Abstract: A device for manipulating circulation in the circulatory system of a body of a subject is disclosed. The device includes a flexible support dimensioned for covering a section of the body of the subject, a vibration inducing element embedded in or attached to the support. The support includes a patch and an attachment layer on the patch. The attachment layer includes a biocompatible adhesive suitable for attaching the patch to skin on the section of the body of the subject. The vibration inducing element is positioned in or on the support such that the vibration inducing element can transmit vibrations to the skin when the patch is adhered to the skin on the section of the body of the subject.
Devices And Methods For Manipulating Circulation
In The Circulatory System Of A Patient

CROSS-REFERENCES TO RELATED APPLICATIONS


STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] Not Applicable.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0003] This invention relates to devices and methods for manipulating circulation in the circulatory system of the body of a subject.

2. Description of the Related Art

[0004] Chronic lower extremity ulcers affect approximately 2.5 million to 4.5 million people in the United States. In addition to pressure ulcers, this growing clinical problem is most prominent among the elderly. Non-healing or slow healing wounds represent a major health burden and a drain on resources, and are sources of substantial disability, morbidity, and costs.

[0005] Multiple factors have been identified as contributors to impaired wound healing, such as ischemia, infection, advanced age, malnutrition, diabetes, and renal disease. Other conditions, such as cardiac and lung disease, decreased cognitive function, endocrine disease, gastrointestinal disease, hematologic disorders, incontinence, musculoskeletal problems, neurological disease, alcohol/drug abuse, immunosuppressives, chemotherapy, steroids, smoking, surgery as well as inadequate wound care have been implicated as well.

[0006] Wound healing involves a complex interaction between epidermal and dermal cells, the extracellular matrix, controlled angiogenesis, and plasma derived proteins, all coordinated by an array of cytokines and growth factors. This dynamic process is divided into three overlapping phases, inflammation,
proliferation, and remodelling. Thrombus formation which requires interaction between endothelial cells, platelets, and coagulation factors achieves haemostasis after tissue injury. Trapped cells within the clot, predominantly platelets, trigger an inflammatory response by the release of vasodilators and chemoattractants and activation of the complement cascade.

Inflammation - In the early phase of inflammation, neutrophils predominate, removing bacteria and other foreign material from the wound by releasing enzymes and by phagocytosis. Later in the inflammatory phase, neutrophils reduce in number and are replaced by macrophages. Macrophages play a role in coordinating the transition from inflammation to proliferation through the release of soluble mediators, which include platelet-derived growth factor, tumor necrosis factor α, transforming growth factor β, and insulin growth factor 1.

Proliferation - Fibroblasts are the key cells involved in the production of the extracellular matrix. In addition to producing collagen, they produce tenasin, fibronectin, and proteoglycans such as hyaluronic acid resulting in the formation of granulation tissue. The combination of new tissue and contraction of surrounding tissues is essential for the healing of ulcers. While new matrix is synthesized, existing matrix in and around the wound margin is degraded by several enzyme systems such as matrix metalloproteinases and plasminogen activators. While some keratinocytes at the wound edge proliferate, others undergo a marked transformation to enable them to phagocytose debris and migrate across the wound bed. Keratinocyte migration coupled with wound contraction results in re-epithelialisation and wound closure.

Remodelling - Once closure of the wound has been achieved, remodelling of the resulting scar takes place over months or years, with a reduction of both cell content and blood flow in the scar tissue.

Restricted blood supply to a living tissue (ischemia) may result in failure of the tissue to function normally. Although ischemia may be the result of many different conditions, the underlining mechanism generally involves vascular dysfunction. Increasing blood flow (perfusion) to an ischemic tissue may facilitate the restoration of tissues functionality. One condition known to be effected by ischemia is chronic wounds. Insufficient circulation in the wound area results in impaired trafficking of effector cells and molecules to and from the wound area,
leading to delayed healing or non-healing wounds. Increasing blood flow to the wound area may therefore enhance the healing of ischemic wounds.


[0012] Still, there is a need for a method and an apparatus for manipulating local and/or regional blood circulation such that the wound healing process can be enhanced.

**SUMMARY OF THE INVENTION**

[0013] In one aspect, the present invention satisfies the foregoing needs by providing a method and apparatus for manipulating local and/or regional circulation, such as inducing vasodilation or vasoconstriction, by means of vibrational stimuli.

[0014] An increase in blood trafficking at the site of an ischemic wound can result in better mobilization of cells and molecules important for the wound healing process. Better trafficking of cells and biomolecules in the wound area may enhance the healing process resulting in improvement of non healing wounds and reduced healing time in slow healing wounds. The present invention provides a device, preferably designed as a stand alone unit, containing an adhesive flexible substrate containing a controller, a power source and one or more vibration actuators that can comprise one unit to be applied at the wound area. The device results in increased blood circulation at the wound area. The unit is designed to be flexible so it will fit around or near the wound area and will not require additional involvement such as an external power supply. By applying the unit around or next to the wound, the device will stimulate blood flow by applying
vibration stimuli to the skin surrounding the wound. The vibrations from the device stimulate the tissue and can result in vasodilatation and in increased blood flow.

[0015] In another aspect, the present invention satisfies the foregoing needs by providing an apparatus for the local enhancement of blood circulation. The device includes a dermal patch having a porous layer and a fluid (e.g., air) sealed outer layer with a vacuum tube connector. Hence, negative pressure can be customized for application to different body locations by attaching the porous layer to a body location and connecting a source of negative pressure to the vacuum tube connector.

[0016] These and other features, aspects, and advantages of the present invention will become better understood upon consideration of the following detailed description, drawings and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 is a block diagram of an example embodiment of a device according to the invention for manipulating circulation in the circulatory system of the body of a subject.

[0018] Figure 2 is a perspective view of an embodiment of a device according to the invention for manipulating circulation in the circulatory system of the body of a subject.

[0019] Figure 3 is a rear view of a left human leg showing a wound in the calf.

[0020] Figure 4 is a top view of a wound map used in preparing another embodiment of a device according to the invention for manipulating circulation in the circulatory system of the body of a subject.

[0021] Figure 5 is a top view of an embodiment of a device according to the invention prepared using the wound map of Figure 4.

[0022] Figure 6 is a rear view of the leg of Figure 3 showing the device of Figure 5 positioned adjacent the wound in the calf.

[0023] Figure 6A is a cross-sectional view taken along line 6A-6A of Figure 6.

[0024] Figure 7 is a perspective view of another embodiment of a device according to the invention with a portion of the perimeter sealing tape not being shown.

[0025] Figure 8 is a perspective view of yet another embodiment of a device according to the invention with a portion of the perimeter sealing tape not being shown.
[0026] Figure 9 is a bottom perspective view of still another embodiment of a device according to the invention.

[0027] Figure 10 is a bottom perspective view of yet another embodiment of a device according to the invention.

[0028] Figure 11 is a left, rear perspective view of a human right foot and ankle having still another embodiment of a device according to the invention positioned in the ankle region and the arch region.

[0029] Figure 12 is a bottom view of a human right foot having yet another embodiment of a device according to the invention positioned in the arch region.

[0030] Figure 13 is a graph showing THI (total hemoglobin index) versus time for a patient using a device according to the invention positioned on the sacrum.

[0031] Figure 14 is a graph showing tissue oxygenation versus time for a patient using a device according to the invention positioned on the sacrum.

[0032] Figure 15 shows graphs of tissue oxygenation (StO2) versus time and total hemoglobin (THI) versus time for a patient using a device according to the invention positioned on the sacrum.

[0033] Like reference numerals will be used to refer to like parts from Figure to Figure in the following description of the drawings.

DETAILED DESCRIPTION OF THE INVENTION

[0034] In one example embodiment, the invention provides a method and an apparatus for manipulating local and/or regional circulation in a subject comprising delivery of at least one signal of vibrational stimulus to at least one area of the body of the subject. By delivering the vibrational stimuli to an area that is adjacent to a wound in accordance with this method, the circulation to certain body parts, preferably surrounding the wound, is changed. Vasodilation or vasoconstriction is induced in target organs (although the target organ is not necessarily the site of stimulation) or the wound area, resulting in increased or decreased blood perfusion in the target tissue or wound area. Clinical benefits effectuated using the method of the present invention include, but are not limited to: improved perfusion for limb ischemia, improved perfusion for ischemic wounds and pressure wounds (decubitus ulcers), improved perfusion for peripheral arterial disease (PAD) and peripheral vascular disease (PVD) patients and restricted blood flow to inflamed or injured body parts, improved perfusion to diabetic foot ulcers, improved perfusion to ischemic tissues resulting from surgery, including but not
limited to plastic surgery and flap surgery, and improved perfusion to injured or inflamed muscle tissue.

