic gel fibers in a two- or three-dimensional arrangement serve as physical lead structure to which the proliferating cells can adhere and can form a usually collagenous matrix which is appropriate for the location. Since the chemical environment of the fiber has an approximately neutral pH (pH 7.0 ± 0.2), and no organic decomposition products are

formed, no foreign-body reactions or irritations of the newly forming cells occur. On the contrary, wound healing is continuously physiologically stimulated by accumulation of the abovementioned morphogenic factors (steroids, cytokines, TNF-alpha, TGF-beta 1/2, interleukins such as IL-1, PDGF, EGF etc.) which are secreted by the wound. In contrast to gelatinous and viscous matrix materials from the organic sector (collagen, hyaluronic acid, fibrin), the inorganic fiber is not associated with a potential risk of infection with known (HIV, HBV, BSE, prions etc.) and hitherto unknown sources of infection. In addition, the material parameters of inorganic materials can be defined and adjusted extremely accurately. The quality and the property profile are considerably improved thereby in comparison with organic materials.

The fiber used according to the invention differs distinctly from conventional biodegradable and bioabsorbable biomaterials by at least the following four features or properties: it permits (1) improved cell adhesion (adhesion of the cells to the fiber), and it enables (in complete contrast to known materials) (2) cell proliferation (cell multiplication), (3) maintenance of the shape and stability of the fiber and (4) long-term maintenance of cell proliferation and cell metabolism.

(1) Cell adhesion:

The particular geometry and morphology of the fibers allows in all cases faster initialization and qualitatively better adhesion of cells to the fiber surface by comparison with conventional bioabsorbable materials (such as polyglycolic acid (PGA), alginates and collagen) (this improvement is depicted in fig. 4). A fast and reliable distribution/sprouting of cells in all regions of the wound along the fiber present in the wound is guaranteed thereby. Starting from cells adhering to fibers, a reliable distribution of newly formed cells even remotely from the fiber is additionally favored (key word: cell compound proliferation). It has been possible impressively to demonstrate this advantageous property of the fiber used according to the invention by use of scanning electron microscopy (SEM), histological and immunohistological investigations, and confocal microscopy.

(2) Cell proliferation:

The particular geometry and morphology of the fibers permits a faster/earlier start, a speeding up/increase and a longer duration/maintenance of cell proliferation by comparison with conventional biodegradable/bioabsorbable materials. This property favors the advantages detailed under (1) in relation to the utilization of the properties of the fiber, of making possible for the cells a faster and qualitatively better adhesion of cells to the fiber surface. The metabolic activity of the cells, measured by the Alamar blue assay as reference parameter for the cell proliferation and activity of the cells, is distinctly increased after a short to medium period of 1, 2 and 4 weeks by comparison with conventional materials such as PGA and collagen. The ratio of the metabolic activity of the cells with the matrix of PGA or collagen or SiX_4 (fiber according to the invention) is 1:5:11 (1 week), 2.5:1:6 (2 weeks) and 1.2:0.8:6 (4 weeks). Initially (after 24 h), however, this ratio was only 1:4.5:4. This demonstrates that the fiber used according to the invention displays its advantages only after a lengthy period of at least one week, better 4 weeks.

(3) Maintenance of shape and stability of the fiber:

As it has been possible to confirm by using SEM, histological and macroscopic investigations, the fiber according to the invention allows long-lasting maintenance of the three-dimensional shape and a delayed contraction of the three-dimensional fiber configuration (geometry and morphology of the fibers are very substantially retained) by comparison with conventional bioabsorbable materials: conventional materials such as PGA and collagen shrink (vitrify) by a factor of 4 and 6, respectively, over a period of 4 weeks and moreover where appropriate also lose their shape, whereas the fiber according to the invention can completely maintain shape and stability over this period (this phenomenon is depicted in fig. 5). This circumstance ensures a reliable construction of newly formed tissue and guarantees, even with large wounds, an adequate diffusion of nutrients and metabolic products. In addition, unlike the less dimensionally stable materials known in the art for this purpose, new vessel formation is made possible and promoted. This means that new vessel and tissue formation even with large wounds, and thus healing thereof, is made possible for the first time by the material according to the invention, unlike the

materials known in the art, such as PGA or collagen. An important aspect in this connection is the dimensional stability of the fiber according to the invention, particularly in the skin region, which brings about a mechanical stabilization. The newly formed tissue can be supplied adequately with nutrients on use of the multilayer dressing according to the invention. This supply takes place not only by diffusion but also by direct transport of the nutrients through the newly formed vessels/tissues in the open-pore nonwoven. In relation to dimensional stability, the beneficial properties (cell proliferation, cell adhesion) described in (1) and (2) add up.

