A device, comprising an NO eluting polymer is provided. Said device is furthermore provided with microencapsulated proton donor (102), such as water, body fluids, alcohols in micro-capsules (101), which water, body fluids, alcohols after breakage of said micro capsules, initiate elution of NO from said device. Furthermore, a manufacturing method for said device is disclosed.
Abstract: A device, comprising an NO eluting polymer is provided. Said device is furthermore provided with microencapsulated proton donor (102), such as water, body fluids, alcohols in micro-capsules (101), which water, body fluids, alcohols after breakage of said micro capsules, initiate elution of NO from said device. Furthermore, a manufacturing method for said device is disclosed.
Field of the Invention

This invention pertains in general to the field of devices comprising nitric oxide (NO) eluting polymers, involving the use of bound liquid to facilitate and initiate the elution of NO therefrom. More particularly the invention relates to devices manufactured of said NO eluting polymer with bound liquid, a system, comprising said NO eluting polymer and bound liquid, and a process for manufacturing of said device and system.

Background of the Invention

Nitric oxide (NO) is a highly reactive molecule that is involved in many cell functions. In fact, nitric oxide plays a crucial role in the immune system and is utilized as an effector molecule by macrophages to protect itself against a number of pathogens, such as fungi, viruses, bacteria etc., and general microbial invasion. This improvement of healing is partly caused by NO inhibiting the activation or aggregation of blood platelets, and also by NO causing a reduction of inflammatory processes at the site of an implant.

NO is also known to have an anti-pathogenic, especially an anti-viral, effect, and furthermore NO has an anti-cancerous effect, as it is cytotoxic and cytostatic in therapeutic concentrations, i.e. it has among other effects tumoricidal and bacteriocidal effects. NO has for instance cytotoxic effects on human haematological malignant cells from patients with leukaemia or lymphoma, whereby NO may be used as a chemotherapeutic agent for treating such haematological disorders, even when the cells have become resistant to conventional anti-cancer drugs.
However, due to the short half-life of NO, it has hitherto been very hard to treat viral, bacteria, virus, fungi or yeast infections with NO. This is because NO is actually toxic in high concentrations and has negative effects when applied in too large amounts to the body.

NO is actually also a vasodilator, and too large amounts of NO introduced into the body will cause a complete collapse of the circulatory system. On the other hand, NO has a very short half-life of fractions of a second up to a few seconds, once it is released. Hence, administration limitations due to short half-life and toxicity of NO have been limiting factors in the use of NO in the field of anti-pathogenic and anti-cancerous treatment so far.

In recent years research has been directed to polymers with the capability of releasing nitrogen oxide when getting in contact with water. Such polymers are for example polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) and B-PEI (Branched PolyEthyleneImine), which polymers have the advantage of being biocompatible.

Other example for NO eluting polymers are given in US-5,770,645, wherein polymers derivatized with at least one $-\text{NO}_x$ group per 1200 atomic mass unit of the polymer are disclosed, X being one or two. One example is an S-nitrosylated polymer and is prepared by reacting a polythioliated polymer with a nitrosylating agent under conditions suitable for nitrosylating free thiol groups.

Akron University has developed NO-eluting L-PEI molecule that can be nano-spun onto the surface of medical devices to be permanently implanted in the body, such as implanted grafts, showing significant improvement of the healing process and reduced inflammation when implanting such devices. According to US-6,737,447, a coating for medical devices provides nitric oxide delivery using nanofibers of linear poly(ethylenimine)-diazeniumdiolate.
Linear poly(ethyleneimine)diazeniumdiolate releases nitric oxide (NO) in a controlled manner to tissues and organs to aid the healing process and to prevent injury to tissues at risk of injury. Electrospun nano-fibers of linear poly(ethyleneimine) diazeniumdiolate deliver therapeutic levels of NO to the tissues surrounding a medical device while minimizing the alteration of the properties of the device. A nanofiber coating, because of the small size and large surface area per unit mass of the nanofibers, provides a much larger surface area per unit mass while minimizing changes in other properties of the device.

When using NO eluting polymers, according to above, in medical applications, said polymers need the presence of water to initiate and facilitate the elution of NO. The present inventor has earlier shown that one way to obtain water or moisture in said usage is to place a water bag or sponge in the vicinity of said NO eluting polymer. This water bag or sponge is then broken to set the polymer in contact with water. One may also use the sweat secreted from the skin underneath the medical application or apply water on the medical application after that said medical application has been placed on the area to be treated.