[0035] In addition to chronic wounds, peripheral ischemia may lead to the development of other conditions including neuropathy characterized by progressive loss of nerve fibers. Enhancement of local perfusion by delivering the vibrational stimuli to an area in or adjacent to a neuropathic tissue with this method may be used for the treatment of neuropathy by increasing perfusion to ischemic nerves resulting in reduced nerve fiber loss and improved nerve function.

[0036] The vibrational stimulus signal can be comprised of a single or multiple waveforms, and it can change over time. The preferred amplitude of the vibrational stimulus signal is from about 1µm to about 15 millimeters, and more preferred is an amplitude of the vibrations ranging between 0.001 millimeters and 2.5 millimeters. The preferred waveform is sinusoidal. The frequency of the vibrational stimulus signal is preferably in the range of about 1Hz to about 15,000 Hz. The force of the vibrational stimulus is preferably in the range of about 0.001 Newtons to 100 Newtons. These ranges of vibrational stimuli can have vasoconstrictive and/or vasodilative effect.

[0037] In another example embodiment of the invention, the vibrational stimulus signal is delivered by a wearable system. The system can be worn directly on the body of the subject, or over one or more layers of clothing. The term "wearable system" as used herein refers to any structure capable of holding in place some or all of the components described hereafter, in a desired location on the subject's body.

[0038] In yet another example embodiment of the invention, the vibrational stimulus signal is delivered by attaching the device directly to the patient's body at the wound location by gluing the device with adhesive or adhesive patches such as polyurethane and fabric based patches. In other embodiments, the device is held pressed against the skin by other mechanisms, for example: one or more elastic bands, Velcro™ hook and loop fasteners, tape, clips, or bandaging.

[0039] Different embodiments can be designed as to be capable of adhering some or all components of the system in place on the upper body of an individual including torso, shoulder, arm, elbow, neck, wrist and hand, as well as on the lower body including waist, hip, leg, knee, ankle and foot. As shown in the block diagram of Figure 1, the wearable system 10 can include one or more output
devices 12 which deliver the vibrational stimuli, a signal generator 14, a controller 16 and a power unit 18. The signal generator 14, controller 16, power unit 18 and other electric / electronics components such as an amplifier may be implemented as separate units or incorporated into a single component. The output devices 12 can be repositionable and/or detachable to the wearable unit. The signal generator 14, the controller/driver 16, and the power unit 18 can be detachable from a substrate. The system 10 can be controlled locally or remotely using a wired or wireless remote control unit. Various parameters of the system will be modifiable by means of the local or remote control unit, such as the frequency, amplitude, force, and duration of the stimuli. The system 10 can also include means for calibration of the vibrational stimulus signal in an initial step of utilization, or continuously throughout the operation, in real-time or near-real-time.

It can also include one or more closed-loop feedback / control circuits 19 to monitor the effect on blood flow or other physiological parameters and modify the output vibrational stimuli delivered to the subject in real-time or in near-real-time. Measurements of stimuli on physiological parameters can be achieved by one or more vibration or perfusion sensors such as piezo-film sensors, temperature sensors, photoplethysmographic sensors, strain-gauge plethysmography sensors, laser Doppler sensors, ultrasound sensors, or other such sensors. The wearable system 10 can be powered from an electrical wall socket, a portable DC power source such as batteries, other power sources, or a combination of several power sources.

[0040] In another example embodiment of the invention, all of the components 12, 14, 16, 18 and 19 are embedded within one system employed topically, locally or regionally, adjacent to or surrounding the wound area. In alternative embodiments one or more of the components, for example, the power supply 18 or the controller 16, can be external to the wearable substrate. For example, in a bed-side console and electrically connected via wire(s) or wirelessly to the wearable substrate.

[0041] The components of the device can include an adhesive substrate comprising a flexible material such as silicone, polyurethane, nylon, fabric, paper, or other polymer material for use as the substrate. With at least one of its sides carrying adhesive, the substrate can attach to the skin or to other bandaging materials or tight clothing and remain attached unless removed. The device
components are located on or within the substrate and include the vibration actuators, controller and power sources.

[0042] In one example embodiment, the output devices can be of an electro-mechanical nature such as linear electro-magnetic actuators, magnetostrictive actuators (DMA), hydro-pressure, asymmetric mass motors, voice coils, electro-active polymers (EPAM) or piezo-electric actuators, or other such devices.

[0043] In another embodiment, the output devices can be of pneumatic or hydraulic nature. These can include gas-containing resonating elements or fluid-containing resonating elements that will create and sustain the mechanical vibrational stimuli; or they can include gas-containing pouches or fluid-containing pouches or chambers that will deliver the vibrational stimuli to the subject's body surface in combination with electro-mechanical elements that will create the vibrational stimuli and deliver them to the pouches.

[0044] In yet another embodiment, the invention provides a method and apparatus for manipulating local and/or regional circulation in a subject comprising delivery of thermal stimuli such as heat or cold combined with delivery of at least one signal of vibrational stimulus to at least one area of the subject's body. In one embodiment, the application of heat or cold is performed by means of electrical and electronic components such as heating coils and thermoelectric coolers. In other embodiments, thermal stimuli can be achieved by other means, such as mechanical, chemical or other methods of heating and cooling surfaces.

[0045] A device according to the invention can be designed for single use, or for repeated use, for example by employing rechargeable or external power sources, or by using the same electronic apparatus while replacing the skin attachable element (adhesive substrate).

[0046] In one example method of using the invention, the system is designed to be used while the subject is in rest (e.g., seating or laying), or in motion, performing mild physical activities such as walking. The device is placed in proximity to the location where increased circulation is desired with the vibration actuator or actuators in direct contact with the skin, in close proximity to the skin or over a reasonably thin layer of bandaging or tight clothing. The device will operate for defined periods of time defined by the specific needs of the subject. For example, the device will be used for fifteen minutes with inactive intervals of fifteen minutes.
[0047] The apparatus used for performing the method of the present invention provides multiple improvements over known units used for manipulating local circulation by means of vibratory stimuli. For example, the present invention provides the ability of the specific design and specification to serve as a therapeutic instrument for targeted indications such as peripheral artery disease and chronic wounds. Current units are not wearable, most commonly they are hand-held and applied by hand to a specific area of the body; they are designed for use on a particular body area - and on it alone - such as the calf or the foot; they employ large vibrating surfaces resulting in large-area or even whole-body vibration; alternatively they employ very small applicators for highly localized stimuli; they typically require AC power supply limiting their use and portability, and they are not designed for continuous treatment - only for short sessions once or more a day; finally, known units do not include feedback loops (physiological or mechanical), and do not combine other types of stimulus together with the vibratory stimulus.

[0048] The current invention provides a system that is fully wearable and portable, is battery-operated, and can be easily applied to any part of the body. Furthermore, the current invention has a local/regional effect and provides continuous therapy over any desired period of time (e.g., from minutes to hours to weeks to months), not limited to short repetitive sessions.

[0049] For all of the above reasons, the current invention provides significant improvements over existing devices, and is particularly suitable for the therapeutic purposes described herein.

[0050] From an application point of view, the study of vibrations effect on circulation is in most cases focused on the damaging effect of vibrations induced by industrial machinery, or on the effect of vibrations on growth of bone mass. Current studies focus on short term application of vibrations (seconds to minutes). The current invention and the research that has lead to it are geared towards continuous application of vibrations and their specific therapeutic purposes as described herein.

[0051] Figure 2 shows one non-limiting example configuration for a device 20 according to the invention for local enhancement of circulation and alleviation of pain in lower limbs, caused due to peripheral artery disease, or an ischemic wound in the leg. The device 20 includes a substrate 22 having a perimeter 24
and an opening 26 which surrounds a wound location 27. The device 20 includes an upper surface 28 and lower surface 29. The lower surface 29 of the device 20 can be coated with an adhesive layer for attachment to a section of the body of a subject. The wound at the wound location 27 can be, for example, a diabetic ulcer, ischemic ulcer, venous ulcer, arterial ulcer, ischemic wound, pressure wound, injury, surgery, burn, inflammation, muscle injury, or internal injury.

The substrate 22 can be formed, for example, from a material selected from silicone, synthetic foam, polyethylene, polyurethane, polyvinyl chloride, plastic, nylon, thermoplastic polyurethane, polypropylene, fabric, hydrogel, collagen, alginate, gelatin, or combinations thereof. The adhesive layer can comprise, for example, a compound selected from urethanes, epoxies, urea, melamine, polyamides, polyesters, polyethers, polyolefins, polyvinyls, sulfonates, acrylates, methacrylates, and combinations thereof.