It has been possible impressively to demonstrate this by using the following analytical methods: scanning electron microscopy (SEM), histology, macroscopy.

(4) Long-term maintenance of cell proliferation and cell metabolism:

The particular geometry and morphology of the fibers permits a long-lasting maintenance of cell proliferation by comparison with conventional bioabsorbable biomaterials, thus achieving reliable tissue construction/regeneration. The metabolic activity of the cells, once again measured by the Alamar blue assay as reference parameter for the cell proliferation and activity of the cells, is distinctly superior after a period of 4 weeks with the SiX_4 fiber used according to the invention by comparison with conventional biomaterials such as PGA and collagen: the collagen:PGA:SiX_4 ratio is 1:1.5:12 (fig. 6).

The abovementioned Alamar blue assay (alamarBlue™ reduction) will be briefly explained here.

The interior of proliferating cells is more greatly reduced than that of non-proliferating cells. In particular, the NADPH/NADP, FADH/FAD, FMNH/FMN, and NADH/NAD ratios are larger during proliferation. Substances such as alamarBlue™ which are reduced by these metabolic intermediates can be used to measure and record the proliferation of cells. The redox potential of alamarBlue™ is +380 mV (pH 7.0, 25°C). alamarBlue™ is therefore reduced by NADPH (Eo=-320 mV), FADH (Eo=-220 mV), FMNH (Eo=-210 mV), NADH (Eo =-320 mV) and cytochromes (Eo=290 mV to +80 mV). Since, as a consequence, alamarBlue™ can

receive electrons from these substances, it also changes its color along with its redox state: from the oxidized, indigo-blue and non-fluorescent state to the reduced fluorescent pink state. The extent of the proliferation can then be followed by spectrophotometry, either by color measurement or by means of fluorescence (concerning this, see also the internet site of Biosource Inc., Camarillo, California, (USA), with the address www.lucernachem.ch/downloads/biosource/alamarbluebooklet.pdf).

The nonwoven is preferably produced, as already mentioned above, in a saturated alcoholic solution. The nonwoven is therefore sterile. The size of the nonwoven can be chosen entirely without restriction and can be adapted to the sizes of current wound dressings, typically 10×10 cm, 5×5 cm or 2.5×2.5 cm (all other dimensions can likewise be chosen).

Two different variants are available for suitable storage of the nonwoven: either the nonwoven is put in a sterile and impermeable package (e.g. in aluminum) and stored or dispatched for later processing. It is additionally possible to introduce into the sterile package a depot, e.g. cotton, impregnated with alcohol in order to maintain the saturated alcohol atmosphere. As an alternative to this, the nonwoven is directly processed further to a multilayer dressing (the structure of one such is described hereinafter and by way of example in fig. 1), i.e. joined to a water-impermeable or semipermeable adhesive membrane (e.g. a polyurethane or polyester sheet). This membrane is referred to hereinafter as adhesive plaster 3 or membrane 3, although the membrane/sheet need not per se be adhesive at all.

The fibers and nonwovens are preferably kept through the preparation and production period (from the production of the fibers to introduction of the nonwoven into the wound) preferably in a saturated alcohol atmosphere in order to prevent further condensation of the Si-containing fiber material and, associated therewith, a loss of biodegradability of the fiber. This is achieved for example by means of a so-called in-line production process which is carried out in a saturated alcohol atmosphere up to the final product. This additionally has the advantage that a

sterilization method (e.g. a gamma sterilization) is not necessary after the nonwoven or the multilayer dressing has been produced.

A typical multilayer dressing according to the present invention, fitted into a wound, is depicted in figure 1. However, other multilayer dressings are also conceivable according to the invention and are presented hereinafter.

A so-called further membrane 2 is applied to the nonwoven 1, i.e. between nonwoven 1 and membrane/adhesive plaster 3, which has in the embodiment described here an adhesive membrane/sheet (but which in other embodiments may also merely be a water-impermeable or semipermeable membrane/sheet) and in this embodiment represents the dressing means, so that the nonwoven 1 is not removed from the wound 4 when the adhesive plaster 3/the membrane 3 lying on top is pulled off or changed. The adhesive plaster 3/the membrane 3 ensures that the wound is reliably sealed against the external environment by the use of the multilayer dressing according to the invention. The further membrane 2 is in one embodiment not firmly connected either to the nonwoven 1 or to the membrane 3/the adhesive plaster 3. Nevertheless, a firm connection with the membrane 3/the adhesive plaster 3 may exist. The crucial factor in this connection is that no portions of the nonwoven 1 and of the newly formed tissue are removed when the membrane 3/the adhesive plaster 3 is removed. Attachment of the membrane 2, which consists of a water-soluble polymer (any polymer which does not adhere to the nonwoven) and preferably of carboxymethylcellulose (CMC) to the nonwoven 1 takes place for example by hydrogen bonds. The choice of the polymer is not crucial in this connection (water-soluble collagens or fibrin gels can also be employed here) because the membrane 2 merely ensures that the adhesive membrane/sheet of the adhesive plaster 3 does not adhere to the nonwoven 1. This embodiment is depicted in fig. 1.