However, even though the idea is genius, the use of a water bag or sponge presents some disadvantages. The water bags need to be delicate, to facilitate breakage by the person using the medical device. This delicacy aggravates transportation and logistic of said medical devices in some extent. Also, the water bag or sponge is somewhat bulky, which impair logistic and use effectiveness. The use of the secreted sweat presents the problem that not all people sweat sufficiently to obtain an adequate elution of NO at the area to be treated. It is a well known fact that some people sweat more than others. Wetting through sweat is also not a time effective way to obtain enough water and/or
moisture, since enough secretion of sweat may take some
time to obtain.

Hence, an improved device, or more advantageous,
comprising NO eluting polymer, involving the use of bound
liquid, such as water or water containing liquid to
facilitate and initiate the elution of NO, is needed in the
art. It is desired that said liquid is bound in said device
in such manner as to eliminate the problems mentioned above
in respect of the prior art, would be advantageous.

**Summary of the Invention**

Accordingly, the present invention preferably seeks
to mitigate, alleviate or eliminate one or more of the
above-identified deficiencies in the art and disadvantages
singly or in any combination and solves among others at
least the above mentioned problems by providing a device
and a system, and a manufacturing method thereof, according
to the appended patent claims.

Surprisingly, the present inventor has discovered
that it is possible to combine NO eluting polymer and micro
encapsulation of a liquid, such as water or a water
containing liquid.

Up to this point no one has developed a device or a
system comprising an NO eluting polymer and micro
encapsulated water or water containing liquid.

In the area of micro encapsulation of liquid, two
methods, urea formaldehyde and gelatine capsules, are
widely used, but other techniques are also available, which
techniques are well known to the skilled artisan. The micro
capsules in this technical field may be as small as
approximately 8 micrometers and as large as 2 millimeters.
They may hold a liquid content of up to approximately 85 %.
In this type of micro capsules, the liquid is released by
physically rupturing the shell of the micro capsule by
pressure, shear forces, or heat.
According to one aspect of the invention, a device is provided comprising an NO eluting polymer and microencapsulated water or water containing liquid, which device may be configured for use as a medical device.

According to another aspect of the present invention a system is provided, which system comprises an NO eluting polymer and microencapsulated water or water containing liquid.

According to another aspect of the invention, a manufacturing process for such a device is provided, wherein the process comprises selecting a plurality of nitric oxide eluting polymeric particles, such as nano fibres, fibres, nano particles, or microspheres, and deploying said nitric oxide eluting particles, and deploying onto said polymeric particles microencapsulated water or water containing liquid.

The present invention has at least the advantage over the prior art that it provides a device and a system that initiates and facilitates elution of NO in a manner that is more prone to withstand transportation, and logistic, and that is pliable to use, hence not bulky.

**Brief Description of the Drawings**

These and other aspects, features and advantages of which the invention is capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which

Fig. 1 is an illustration of a micro capsule according to an embodiment of the present invention,

Fig. 2 is an illustration of a micro capsule, that has been covered with an NO eluting polymer, according to an embodiment of the invention,
Fig. 3 is an illustration of a mixture of micro capsules and nano-particles or micro spheres according to an embodiment of the present invention,

Fig. 4 is an illustration of a plurality of micro capsules, in for example a film, according to an embodiment of the present invention,

Fig. 5 is an illustration of NO eluting polymer that has been spun onto micro capsules according to an embodiment of the present invention,

Fig. 6 is a planar view of a film of NO eluting polymer that has been combined with a film of micro capsules,

Fig. 7 is a cross-section of a film of NO eluting polymer that has been combined with a film of micro capsules,

Fig. 8 is an illustration of a combination of films, according to Fig. 6 and 7, that has been applied on a target area, and

Fig. 9 illustrates two elution profiles (NO concentration vs. time) for two different polymer mixtures of nitric oxide eluting polymer and carrier material.

**Embodiments of the Invention**

The following description focuses on embodiments of the present invention applicable to a device, and a system, that for example may be configured for medical applications. However, it will be appreciated that the invention is not limited to this application but may be applied to many other technical fields, wherein elution of NO is sought.

With regard to nitric oxide (nitrogen monoxide, NO), its physiological and pharmacological roles have attracted much attention and thus have been studied. NO is synthesized from arginine as the substrate by nitric oxide synthase (NOS). NOS is classified into a constitutive
enzyme, cNOS, which is present even in the normal state of a living body and an inducible enzyme, iNOS, which is produced in a large amount in response to a certain stimulus. It is known that, as compared with the concentration of NO produced by cNOS, the concentration of NO produced by iNOS is 2 to 3 orders higher, and that iNOS produces an extremely large amount of NO.