The substrate 22 can be of an area size and shape designed based on the location of ischemic ulcers. For example, a foot ulcer will require a different design compared with facial or back wounds. While the opening 26 of the embodiment of Figure 2 completely surrounds the wound location 27, other shapes for the substrate 22 and opening 26 such that the substrate 22 partially surrounds the wound location 27 are possible. For example, the substrate 22 may have a crescent shape, or the substrate 22 can be split into two pieces such as at a horizontal line of symmetry.

The device 20 includes an electrical power source such as batteries 32, which can be non-rechargeable or rechargeable. The batteries 32 are connected via electrical lines 34,35 to a controller 36, which can be a programmable microprocessor. The device 20 includes wide range frequency vibration energy generators 38 which are in electrical communication with the controller 36 via electrical line 39. The vibration generators 38 can transmit vasodilating or vasoconstricting frequencies to the tissue (e.g., foot sole or lower leg) surrounding the ischemic wound resulting in enhancement of local circulation. The vibration generators 38 can be an actuator such as a piezo electric actuator. The controller 36 executes an internally or externally stored program for providing electrical signals to the vibration generators 38 for adjusting vibrational stimulus frequency, amplitude, force, and/or timing of the vibration energy generators 38.
The vibrational stimulus signal in the device 20 of Figure 2 can be a single or multiple waveforms, sinusoidal, square, pulse, triangle or combination thereof, can be unidirectional or multidirectional, and can change over time. The preferred amplitude of the vibrational stimulus signal is from about 1µm to about 15 millimeters. The frequency of the vibrational stimulus signal is preferably in the range of about 1 Hz to about 15,000 Hz. The force of the vibrational stimulus is preferably in the range of about 0.001 Newtons to 100 Newtons.

Optionally, a vibration sensor or a perfusion sensor can be applied to tissue adjacent the substrate 22. The vibration or perfusion sensor monitors the physiological response to specific frequency and power of stimulus. The vibration or perfusion sensor is in electrical communication with the controller 36, which can execute a stored program for adjusting vibrational stimulus frequency and power based on electrical signals representing readings taken by the vibration or perfusion sensor. The controller 36 can integrate data collected by the vibration or perfusion sensor to adjust the vibration frequency and energy transmitted by the vibration generators 38. The vibration feedback can be a skin sensor, or a sensor that is embedded within the vibration inducing element, or a sensor that is attached to the vibration inducing element, or software and/or hardware within the controller 36 that detects current and/or voltage drawn by the vibration inducing elements and can infer on the element's performance based on that.

The controller 36 can be programmed with various algorithms to control the vibration generators 38. In one non-limiting example algorithm, the controller 36 executes an internally or externally stored program to provide a first electrical signal for a first time duration to the vibration inducing element. The first electrical signal controls the frequency and/or amplitude and/or force of vibrations of the vibration inducing element. After the first time duration ends, the controller 36 either ceases providing the first electrical signal to the vibration inducing element or decreases or increases the intensity of the first electrical signal provided to the vibration inducing element for a second time duration. After the second time duration ends, the controller 36 resumes providing the first electrical signal to the vibration inducing element or increases or decreases the intensity of the first electrical signal provided to the vibration inducing element for a third time duration. Optionally, one or more of the frequency and the amplitude and force of vibrations of the vibration inducing element during the third time duration can be
different than the frequency and the amplitude of vibrations of the vibration inducing element during the first time duration.

[0058] In another non-limiting example algorithm, the controller 36 ceases providing the first electrical signal to the vibration inducing element or decreases or increases the intensity of the first electrical signal provided to the vibration inducing element for a fourth time duration, and thereafter resumes providing the first electrical signal to the vibration inducing element or increases or decreases intensity of the first electrical signal provided to the vibration inducing element for a fifth time duration.

[0059] In still another non-limiting example algorithm, the controller 36 provides a first electrical signal to the vibration inducing element wherein the first electrical signal controls the frequency and amplitude and force of vibrations of the vibration inducing element, and varies the first electrical signal to the vibration inducing element such that at least one of the frequency or amplitude or force of vibrations of the vibration inducing element is varied.

[0060] In yet another non-limiting example algorithm, the controller 36 provides a first electrical signal for a first time duration to the vibration inducing element for controlling the frequency and/or amplitude and/or force of vibrations of the vibration inducing element, and can vary the first electrical signal provided to the vibration inducing element based on a second electrical feedback signals received from the perfusion sensor or the vibration sensor applied to tissue adjacent the substrate 22.

[0061] In still another non-limiting example algorithm, the controller 36 provides a first electrical signal for a first time duration to a first vibration inducing element for controlling the frequency and/or amplitude and/or force of vibrations of the first vibration inducing element, ceases providing the first electrical signal to the first vibration inducing element for a second time duration, and thereafter provides a second electrical signal to the second vibration inducing element for a third time duration for controlling the frequency and amplitude and force of vibrations of the second vibration inducing element.

[0062] It can be appreciated that the programmable controller 36 allows for an infinite number of programs that provide for various time periods of operation or non-operation at various frequencies and amplitudes and forces for the vibration generators 38, either individually or as a group of vibration generators. For
example, during a first time duration the vibration generators 38 may operate for one minute to two hours in which the vibration generators 38 transmit vibrations to the skin at a first frequency and amplitude and force, and then during a second time duration of one minute to six hours the vibration generators 38 do not transmit vibrations to the skin. The timing of operation (e.g., a sequence of time durations) can be repeated, for example, over a number of days, weeks, or months.

[0063] A kit according to the invention can include one or more of the following: the batteries 32, the electrical lines 34,35, the controller 36, vibration generators 38, the electrical line 39, the substrate 22, a perfusion sensor, a vibration sensor, and instructions for use. The batteries 32, electrical lines 34,35, controller 36, vibration generators 38, and electrical line 39 can be attached to the upper surface 28 of the substrate 22 with suitable attachment means such as an adhesive, fasteners such as Velcro™ hook and loop fasteners, or a designated pouch. Alternatively, the batteries 32, electrical lines 34, 35, controller 36, vibration generators 38, and electrical line 39 can be embedded between the upper surface 28 of the substrate 22 and a second substrate (not shown). Alternatively, the batteries 32, electrical lines 34, 35, controller 36, vibration generators 38, and electrical line 39 can be encased in a hard or soft shell, which is in turn attached to the upper surface 28 of the substrate 22 or embedded between the upper surface 28 of the substrate 22 and a second outer substrate. By removably attaching (such as with Velcro™ hook and loop fasteners) the batteries 32, electrical lines 34,35, controller 36, vibration generators 38, and electrical line 39 to the upper surface 28 of the substrate 22, it is possible to reuse the electrical components on disposable substrates that can be changed at various intervals (e.g., every day). Alternatively, the batteries 32 and controller 36 can be placed in a suitable housing and an electrical line can be plugged into a suitable plug on the substrate 22 for electrical connection with the vibration generators 38. The housing can be attached to a bed support, a belt or a body part (e.g., arm, leg), or placed in a container such as a pocket or a hand bag.

[0064] The device 20 can be used at the same time with other treatments. For example, the device 20 can be used at the same time with hydrogel matrices (which can be separately) applied over the wound wherein the hydrogel comprises one or more of polylactic acid, polyglycolic acid, other polyhydroxy acids,
copolymers of two or more polyhydroxy acids, polyorthoesters, polyanhydrides, gelatin, collagen, cellulose, derivatized cellulose, chitosan, alginate, thiol modified hyaluronan, and combinations or copolymers thereof. The hydrogel can also be made of synthetic material such as silicone plastic or fabric. The other treatment can include growth factors like vascular endothelial growth factor of platelet derived growth factor, fibroblast growth factor, cell therapies like stem cells, progenitor cells, fibroblasts or any other cell, gene therapies, and combinations thereof. The hydrogel matrix can include a bioactive agent selected from growth factors, stem cells, progenitor cells, fibroblasts, gene therapies, and combinations thereof. The substrate 22 can include a bioactive agent selected from cells, precursors, drugs, enzymes, organic catalysts, ribozymes, organometallics, proteins, glycoproteins, peptides, polyamino acids, antibodies, nucleic acids, steroidal molecules, antibiotics, antimycotics, cytokines, growth factors, carbohydrates, oleophobics, lipids, pharmaceuticals, therapeutics, and mixtures thereof. The substrate 22 can include a cosmetic for cosmetic uses in the enhancement of skin appearance. The other treatment can be selected from negative pressure, hyperbaric oxygen, compression devices, shock wave and ultrasound devices, and electric current stimulation.