In a further embodiment, the further membrane 2 can be dispensed with since the dressing means used does not adhere to the wound and acts as further membrane 2 and makes the latter redundant. Such dressing means which do not adhere to the wound include alginates (in compress form or as tamponade), collagen sponges, polyurethane foams and foam dressings, hydrocolloids, hydrogels and

hydropolymers. In this case, the membrane 3 is once again, for sealing the wound, fastened as shown in figure 1 with an adhesive (on the undamaged skin surrounding the wound), the adhesive preferably being a polyacrylate adhesive, a rubber adhesive, or a synthetic rubber adhesive produced by the hotmelt process.

In a further embodiment of the present invention, a dressing means is applied to the nonwoven 1 and firstly does not adhere to the wound (and therefore again acts as further membrane 2 and makes the latter redundant) and secondly has adhesive properties and thus seals the wound to the outside. Such a dressing means can be selected for example from the group of "foam dressings" (hydropolymer dressings, especially polyurethane foam dressings, e.g. foam dressings from 3M, Silastic from Dow Corning, marketed by Calmic Medical Division, Allevyu from Smith and Nephew, Lyofoam from Seton Healthcare Group plc), since these foam dressings have inter alia a large liquid storage capacity (see Bello (2000) JAMA 283(6): 716-8; Degreef (1998) Dermatologic Clinics 16(2): 362-75; Findlay (1996) Am Fam Physician 54(5): 1519-28; Habif (1996) Clinical Derm. Mosby, 810-13; Knapp (1999) Ped Clin N Am 46(6):1201-13; Krasner (1995) Prevention Management Pressure Ulcers; Lewis (1996) Med-Surg Nursing, Mosby, p. 199-200; Lueckenotte (1996) Gerontologic Nurs., Mosby, 800-7; PUGP (1995) Am Fam Physician 51(5):1207-22; PUGP (1994) Pressure Ulcer Treatment, AHCPR 95-0653; Way (1991) Current Surgical, Lange, 95-108; or at the following internet addresses: http://med2med.de/pages/produktdetail.cfm?prod=85696&katid=6618 and http://wound.smithnephew.com/de/node.asp?NodeId=2692). In a further embodiment of the invention, however, it is also possible to dispense completely (entirely) with the further membrane 2 when the adhesive plaster 3 (which in this case does not necessarily have adhesive properties) can be applied directly to the nonwoven 1, because it is ensured that the adhesive membrane/sheet of the adhesive plaster 3 bonds exclusively to the skin surrounding the wound, and thus adhesion of the adhesive plaster 3 to the nonwoven 1 is impossible. This can be achieved for example by either wetting, before the covering process, exclusively the skin surrounding the wound with an adhesive (e.g. with Leukospray® from Baiersdorf) (in this case, therefore, the adhesive plaster 3 itself has no adhesive property and is

therefore more appropriately designated membrane 3), or the adhesive plaster 3 being chosen or cut appropriate for the wound size (in this case, the adhesive plaster 3 has an adhesive property only at the places which are not to be brought into contact with the wound).

The adhesive plaster 3/the membrane 3 consists according to the invention of a water-impermeable sheet of at least one water-insoluble polymer, preferably PP, PVC or PU. It additionally has where appropriate (see the various embodiments described above) an adhesive normally used in dressing techniques (preferably a polyacrylate adhesive or a synthetic rubber adhesive produced by the hotmelt process, where appropriate also a rubber adhesive), which ought preferably to have particularly good compatibility with skin. The adhesive can be applied to the water-impermeable sheet even during or before the production of the multilayer dressing. However, it is also possible, as mentioned above, for it to be applied or sprayed only by the user to the regions surrounding the wound, or to the membrane/sheet.

The water-impermeable adhesive plaster 3/the water-impermeable membrane 3 ensures that no moisture evaporates outwards and thus a moist wound environment is permanently maintained, thus contributing to the absorption of the fibers of the nonwoven. The absorption of the fibers also brings about the release of the substances bound where appropriate to the fibers, i.e. for example a release and accumulation of ions (e.g. Ag ions), medicaments (e.g. antibiotics, corticoids) or morphogenic factors. These morphogenic factors (also called morphogens), which are also formed by the body during the wound healing, have a beneficial influence on wound healing and are indispensable for good wound healing, include interleukins, bone morphogenetic proteins (BMPs), antibodies, TGF-β and IGF.

The water-solubility of the polymer of further membrane 2 makes it easy to detach this membrane (where present) after acting for a certain time (the aqueous wound secretion gradually detaches the nonwoven from the further membrane 2, so that no damage to the tissue occurs when the membrane 2 is lifted). Advantageously, silver-doped polymers are employed as further membrane 2 in order to reduce the risk of infection.

A floating dressing is sensible for particularly large wounds (>10 cm^2) because in some circumstances the adhesive forces of the further membrane 2 for the nonwoven 1 then become too large. In these cases, hydrogels are possible as thin (< 5 mm) floating layer as separating medium.

Embodiments preferred according to the invention are described by the following multilayer dressings.

1. A multilayer dressing which comprises a nonwoven 1, which is intended to come into contact with the wound, and a membrane 3, which is water-impermeable and includes at least one water-insoluble polymer, where the membrane 3 is an adhesive plaster 3 and includes an adhesive portion which adheres to the skin surrounding the wound, and where the bonding between membrane 3 and nonwoven 1 is loose and easily broken or non-existent.
2. A multilayer dressing which comprises a nonwoven 1, which is intended to come into contact with the wound, and a membrane 3, which is water-impermeable and includes at least one water-insoluble polymer, where the membrane 3 includes no adhesive portion and adheres to the skin surrounding the wound only when an adhesive has been applied to the skin surrounding the wound, and where the bonding between membrane 3 and nonwoven 1 is loose and easily broken or non-existent.
3. A multilayer dressing as claimed in claim 1 or according to embodiment 1 or 2, where the at least one water-insoluble polymer of the membrane 3 is PP, PVC or PU.
4. A multilayer dressing according to embodiment 3, where the membrane 3 is a self-adhesive hydropolymer.
5. A multilayer dressing as claimed in claim 1 or according to embodiment 1, 2 or 3, where the multilayer dressing further comprises a further membrane 2 between membrane 3 and nonwoven 1, which includes at least one water-soluble polymer.

6. A multilayer dressing according to embodiment 5, where the at least one water-soluble polymer is CMC.

7. A multilayer dressing according to embodiment 5 or 6, where the bonding between further membrane 2 and nonwoven 1 is loose and easily broken.

8. A multilayer dressing according to embodiment 5 or 6, where the bonding between further membrane 2 and nonwoven 1 is non-existent.

9. A multilayer dressing according to embodiment 5, 6, 7 or 8, where the bonding between further membrane 2 and membrane 3 (i) is non-existent, (ii) is loose and easily broken or (iii) is stable and unbreakable.

10. A multilayer dressing as claimed in claim 1 or according to embodiment 1 to 4, where the multilayer dressing further comprises an alginate, a collagen sponge, a polyurethane foam or foam layer, a hydrocolloid, a hydrogel or a hydropolymer between membrane 3 and nonwoven 1.

11. A multilayer dressing according to embodiment 10, where the bonding between the alginate, the collagen sponge, the polyurethane foam or foam layer, the hydrocolloid, the hydrogel or the hydropolymer and nonwoven 1 is loose and easily broken.

12. A multilayer dressing according to embodiment 10, where the bonding between the alginate, the collagen sponge, the polyurethane foam or foam layer, the hydrocolloid, the hydrogel or the hydropolymer and nonwoven 1 is non-existent.

13. A multilayer dressing according to embodiment 10, 11 or 12, where the bonding between the alginate, the collagen sponge, the polyurethane foam or foam layer, the hydrocolloid, the hydrogel or the hydropolymer and membrane 3 (i) is non-existent, (ii) is loose and easily broken or (iii) is stable and unbreakable.

It is possible if required also to apply (further) dressing material (e.g. absorbent gauze) or other material (e.g. for padding or protecting the wound) to the multilayer dressing according to the invention described on this and the preceding page in its various embodiments. In the context of this disclosure, therefore, a distinction is

made herein between dressing means (as constituent of the multilayer dressing) and dressing material.

Before the nonwoven is put onto/into the wound or processed to the multilayer dressing (i.e. after its production, i.e. during its storage or its transport, either as simple nonwoven or as multilayer dressing), it is preferably sealed on the surface which later comes into contact with the wound, by an impermeable membrane which prevents the alcohol escaping. The membrane is pulled off by the user where appropriate immediately before application into the wound. In this preferred embodiment, however, it is necessary to remember that alcohol, as explained above, although it stabilizes the sterility and the fiber chemistry, is extremely painful when brought into contact with the wound. It is therefore possible in a further preferred embodiment to use physiological saline solution as medium. Alternatively, the alcohol can be evaporated or washed out before use, thus making the use complicated overall, however.