[0065] The device 20 can be used in combination with other devices such as devices for applying negative pressure below the support, hyperbaric oxygen devices, compression devices, shock wave devices, heating devices, cooling devices, light emitting devices, ultrasound devices, and electric current stimulation devices. The device can be used in combination with wound negative pressure therapy, a skin system, a skin implant, a biological or bioactive wound dressing, a drug delivery wound dressing, a wound drainage system, and combinations thereof.

[0066] Figure 11 is a left, rear perspective view of a human right foot 111 and ankle 112 having a device 20 according to the invention positioned in the ankle region and the arch region. Figure 12 is a bottom view of a human right foot 111 having a device 20 according to the invention positioned in a foot sole plantar configuration. The device 20 can induce vasoconstriction or vasodilatation in the foot and/or ankle by means of vibrational stimuli. The device is shaped to fit right foot 111 and/or ankle 112.
Turning now to Figures 3-10, there is shown another embodiment of a device 50 according to the invention. The device 50 can be called a Shape and Surface Adjustable Negative Pressure Applicator (SSANPA). The SSANPA device 50 provides a method for the application of negative pressure to the skin surface where the shape of the device 50 can be customized to the desired anatomy and area to be exposed to negative pressure. The device 50 is especially appropriate for applying negative pressure (vacuum) to normal skin and/or skin of the peri-wound area.

Referring now to Figures 3 and 4, a chronic wound 52 having a perimeter 54 is diagnosed on the calf 56 of the lower leg 58 of a human patient. Following diagnosis of the chronic wound 52, the wound measurements (e.g., the perimeter 54 of the wound 52) can be taken from the patient by direct measurement or by imaging. These measurements can be used to create wound map 62 as shown in Figure 4. The wound map 62 has an opening 63 with an inner edge 64 that corresponds to the perimeter 54 of the wound 52. The wound map 62 has an outer perimeter 65. A flexible plastic material is suitable for forming the wound map 62.

Turning now to Figures 5, 6 and 6A, a non-limiting example device 50 created using the wound map 62 is shown. The device 50 includes a flexible dermal patch 70 dimensioned for covering a section of the body of the subject. The patch 70 including a porous layer 72 structured such that fluid (e.g., air) can pass from a first side 74 of the porous layer 72 to an opposite second side 75 of the porous layer 72. The patch 70 further includes a fluid impermeable outer layer 76 covering the second side 75 of the porous layer 72. The patch 70 further includes a fluid passageway 78 extending from the second side 75 of the porous layer 72 to an outer surface 79 of the outer layer 76. The fluid passageway 78 terminates at a hollow connector 80 at the outer surface 79 of the outer layer 76. While the embodiment shown includes one fluid passageway that terminates at a hollow connector, more than one fluid passageway that terminates at a hollow connector can be provided in the device 50.

The dermal patch 70 can be supplied in an uncut rectangular shape similar to the outer perimeter 65 of the wound map 62. The outer perimeter 65 of the wound map 62 is aligned with the outer perimeter of the uncut dermal patch and the dermal patch is cut to follow the inner edge 64 of the wound map 62 (see
Figure 4). The dermal patch 70 can be cut approximately in half to form the example dermal patch 70 shown in Figures 5 and 6. The shaped flexible dermal patch 70 is placed next to the wound 52 and a sealing tape 82 is applied along the dermal patch outer perimeter edges covering both the flexible dermal patch 70 and the skin of the calf 56 of the lower leg 58 of a human patient. A vacuum pump can be connected to the connector 80 by way of tubing 84.

[0071] In one form, the sealing tape 82 is a flexible, stretchable tape having a width ranging from 0.1 centimeters to 30 centimeters and more preferably 0.5 centimeters to 5 centimeters. The thickness of the tape 82 can be 0.001 millimeters to 5 millimeters, and more preferably 0.01 millimeters to 2.5 millimeters wherein the tape is coated with adhesive on one side such as when attached to both the perimeter of the dermal patch 70 and the skin, it will result in air sealing of the dermal patch 70. The sealing tape adhesive composition can include urethane, epoxy, urea, melamine, polyamide, polyester, polyether, saturated or unsaturated polyolefin, polyvinyl, sulfonate, acrylate or methacrylate compounds and/or combinations thereof. The substrate of the sealing tape 82 can include a polymer material, latex, rubber, silicone, fabric, cellulose, or combinations thereof.

[0072] In another embodiment, the sealing tape can be replaced with an adhesive film fully covering the flexible dermal patch 70 and overlapping the skin to form an air tight chamber. The adhesive film may contain a gas and liquid connector (such as connector 80) to allow connection to a vacuum pump. The thickness of the adhesive film can be 0.001 millimeters to 5 millimeters, and more preferably 0.01 millimeters to 2.5 millimeters wherein the tape is coated with adhesive on one side such as when attached to both the perimeter of the dermal patch 70 and the skin, it will result in air sealing of the dermal patch 70.

[0073] The adhesive film adhesive composition can include urethane, epoxy, urea, melamine, polyamide, polyester, polyether, saturated or unsaturated polyolefin, polyvinyl, sulfonate, acrylate or methacrylate compounds and/or combinations thereof. The substrate of the sealing tape 82 can include a polymer material, polyurethane, nylon, latex, rubber, silicone, fabric, cellulose, or combinations thereof.

[0074] For example, the products OpSite™ made by Smith and Nephew and Tegaderm™, a nylon film made by 3M, can be used for sealing film. The product OpSite™ is a semi-permeable, adhesive-coated polyurethane film. Sealing film is
approximately 0.003 inches (0.076 mm) thick, however, it is within the scope of this disclosure to include any occlusive or semi-occlusive film having another thickness. The sealing film is provided to create a sealed environment below the film and around the dermal patch 70 in which a vacuum or negative pressure can be maintained.

[0075] In the embodiment shown in Figures 6 and 6A, the device 50 serves as an apparatus within which vacuum is created and applied to the skin of the calf 56 of the lower leg 58 of a human patient above the wound 52. It can be appreciated that the device 50 can be used to apply vacuum to other areas of skin on the body of the patient. Since the skin or tissue in contact with the device 50 serves as a sealing wall at the bottom of the device 50, negative pressure inside the device 50 is applied to the skin or tissue serving as a sealing wall to the device 50. When the tubing 84 is connected to the connector 80 and a source of negative pressure (e.g., a vacuum pump), negative pressure can be inflicted on the body area under the dermal patch 70 such that blood flow is increased in the body area. Negative pressure is applied to the dermal patch 70 or dermal patch 70a through the connector 80 using a vacuum pump to induce negative pressure ranging from 1 to 2000 mmHg, and more preferably between 25 and 500 mmHg.

[0076] The combination of the porous layer 72 and outer layer 76 of the device 50 is thin (preferably between 1 and 10 millimeters, but can also be between 10 millimeters and 500 millimeters or more). The porous layer 72 can be made of, for example, an elastic polymeric material such as open-cell polyurethane foam and open-cell polyvinyl alcohol foam, polyethylene, Ether-Like-Ester, polystyrene or other synthetic, biological or biodegradable polymers, fabric, layers of different polymers, layers of fabric and/or combinations thereof, preventing the dermal patch 70 from collapsing under normal negative pressure used during negative pressure treatment, yet allowing flexibility for bending and cutting such that the dermal patch 70 can be adjusted to cover and bind to different shapes and topographies. The porous layer 72 of the dermal patch 70 allows fluid (e.g., air) flow. In one form, the thickness of the porous layer 72 is between 0.1 centimeters and 10 centimeters, and more preferably between 0.2 millimeters and 2 centimeters.

[0077] In one embodiment, the base surface (skin contacting side) of the porous layer 72 is at least partially coated by an adhesive layer allowing the
attachment of the dermal patch 70 to the skin or tissue. In another embodiment, the base surface of the porous layer 72 is not coated with adhesive. The top side of the outer layer 76 of the dermal patch 70 can be sealed to fluids (e.g., air) by applying a thin layer of air sealing polymer or other material that will prevent fluid from crossing the top barrier. The outer layer 76 can be made of synthetic or natural polymer such as rubber, latex, silicone, nylon or other flexible polymeric material, fabric and/or combination thereof.