Typical dressing means with which the nonwoven can be combined are for example the following products (trademark designations):
Dermaplast Film/Active und Hydractive®; Hydrofilm Plus®; Hydrocoll® (Hartmann);
Comfeel(-Plus)®, Biatain®, Seasorb®, Contreet® (Coloplast)
Cutinova Hydro®, Acticoat®, Allevyn® (Smith&Nephew)

The nonwoven may, however, also be combined with all variants of products or be available on the market, e.g. with the following products of Smith & Nephew (all registered trademarks):
Hydrogel dressings, IntraSite Conformable, IntraSite Gel, hydroselective wound dressings, Cutinova Hydro (e.g. hydrocellular foam wound dressings), Allevyn product group (e.g. alginates, antimicrobial wound dressings, enzymatic debridement, odor-absorbing dressings, postoperative dressings), Cutiplast Steril, Hansapor Steril, OpSite Post-Op, Primapore (e.g. special dressings), Allevyn tracheostomy, Cavi-Care, EXU-DRY.

Thus, the nonwoven can for example be combined with polyurethane or PVA sponge dressings in order to increase the absorbency for heavily secreting wounds. The advantages which have been mentioned for the invention are evident in particular when vacuum systems (e.g. V.A.C®) are used, e.g. in the treatment of septic wounds and when there is a need for antibiotic irrigations. In addition, the nonwoven can also be combined with the alginate tamponades mentioned hereinabove as covering in the contex t of hydrocolloid wound dressings.

The shape of the multilayer dressing may be varied according to the location of the wound and its shape and extent in order to achieve adaption as accurately as possible to the anatomy of the wound. A possible shape of the dressing is the butterfly shape, which can be used in the anal region.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as, an acknowledgement or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The claims defining the invention are as follows:

1. A multilayer dressing comprising:
a nonwoven, which is intended to come into contact with a wound, and
a water-impermeable membrane comprising at least one water-insoluble polymer, wherein the membrane is an adhesive plaster comprising an adhesive portion that adheres to the skin surrounding the wound, or comprises no adhesive portion and adheres to the skin surrounding the wound only when an adhesive has been applied to the skin surrounding the wound,
wherein the nonwoven includes biodegradable and/or -absorbable fibrous structures obtained by drawing threads from a spinning dope, wherein the spinning dope comprises one or more partially or completely hydrolytically condensed compounds of silicon which are derived by hydrolytic condensation from monomers of the general formula SiX_4 in which the X radicals are identical or different and are hydroxy, hydrogen, halogen, amino, alkoxy, alkyloxy, alkylcarbonyl or alkoxycarbonyl or are derived from alkyl radicals and may be interrupted by oxygen or sulfur atoms or by amino groups,
and wherein the bonding between the membrane and the nonwoven is loose and easily broken or non-existent.

2. The multilayer dressing as claimed in claim 1, wherein the at least one water-insoluble polymer of the membrane is PP, PVC or PU.

3. The multilayer dressing as claimed in claim 1 or 2, where the membrane is a self-adhesive hydropolymer.

4. The multilayer dressing as claimed in any one of claims 1 to 3, further comprising a further membrane between the water-impermeable membrane and the nonwoven, the further membrane comprising at least one water-soluble polymer.

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5. The multilayer dressing as claimed in claim 4, wherein the at least one water-soluble polymer is CMC.

6. The multilayer dressing as claimed in claim 4 or 5, wherein the bonding between the further membrane and the nonwoven is loose and easily broken.

7. The multilayer dressing as claimed in claim 4 or 5, wherein the bonding between the further membrane and the nonwoven is non-existent.

8. The multilayer dressing as claimed in any one of claims 4 to 7, wherein the bonding between the further membrane and the water-impermeable membrane (i) is non-existent, (ii) is loose and easily broken or (iii) is stable and unbreakable.

9. The multilayer dressing as claimed in any one of claims 1 to 3, wherein the multilayer dressing further comprises an alginate, a collagen sponge, a polyurethane foam or foam layer, a hydrocolloid, a hydrogel or a hydropolymer between the water-impermeable membrane and the nonwoven.

10. The multilayer dressing as claimed in claim 9, wherein the bonding between the alginate, the collagen sponge, the polyurethane foam or foam layer, the hydrocolloid, the hydrogel or the hydropolymer and the nonwoven is loose and easily broken.

11. The multilayer dressing as claimed in claim 9, wherein the bonding between the alginate, the collagen sponge, the polyurethane foam or foam layer, the hydrocolloid, the hydrogel or the hydropolymer and the nonwoven is non-existent.