[0078] The flexible sealing tape 82 is used to seal the dermal patch 70 following attachment of the porous layer 72 to the body. The sealing tape 82 can be made of thin elastic polymer such as latex (vinyl acetate, styrene-butadiene, acrylates) coated with adhesive on one side. The sealing tape 82 is designed with maximal elasticity to allow it to conform with the shape and topography of the dermal patch 70 following its attachment to the skin or tissue. The sealing tape 82 is preferably in a width which will allow convenient and safe attachment both to the dermal patch 70 as well as to the skin or tissue. In one example embodiment, the sealing tape 82 may be of a size that will entirely cover the vacuum dressing thereby it can serve as a top sealant for the vacuum dressing.

[0079] The dermal patch can be used without modifying its shape (as a pre-shaped design). Looking at Figures 7 and 9, the dermal patch 70a of the device 50a includes an outer perimeter 86. The outer perimeter 86 of the dermal patch 70a can be sealed by coating or covering with a sealing material 88 (which is shown partially broken away in Figure 7). In order to attach the dermal patch 70a to the skin and maintain vacuum, the edges in contact with the skin should be sealed. In order to achieve this, the outer perimeter 86 of the base side of the dermal patch 70a can be air sealed as the top side of the dermal patch 70a is and then coated with an adhesive 89 in Figure 9, such as following attachment to the skin the dermal patch 70a is secured to the skin in an airtight manner creating an air sealed or semi-sealed (i.e., a breathable film) space between the dermal patch 70a and the skin. Example adhesives include urethane, epoxy, urea, melamine, polyamide, polyester, polyether, saturated or unsaturated polyolefin, polyvinyl, sulfonate, acrylate or methacrylate compounds and/or combinations thereof.

[0080] Turning to Figure 10, an additional way to secure the dermal patch 70a and create an air sealed space is to apply thin layers of elastic polymer 91 with or without adhesive along the outer perimeter 86 with their direction from the dermal
patch 70a base to the external skin (facing opposite from the center of the dermal
patch 70a), such as when vacuum is applied the thin flexible layer or layers will be
pulled in by the vacuum pressure and secure the dermal patch 70a from air
leakage. The thin flexible layers can, for example, be 0.01 millimeters to 2
millimeters in width and more preferably 0.05 to 0.5 millimeters. The thin flexible
layer can be fragmented or continuous along the perimeter of the dermal patch
70a forming a closed line. The thin flexible layer can be between 0.01 centimeters
and 4 centimeters long as measured from their connection point to the dermal
patch 70a base or more preferably between 0.5 millimeters and 10 millimeters.
Such sealing configuration is shown in Figure 10.

[0081] The device can be combined with other elements to enhance blood
flow. In one embodiment shown in Figure 8, the device 50b includes one or more
vibrating elements 92 such as piezoelectric actuator(s), vibration motor(s), voice
coil(s), electroactive polymer artificial muscle (EPAM) or other vibrating elements
that will transmit vibrations to the skin or tissue. These vibrations may vary
between low frequency ranging from 1 to 1000 Hz, high frequencies ranging from
1000 - 20,000 Hz or ultrasound. When a vibrating device is embedded in the
dermal patch 70a, a power inlet can be attached to the dermal patch 70a and a
controller 95 and power supply of the vibrating unit 92 as well as a vacuum pump
96 are connected to the dermal patch 70a through a connecting air tube 84 and
electric wire 97.

[0082] The controller 95 can be programmed with various algorithms to control
the vacuum pump 96. In one non-limiting example algorithm, the controller 95
executes an internally or externally program to provide a first electrical signal for a
first time duration to the vacuum pump 96 for running the vacuum pump 96. After
the first time duration ends, the controller 95 ceases providing the first electrical
signal to the vacuum pump 96 for a second time duration such that the vacuum
pump 96 does not operate. After the second time duration ends, the controller 95
resumes providing the first electrical signal to the vacuum pump 96 for a third time
duration for running the vacuum pump 96. It can be appreciated that the
programmable controller 95 allows for an infinite number of programs that provide
for various time periods of operation or non-operation for the vacuum pump 96
and for various pump pressures. The controller 95 can also be programmed with
various algorithms in stored programs to control the vibrating unit 92. Example
algorithms are detailed above with reference to the controller 36.

**[0083]** The vibrational stimulus signal in the embodiment of Figure 8 can be a
single or multiple waveforms, sinusoidal, square, pulse, triangle or combination
thereof, can be unidirectional or multidirectional, and can change over time. The
preferred amplitude of the vibrational stimulus signal is from about 1µm to about
15 millimeters. The frequency of the vibrational stimulus signal is preferably in the
range of about 1 Hz to about 15,000 Hz. The force of the vibrational stimulus is
preferably in the range of about 0.001 Newtons to 100 Newtons.

**[0084]** Another embodiment of the dermal patch 70 or the dermal patch 70a
includes a vibrating element, such as vibration generators 38 described earlier,
and also contains a controller 95 which controls the operation of the vibrating
element and a power unit which powers the vibrating element and controller all
embedded within the dermal patch 70a.

**[0085]** In another embodiment, the dermal patch 70 or the dermal patch 70a
contain a micro vacuum pump such as piezoelectric pump or motorized pump,
vacuum controller, and power supply such that the dermal patch 70 or the dermal
patch 70a does not need to be connected to an external vacuum pump and
controller.

**[0086]** In another embodiment, the dermal patch 70 or the dermal patch 70a
including the vibrating element also contain within the dermal patch 70 or the
dermal patch 70a both the vacuum pump, controller for the vacuum pump,
controller for the vibrating device and power supply for the vacuum pump, vacuum
controller, vibration controller and vibrating element.

**[0087]** In another embodiment, the dermal patch 70 or the dermal patch 70a -
with or without vibrating element(s) - also contain a heating element to transmit
heat to the skin or tissue, or a cooling element to transmit cooling to the skin or
tissue.

**[0088]** In another embodiment, the dermal patch 70 or the dermal patch 70a
can be combined with an electro stimulation device embedded in the dermal patch
70 or the dermal patch 70a or connected to the dermal patch 70 or the dermal
patch 70a. Electric stimulation can be a benefit in wound healing, and the use of
both technologies can result in improved efficacy and better outcome. In addition
to electric stimulation elements, the dermal patch 70 or the dermal patch 70a can
include drug delivery element(s), massaging element(s), compression element(s), vibration element(s) and/or combinations thereof.

[0089] A kit according to the invention can include the dermal patch 70 or the dermal patch 70a, sealing film, the vacuum pump 96, the vacuum tubing 84, the vibration controller 95, and instructions for use. The dermal patch 70 or the dermal patch 70a can be used in combination with wound negative pressure therapy, skin system(s), skin implants, biological or bioactive wound dressings, drug delivery wound dressings, wound drainage systems and/or combinations thereof. Among other things, the dermal patch 70 or the dermal patch 70a are suitable for cosmetic use in the enhancement of skin appearance such as in the reduction of wrinkles and cellulites, in the treatment of sport injury such as muscle injuries and muscle inflammation by enhancing healing, in skin conditions by enhancing skin perfusion, in plastic and reconstructive surgery and/or in combinations thereof. The dermal patch 70 or the dermal patch 70a can include a cosmetic for cosmetic uses in the enhancement of skin appearance.

[0090] The device 50 and the device 50a have many benefits. For example, negative pressure can be used for the treatment of chronic wounds, as well as surgical incisions and other types of wounds. The technology of the present invention targets the skin surrounding the wound and not particularly the wound itself. The technology described in the present invention provides the care giver more flexibility in optimizing the size and shape of the vacuum applicator by simply cutting the dermal patch to the desired shape and attaching the vacuum dermal patch to the treated area. While vacuum applied over a wound effects blood circulation at the wound edges, the technology described in the present invention allows for more substantial improvement in circulation in the skin and subdermal tissues surrounding the wound, thereby allowing for better perfusion in the wound area and better healing of the wound. The combination of a vibrating element in the dermal patch provides two complementary mechanisms for the induction of blood flow. This can result in higher efficacy due to the dual response, higher response rate to the treatment due to better chances that the patient will positively respond to one of the stimulations.

[0091] The device 50 and the device 50a can be used in combination with other devices such as compression devices, shock wave devices, heating
devices, cooling devices, light emitting devices, ultrasound devices, and electric current stimulation devices.

Examples

[0092] The following Examples have been presented in order to further illustrate the invention and are not intended to limit the invention in any way.