12. The multilayer dressing as claimed in any one of claims 9 to 11, wherein the bonding between the alginate, the collagen sponge, the polyurethane foam or foam layer, the hydrocolloid, the hydrogel or the hydropolymer and the water-

impermeable membrane (i) is non-existent, (ii) is loose and easily broken or (iii) is stable and unbreakable.

13. The multilayer dressing as claimed in any one of claims 1 to 12, wherein the X radicals are identical and are ethyl.

14. The multilayer dressing as claimed in any one of claims 1 to 13, wherein the hydrolytic condensation takes place in the presence of one or more amino acids, one or more peptides or one or more DNA molecules or fragments.

15. A multilayer dressing as claimed in claim 1, substantially as herein described with reference to the drawings.

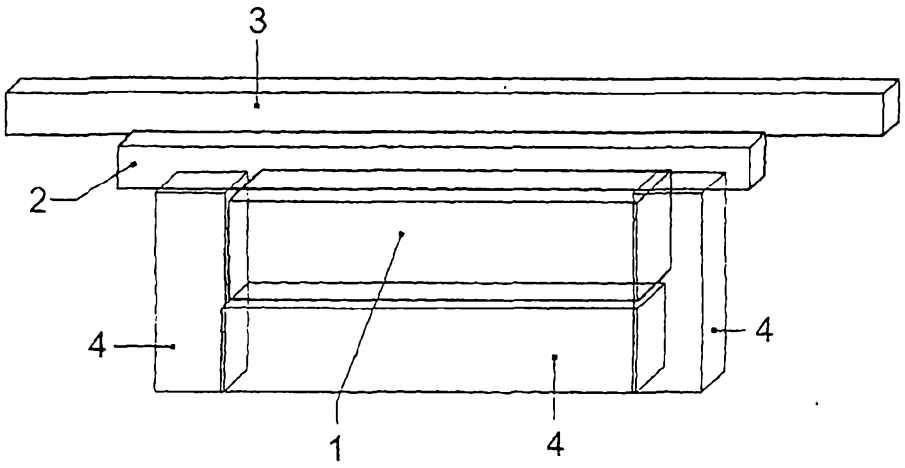


Fig. 1

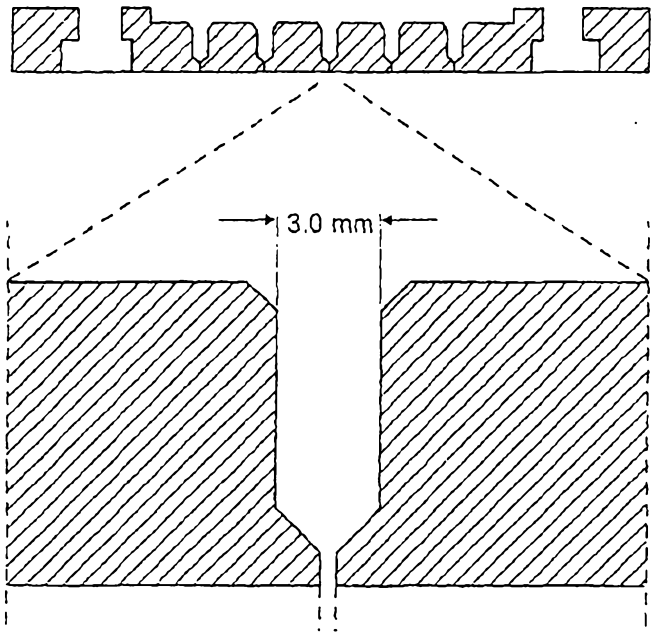
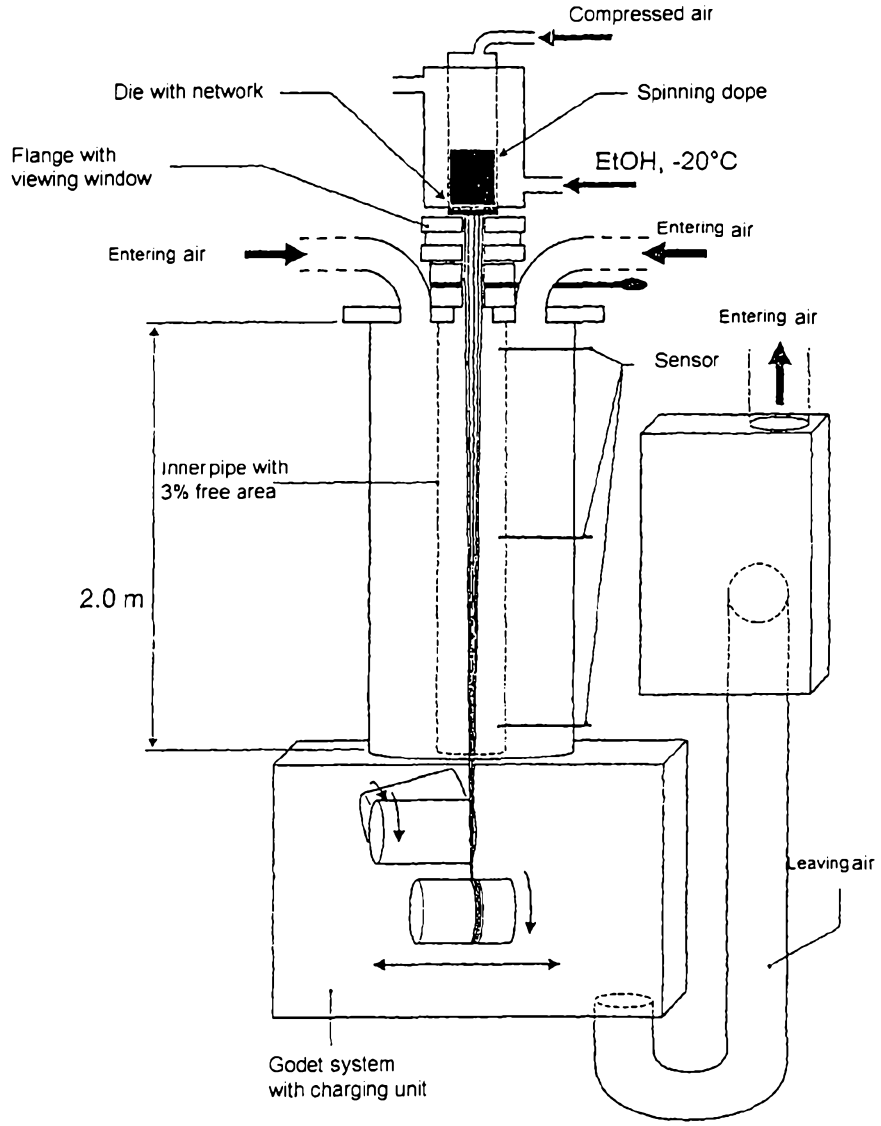