Example 1

[0093] Assay method and results: A piezoelectric actuator (1 inch in diameter) was enclosed within a plastic enclosure controlled by a controller unit. The enclosure was attached to the sacrum skin of a human patient by applying adhesive tape over the actuator. After an acclimatization period of 15 to 30 minutes, vibration stimulation was started (20 Hz, 8 mils amplitude) and was continued as intermittent stimulation in 5 minute on/off cycles. THI (total hemoglobin index) was recorded versus time. After 50 minutes, the THI levels reached a plateau and the stimulation was terminated. Following a decline period and a return to baseline levels of THI, stimulation was renewed and a new cycle started at 267 minutes. The blood flow stimulation cycle can be used for the development of a continuous operation algorithm such that the device can be self regulated and increase blood flow over prolonged periods of time. For example, the plot of THI vs. time in Figure 13 teaches that an actuator with equivalent parameters of operation when attached to the skin can be activated for 50 minutes with 5 minute on/off cycles and then turned off for 200 minutes before a new cycle of stimulation is initiated. The on and off cycles can vary between subjects and between body locations. Measuring how this kinetics changes between subjects and/or body locations can be used for the development of specific algorithms for long term (hours to days) of operation. In the present study, we used the InSpectra™ StO2 Tissue Oxygenation Monitor. Similar devices or other devices used for measurement of blood flow can be used for the measurement of tissue blood flow, temperature, tissue oxygenation, or THI in the development of long term operation algorithms for use with vibration based blood flow stimulation.

Example 2

[0094] A vibration device as in Example 1 was applied to the ankle of a human patient. The device increased blood flow in the heel and toes (prime location for diabetes and arterial foot ulcers) by over two fold as measured using moorFLPI
system, a full-field video frame rate blood flow imaging system which uses a laser Doppler speckle technology.

Example 3

[0095] A vibration device as in Example 1 was applied to the sacrum of a human patient. The vibration device increased tissue oxygenation at the sacrum (lower back, location of 80% of pressure ulcers) by more than 2.5 fold, measured using InSpectra™ StO2 Tissue Oxygenation Monitor with the protocol similar to Example 1. See Figure 14.

Example 4

[0096] A vacuum chamber containing a vibrating piezoelectric element was placed on the sacrum. Following a fifteen minute acclimatization period, vibration stimulation was started (20 Hz, 8 mils amplitude) and was continued as intermittent stimulation in 5 minute on/off cycles. Tissue oxygenation (StO2) (see chart a in Figure 15) and total hemoglobin (THI) (see chart b in Figure 15) increased 270% and 70% respectively. Intermittent vacuum (25 mmHg) was applied when StO2 levels were approaching a plateau resulting in an additional 10% and 20% increase in StO2 and THI respectively.

[0097] Thus, the invention provides a method and apparatus for manipulating local and/or regional circulation, such as inducing vasodilation or vasoconstriction, by means of vibrational stimuli and/or negative pressure. The devices of the invention can increase blood flow, increase tissue oxygenation, and increase total hemoglobin in a patient. Accordingly, it is contemplated that the devices of the invention can be beneficial in: methods for enhancing skin appearance; methods for the treatment of sport injury and other traumatic injuries by enhancing healing; methods for enhancing healing after surgery (e.g., plastic and reconstructive surgery); methods for treating peripheral artery disease or peripheral vascular disease in a subject; methods for improving wound healing in a subject; methods for increasing tissue oxygenation in a subject; methods for improving healing of a skin ulcer in a subject; methods for improving blood flow to ischemic tissue in a subject; methods for treating erectile dysfunction; methods for treating a migraine; methods for treating hair loss, methods for treating neuropathy, and methods for treating plantar fasciitis.

[0098] Although the invention has been described in considerable detail with reference to certain embodiments, one skilled in the art will appreciate that the
present invention can be practiced by other than the described embodiments, which have been presented for purposes of illustration and not of limitation. Therefore, the scope of the appended claims should not be limited to the description of the embodiments contained herein.

INDUSTRIAL APPLICABILITY

[0099] The invention provides devices and methods for manipulating circulation in the circulatory system of the body of a subject.
What Is Claimed Is:

1. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a section of the body of the subject; and
   a vibration inducing element embedded in or attached to the support,
   wherein the support includes a patch and an attachment layer on the patch,
   the attachment layer including a biocompatible adhesive suitable for attaching the patch to skin on the section of the body of the subject, and
   wherein the vibration inducing element is positioned in or on the support such that the vibration inducing element can transmit vibrations to the skin when the patch is adhered to the skin on the section of the body of the subject.

2. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a section of the body of the subject; and
   a vibration inducing element embedded in or attached to the support,
   wherein the support includes an opening dimensioned to fully or partially surround a wound on the section of the body of the subject when the patch is placed over skin on the section of the body of the subject, and
   wherein the vibration inducing element is positioned in or on the support such that the vibration inducing element can transmit vibrations to the skin when the patch is placed over skin on the section of the body of the subject.

3. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a section of the body of the subject;
   a vibration inducing element embedded in or attached to the support;
   a power source; and
a controller in electrical communication with the vibration inducing element and the power source, the controller being configured to execute a program to:

(i) provide a first electrical signal for a first time duration to the vibration inducing element, the first electrical signal controlling the frequency and amplitude and force of vibrations of the vibration inducing element,

(iii) cease providing the first electrical signal to the vibration inducing element or decrease intensity of the first electrical signal provided to the vibration inducing element or increase intensity of the first electrical signal provided to the vibration inducing element for a second time duration, and

(iv) resume providing the first electrical signal to the vibration inducing element or increase intensity of the first electrical signal provided to the vibration inducing element or decrease intensity of the first electrical signal provided to the vibration inducing element for a third time duration.

4. The device of claim 3 wherein:

the controller is further configured to execute the program to:

(v) cease providing the first electrical signal to the vibration inducing element or decrease intensity of the first electrical signal provided to the vibration inducing element or increase intensity of the first electrical signal provided to the vibration inducing element for a fourth time duration, and

(vi) resume providing the first electrical signal to the vibration inducing element or increase intensity of the first electrical signal provided to the vibration inducing element or decrease intensity of the first electrical signal provided to the vibration inducing element for a fifth time duration.

5. The device of claim 3 wherein:

at least one of the frequency and the amplitude and the force of vibrations of the vibration inducing element during the third time duration is different than the frequency and the amplitude and the force of vibrations of the vibration inducing element during the first time duration.
6. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a section of the body of the subject;
   a first vibration inducing element embedded in or attached to the support;
   a second vibration inducing element embedded in or attached to the support;
   a power source; and
   a controller in electrical communication with the first vibration inducing element and the second vibration inducing element and the power source, the controller being configured to execute a program to:
      (i) provide a first electrical signal for a first time duration to the first vibration inducing element, the first electrical signal controlling the frequency and amplitude and force of vibrations of the first vibration inducing element,
      (ii) cease providing the first electrical signal to the first vibration inducing element for a second time duration, and
      (iii) provide a second electrical signal to the second vibration inducing element for a third time duration, the second electrical signal controlling the frequency and amplitude and force of vibrations of the second vibration inducing element.
7. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a section of the body of the subject;
   a vibration inducing element embedded in or attached to the support;
   a power source; and
   a controller in electrical communication with the vibration inducing element and the power source, the controller being configured to execute a program to:
   (i) provide a first electrical signal to the vibration inducing element, the first electrical signal controlling the frequency and amplitude and force of vibrations of the vibration inducing element, and
   (iii) vary the first electrical signal to the vibration inducing element such that at least one of the frequency or amplitude or force of vibrations of the vibration inducing element is varied.
8. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a first section of the body of the subject;
   a vibration inducing element embedded in or attached to the support;
   a perfusion sensor for covering a second section of the body of the subject, the second section being adjacent to or within the first section of the body of the subject;
   a power source; and
   a controller in electrical communication with the vibration inducing element and the power source and the perfusion sensor, the controller being configured to execute a program stored in the controller to:
      (i) provide a first electrical signal for a first time duration to the vibration inducing element, the first electrical signal controlling the frequency and amplitude and force of vibrations of the vibration inducing element, and
      (ii) vary the first electrical signal provided to the vibration inducing element based on a second electrical signal received from the perfusion sensor.

9. The device of claim 8 wherein:
   the perfusion sensor is selected from piezo-film sensors, temperature sensors, photoplethysmographic sensors, strain-gauge plethysmography sensors, laser Doppler sensors, laser speckle sensors, infra-red imaging, infra-red spectroscopy, and ultrasound sensors.
10. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:
   a flexible support dimensioned for covering a first section of the body of the subject;
   a vibration inducing element embedded in or attached to the support;
   a vibration sensor for covering a second section of the body of the subject, the second section being adjacent to or within the first section of the body of the subject;
   a power source; and
   a controller in electrical communication with the vibration inducing element and the power source and the vibration sensor, the controller being configured to execute a program stored in the controller to:
   (i) provide a first electrical signal for a first time duration to the vibration inducing element, the first electrical signal controlling the frequency and amplitude and force of vibrations of the vibration inducing element, and
   (ii) vary the first electrical signal provided to the vibration inducing element based on a second electrical signal received from the vibration sensor.