Fig. 2


Compressed air
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viewing window
EtOH, -20°C
Entering air
Entering air
Entering air
Sensor
Inner pipe with
3% free area
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with charging unit

Fig. 3

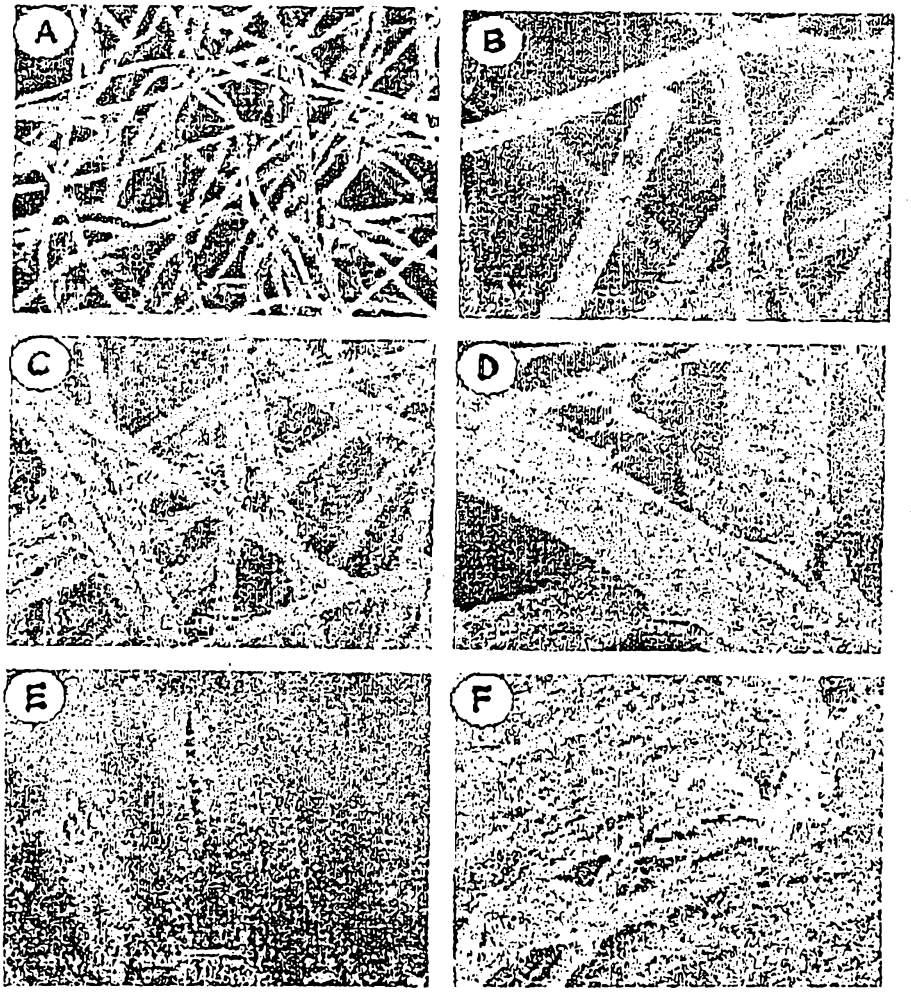