11. The device of any of claims 1 to 5 or claims 7 to 10 wherein:
   the device includes a plurality of the vibration inducing element embedded in or attached to the support.

12. The device of any of claims 2 to 11 wherein:
   the support comprises a patch formed from a material selected from silicone, synthetic foam, polyethylene, polyurethane, polyvinyl chloride, plastic, thermoplastic polyurethane, polypropylene, fabric, hydrogel, collagen, alginate, gelatin, or combinations thereof.

13. The device of claim 12 wherein:
   the support further comprises an adhesive layer on the patch.

14. The device of claim 13 wherein:
the adhesive layer comprises a compound selected from urethanes, epoxies, urea, melamine, polyamides, polyesters, polyethers, polyolefins, polyvinyls, sulfonates, acrylates, methacrylates, and combinations thereof.

15. The device of any of claims 1 to 15 wherein:
   each vibration inducing element is selected from linear electromagnetic actuators, asymmetric mass motors, voice coils, electro-active polymers, piezoelectric actuators, fluid-containing resonating elements, gas-containing resonating elements, and combinations thereof.

16. The device of any of claims 1 to 2 further comprising:
   a controller in electrical communication with the vibration inducing element and a power source, the controller being configured to execute a program stored in the controller to provide an electrical signal to the vibration inducing element, the electrical signal controlling timing of operation of the vibration inducing element.

17. The device of any of claims 1 to 2 further comprising:
   a controller in electrical communication with the vibration inducing element and a power source, the controller being configured to execute a program stored in the controller to provide an electrical signal to the vibration inducing element, the electrical signal controlling frequency of the vibrations of the vibration inducing element.

18. The device of any of claims 1 to 2 further comprising:
   a controller in electrical communication with the vibration inducing element and a power source, the controller being configured to execute a program stored in the controller to provide an electrical signal to the vibration inducing element, the electrical signal controlling amplitude of the vibrations of the vibration inducing element.

19. The device of any of claims 1 to 2 further comprising:
   a controller in electrical communication with the vibration inducing element and a power source, the controller being configured to execute a program stored
in the controller to provide an electrical signal to the vibration inducing element, the electrical signal controlling force of the vibrations of the vibration inducing element.

20. The device of any of claims 3 to 19 wherein:
the controller and the power source are embedded in or attached to the support.

21. The device of any of claims 3 to 19 wherein:
an electrical line in communication with the controller and power source is removably attached to the support by a plug.

22. The device of any of claims 3 to 19 wherein:
the controller, the power source, and the vibration inducing element are removably attached to the support.

23. The device of any of claims 3 to 19 wherein:
the controller, the power source, and the vibration inducing element are removably attached to the support by hook and loop fasteners, adhesive, or a pouch.

24. The device of any of claims 3 to 19 wherein:
the electrical signal is (i) a single or multiple waveform, (ii) unidirectional or multidirectional, and (iii) sinusoidal, square, pulse, triangle or a combination thereof.

25. The device of any of claims 3 to 19 wherein:
the vibrations of the vibration inducing element range from 1 Hz to 15,000 Hz.

26. The device of any of claims 3 to 19 wherein:
the vibrations of the vibration inducing element have an amplitude ranging from 0.001 to 2.5 millimeters.

27. The device of any of claims 3 to 19 wherein:
the vibrations of the vibration inducing element have a force ranging from 0.001 Newtons to 100 Newtons.

28. The device of any of claims 1 to 10 wherein:
the section of the body of the subject includes a wound.

29. The device of claim 28 wherein:
the wound is selected from the group consisting of diabetic ulcers, ischemic ulcers, venous ulcers, arterial ulcers, ischemic wounds, pressure wounds, injuries, surgeries, surgical incisions, surgical wounds, burns, inflammation, muscle injuries, muscle inflammation, musculo-skeletal injuries, and internal injuries.

30. The device of claim 29 wherein the device is used to increase blood circulation at the section of the body of the subject.

31. The device of any of claims 1 to 10 wherein:
the device increases blood circulation.

32. The device of any of claims 1 to 10 wherein:
the section of the body of the subject includes a wound, and
the device further includes a hydrogel matrix for covering the wound.

33. The device of claim 32 wherein:
the hydrogel is selected from polylactic acid, polyglycolic acid, other polyhydroxy acids, copolymers of two or more polyhydroxy acids, polyorthoesters, polyanhydrides, gelatin, collagen, cellulose, derivatized cellulose, chitosan, alginate, thiol-modified hyaluronan, emulsion, and combinations or copolymers thereof.

34. The device of claim 32 wherein:
The hydrogel matrix includes a synthetic material selected from silicone, synthetic foam, polyethylene, polyurethane, polyvinyl chloride, plastic, thermoplastic polyurethane, polypropylene, fabric, hydrogel, collagen, alginate, gelatin, or combinations thereof.

35. The device of claim 32 wherein:
the hydrogel matrix includes a bioactive agent selected from growth factors, stem cells, progenitor cells, fibroblasts, gene therapies, and combinations thereof.

36. The device of any of claims 1 to 10 wherein:
the support includes a bioactive agent selected from cells, precursors, drugs, enzymes, organic catalysts, ribozymes, organometallics, proteins, glycoproteins, peptides, polyamino acids, antibodies, nucleic acids, steroidal molecules, antibiotics, antimycotics, cytokines, growth factors, carbohydrates, oleophobics, lipids, pharmaceuticals, therapeutics, cosmetics, and mixtures thereof.

37. The device of any of claims 1 to 10 further comprising:
at least one of: devices for applying negative pressure below the support, hyperbaric oxygen devices, compression devices, shock wave devices, heating devices, cooling devices, light emitting devices, ultrasound devices, and electric current stimulation devices.

38. The device of any of claims 1 to 10 further comprising:
a device for applying negative pressure below the support.

39. The device of any of claims 1 to 10 further comprising:
a device for applying negative pressure adjacent to the support.

40. A treatment method comprising:
using the device of any of claims 1 to 39 in combination with wound negative pressure therapy, a skin system, a skin implant, a biological wound dressing, a drug delivery wound dressing, a wound drainage system, and combinations thereof.
41. The method of claim 40 wherein:
the biological wound dressing is a hydrogel matrix.

42. A method for enhancing skin appearance, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to or
on the skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

43. The method of claim 42 wherein:
the support includes a cosmetic material.

44. The method of claim 43 wherein:
the vibration inducing element is removably attached to the support.

45. A method for the treatment of sport injury by enhancing healing, the
method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

46. A method for enhancing healing after surgery, the method
comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

47. A method for treating peripheral artery disease or peripheral
vascular disease in a subject, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.
48. A method for improving wound healing in a subject, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

49. A method for increasing tissue oxygenation in a subject, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

50. A method for improving healing of a skin ulcer in a subject, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

51. A method for improving blood flow to ischemic tissue in a subject, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

52. A method for treating erectile dysfunction, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

53. A method for treating a migraine, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the
skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.
54. A method for treating hair loss, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.

55. A method for treating neuropathy, the method comprising:
positioning the support of the device of any of claims 1 to 39 adjacent to the skin on the section of the body of the subject; and
activating the device to transmit vibrations to the skin.
56. A device for manipulating circulation in the circulatory system of the body of a subject, the device comprising:

a flexible dermal patch dimensioned for covering a section of the body of the subject, the patch including a porous layer structured such that fluid can pass from a first side of the porous layer to an opposite second side of the porous layer, the patch further including an impermeable outer layer covering the second side of the porous layer, and the patch further including a fluid passageway extending from the second side of the porous layer to an outer surface of the outer layer, the fluid passageway terminating at a hollow connector at the outer surface of the outer layer,

wherein the connector, the fluid passageway and the porous layer are structured such that when the first side of the porous layer of the patch is positioned on the section of the body of the subject and the connector is connected to a source of negative pressure, negative pressure is inflicted on the section of the body of the subject under the patch whereby blood flow is increased.

57. The device of claim 56 further comprising:

a vibration inducing element embedded in or attached to the patch for transmitting vibrations to skin or tissue of the section of the body of the subject under the patch.

58. The device of claim 57 wherein:

the vibration inducing element is selected from linear electromagnetic actuators, asymmetric mass motors, vibration motors, voice coils, electro-active polymers, electroactive polymer artificial muscle, piezoelectric actuators, fluid-containing resonating elements, gas-containing resonating elements, and combinations thereof.

59. The device of claim 56 further comprising:

at least one of: an electric stimulation element, a drug delivery element, a massaging element, a compression element, a vibration element, compression devices, shock wave devices, heating devices, cooling devices, light emitting
devices, ultrasound devices, and electric current stimulation devices, and combinations thereof.

60. The device of claim 56 wherein:
the first side of the porous layer is at least partially coated with an adhesive.

61. The device of claim 56 wherein:
the porous layer has a thickness between 0.1 centimeters and 10 centimeters.

62. The device of claim 56 wherein:
the porous layer has a thickness between 0.2 millimeters and 2 centimeters.

63. The device of claim 56 further comprising:
a tube attachment element having a first end dimensioned to engage the connector and a second end adapted for connection to a vacuum pump.

64. The device of claim 56 wherein:
the porous layer comprises a polymeric material.

65. The device of claim 56 wherein:
the polymeric material is selected from polyurethane foam, polyvinyl alcohol, polyethylene, Ether-Like-Ester, polystyrene, other biocompatible polymers, fabric, layers of different polymers, layers of fabric, and combinations thereof.

66. The device of claim 56 wherein:
the outer layer comprises a synthetic or natural polymer.

67. The device of claim 66 wherein:
the polymer is selected from rubber, polyurethane, latex, silicone, nylon, other flexible polymers, fabric, and combinations thereof.
68. The device of claim 56 wherein:

the dermal patch includes an edge region sealed and coated with adhesive
on the edge region whereby the edge region defines an air sealed space between
skin and the dermal patch when the patch is positioned on the section of the body
of the subject.

69. The device of claim 56 wherein:

the dermal patch includes an outer edge shaped to complement a
perimeter section of a wound on the section of the body of the subject.

70. The device of claim 56 wherein:

the dermal patch includes a flexible layer of polymeric material applied to a
perimeter of the dermal patch such that when negative pressure is inflicted on the
section of the body of the subject under the patch the flexible layer will be pulled in
by the negative pressure thereby forming an airtight barrier around the perimeter
of the dermal patch.

71. The device of claim 70 wherein:

the flexible layer is coated with an adhesive.

72. The device of any of claims 60, 68 and 71 wherein:

the adhesive comprises a compound selected from urethanes, epoxies,
urea, melamine, polyamides, polyesters, polyethers, polyolefins, polyvinyls,
sulfonates, acrylates, methacrylates, and combinations thereof.

73. The device of claim 56 further comprising:

a sealing tape coated with an adhesive on one side such that when the
tape is attached to both a perimeter of the patch and skin, fluid tight sealing of the
perimeter of the patch results.

74. The device of claim 73 wherein:
the tape is flexible and stretchable and has a width ranging from 0.1 centimeters to 30 centimeters and has a thickness of 0.001 millimeters to 5 millimeters.

75. The device of claim 73 wherein:
the adhesive comprises a material selected from urethane, epoxy, urea, melamine, polyamide, polyester, polyether, saturated or unsaturated polyolefin, polyvinyl, sulfonate, acrylate, methacrylate and combinations thereof.

76. The device of claim 73 wherein:
the tape comprises a polymeric material, polyurethane, nylon, latex, rubber, silicone, fabric, cellulose, or combinations thereof.

77. The device of claim 56 wherein:
the outer layer comprises a sealing film having a perimeter greater than a perimeter of the patch such that when the film covers the porous layer and skin a fluid tight sealing of the perimeter of the patch results.

78. The device of claim 56 wherein:
the outer layer comprises a sealing film having a perimeter greater than a perimeter of the patch, the film being coated with an adhesive on one side such that when the film is attached to the porous layer and skin, fluid tight sealing of the perimeter of the patch results.

79. A kit comprising:
the device of any of claims 56 to 78; and
any of the following: vacuum pump, vacuum tubing, vibration controller, sealing film, and instructions for use.

80. A treatment method comprising:
using the device of any of claims 56 to 78 in combination with wound negative pressure therapy, a skin system, a skin implant, a biological wound dressing, a drug delivery wound dressing, a hydrogel wound dressing, a wound drainage system, and combinations thereof.
81. A method for enhancing skin appearance, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the
subject under the patch.

82. The method of claim 81 wherein:

the patch includes a cosmetic material.

83. A method for the treatment of sport injury by enhancing healing, the
method comprising:

applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the
subject under the patch.

84. A method for plastic and reconstructive surgery, the method
comprising:

applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the
subject under the patch.

85. A method for treating peripheral artery disease or peripheral
vascular disease in a subject, the method comprising:

applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the
subject under the patch.

86. A method for improving wound healing in a subject, the method
comprising:

applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the
subject under the patch.
87. A method for increasing tissue oxygenation in a subject, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the subject under the patch.

88. A method for improving healing of a skin ulcer in a subject, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the subject under the patch.

89. A method for improving blood flow to ischemic tissue in a subject, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the subject under the patch.

90. A method for treating erectile dysfunction in a subject, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the subject under the patch.

91. A method for treating a migraine in a subject, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the subject under the patch.

92. A method for treating hair loss in a subject, the method comprising:
applying the patch of the device of any of claims 56 to 78 to skin; and
applying negative pressure on the skin of the section of the body of the subject under the patch.
93. A method for treating neuropathy in a subject, the method comprising:
   applying the patch of the device of any of claims 56 to 78 to skin; and
   applying negative pressure on the skin of the section of the body of the subject under the patch.

94. The method of any of the preceding claims wherein the subject is a human.

95. The method of any of the preceding claims wherein the subject is a mammal other than a human.
96. A method for manipulating circulation in the circulatory system of the body of a subject, the method comprising:

(a) providing a flexible dermal patch including (i) a porous layer structured such that fluid can pass from a first side of the porous layer to an opposite second side of the porous layer, (ii) an impermeable outer layer covering the second side of the porous layer, and (iii) a fluid passageway extending from the second side of the porous layer to an outer surface of the outer layer, the fluid passageway terminating at a hollow connector at the outer surface of the outer layer,

(b) locating a wound on a section of the body of the subject;

(c) creating a wound map including a region having an outer line corresponding to a perimeter of the wound;

(d) using the outer line of the region of the wound map as a template for creating an edge in the dermal patch;

(e) aligning the edge of the dermal patch with at least a portion of the perimeter of the wound and securing the porous layer of the dermal patch to the section of the body of the subject; and

(f) connecting the connector to a source of negative pressure such that negative pressure is inflicted on the section of the body of the subject under the patch whereby blood flow is increased.

97. The method of claim 96 wherein:

the edge of the dermal patch is an outer edge that is aligned with less than the entire perimeter of the wound.

98. The method of claim 96 wherein:

the edge of the dermal patch is an inner edge that is aligned with the entire perimeter of the wound.
Fig. 14

Fig. 15
INTERNATIONAL SEARCH REPORT

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/023832

A CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61F 13/00 (201.01)
USPC - 601/2

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) - A61F 5/00, 13/00, A61H 1/00 (2010 01)
USPC - 601/2, 602/2

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>Y</td>
<td>US 2004/0077978 A1 (NELSON et al) 22 April 2004 (22 04 2004) entire document</td>
<td>2-6, 8, 9, 16-19, 35, 36, 38, 39</td>
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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
24 May 2010

Date of mailing of the international search report
11 Jun 2010

Name and mailing address of the ISA/AJS
Mail Stop PCT, Attn: ISA/AJS, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No 571-273-3200

Authorized officer
Blame R. Copenhagen
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<tr>
<td>1</td>
<td>Claims Nos because they relate to subject matter not required to be searched by this Authority, namely</td>
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<td>2</td>
<td>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</td>
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<td>3</td>
<td>Claims Nos because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)</td>
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<td>As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims</td>
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<td>2</td>
<td>As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees</td>
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<td>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</td>
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<td>4</td>
<td>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 1-1, 16-19, 28-39</td>
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</table>

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
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 need to be paid.

Group I, claims 1-11, 16-19, 28-39 are drawn to a device including a flexible support and a controller.

Group II, claims 56-78, 96-98 are drawn to a device including a dermal patch, a fluid passageway, and a hollow connector.

The inventions listed in Groups I and II 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:

The special technical features of Group I, a flexible support including a controller in electrical communication with a vibration inducing element and a power source, are not present in Group II, and the special technical features of Group II, a dermal patch including a porous layer structured such that fluid can pass, including a fluid passageway that terminates at a hollow connector at the outer surface of the outer layer, are not present in Group I.

Since none of the special technical features of the Group I and II inventions are found in more than one of the inventions, unity is lacking.