Fig. 4

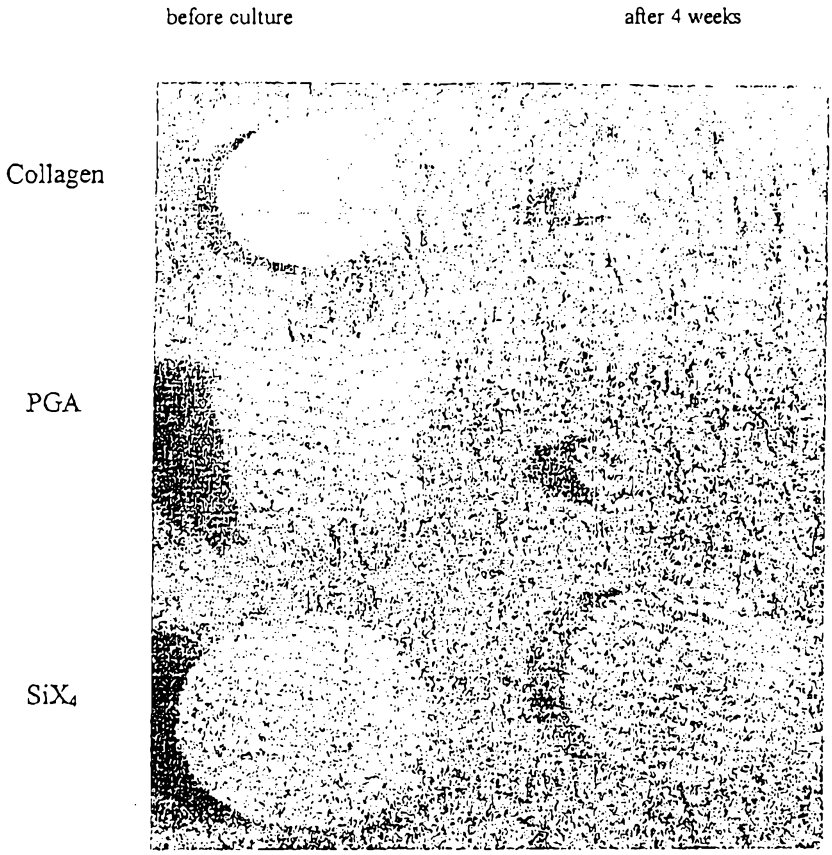
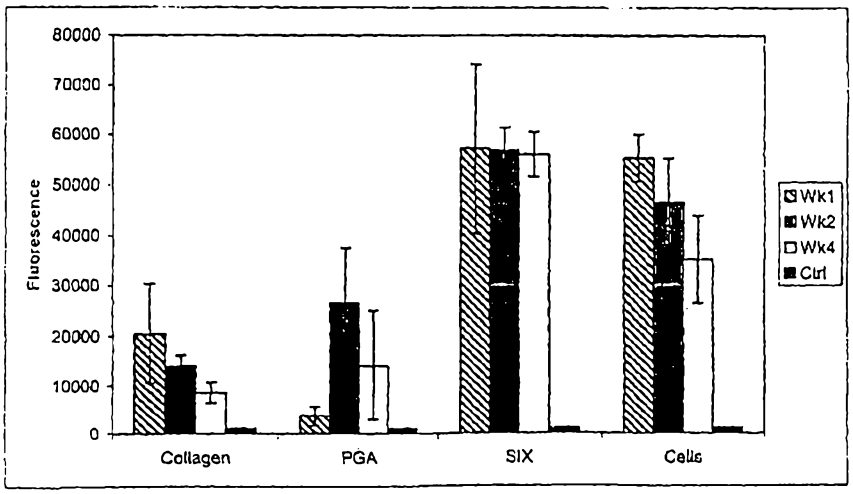

before culture
after 4 weeks
Collagen
PGA
SiX4

Fig. 5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Fluorescence
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Wk4
Ctrl

Fig. 6