In the case of the generation of a large amount of NO as in the case of the production by iNOS, it is known that NO reacts with active oxygen to attack exogenous microorganisms and cancer cells, but also to cause inflammation and tissue injury. On the other hand, in the case of the generation of a small amount of NO as in the case of the production by cNOS, it is considered that NO takes charge of various protective actions for a living body through cyclic GMP (cGMP), such as vasodilator action, improvement of the blood circulation, anti-platelet-aggregating action, anti-bacterial action, anti-viral action, anti-inflammatory action, anticancer action, acceleration of the absorption at the digestive tract, renal function regulation, neurotransmitting action, erection (reproduction), learning, appetite, and the like. Heretofore, inhibitors of the enzymatic activity of NOS have been examined for the purpose of preventing inflammation and tissue injury, which are considered to be attributable to NO generated in a large amount in a living body. However, the promotion of the enzymatic activity (or expressed amount) of NOS (in particular, cNOS) has not been examined for the purpose of exhibiting various protective actions for a living body by promoting the enzymatic activity of NOS and producing NO appropriately.

In recent years research has been directed to polymers with the capability of releasing nitrogen oxide when getting in contact with water. Such polymers are for example polyalkyleneimines, such as L-PEI (Linear
PolyEthyleneImine) B-PEI ( Branched PolyEthyleneImine), PEI-C (PolyEthyleneImine Cellulose), which polymers have the advantage of being biocompatible. Another advantage is that NO is released without any secondary products that could lead to undesired side effects.

"Regulate or control", according to the present invention is intended to be interpreted as the possibility to vary the elution of nitric oxide to thereby achieve different elution profiles.

A polymer comprising an O-nitrosylated group is also a possible nitric oxide eluting polymer. Thus, in one embodiment of the present invention, the nitric oxide eluting polymer comprises diazeniumdiolate groups, S-nitrosylated and O-nitrosylated groups, or any combinations thereof.

In still another embodiment of the present invention said nitric oxide eluting polymer is a poly(alkyleneimine)diazeniumdiolate, such as L-PEI-NO (linear poly(ethyleneimine)diazeniumdiolate), where said nitric oxide eluting polymer is loaded with nitric oxide through the diazeniumdiolate groups and arranged to release nitric oxide at a treatment site.

Some other examples of a suitable nitric oxide eluting polymer are selected from the group comprising amino cellulose, amino dextrins, chitosan, aminated chitosan, polyethyleneimine, PEI-cellulose, polypropyleneimine, polybutyleneimine, polyurethane, poly(buthanediol spermate), poly(iminocarbonate), polypeptide, Carboxy Methyl Cellulose (CMC), polystyrene, poly(vinyl chloride), and polydimethylsiloxane, or any combinations of these, and these mentioned polymers grafted to an inert backbone, such as a polysaccharide backbone or cellulosic backbone.

In still another embodiment of the present invention the nitric oxide eluting polymer may be a O-derivatized
NONOate. This kind of polymer often needs an enzymatic reaction to release nitric oxide.

Other ways of describing polymers, which may be suitable as nitric oxide eluting polymer, is polymers comprising secondary amine groups (≡N–H), such as L-PEI, or have a secondary amine (≡N–H) as a pendant, such as aminocellulose.

The nitric oxide eluting polymer may comprise a secondary amine, either in the backbone or as a pendant, as described previously. This will make a good nitric oxide eluting polymer. The secondary amine should have a strong negative charge to be easy to load with nitric oxide. If there is a ligand close to the secondary amine, such as on a neighbour atom, such as a carbon atom, to the nitrogen atom, with higher electronegativity than nitrogen (N), it is very difficult to load the polymer with nitric oxide. On the other hand, if there is a electropositive ligand close to the secondary amine, such as on a neighbour atom, such as a carbon atom, to the nitrogen atom, the electronegativity of the amine will increase and thereby increase the possibility to load the nitric oxide elution polymer with nitric oxide.

In an embodiment of the present invention the nitric oxide polymer may be stabilized with a salt. Since the nitric oxide eluting group, such as a diazeniumdiolate group, usually is negative, a positive counter ion, such as a cation, may be used to stabilize the nitric oxide eluting group. This cation may for example be selected from the group comprising any cation from group 1 or group 2 in the periodic table, such as Na⁺, K⁺, Li⁺, Be²⁺, Ca²⁺, Mg²⁺, Ba²⁺, and/or Sr²⁺. Different salts of the same nitric oxide eluting polymer have different properties. In this way a suitable salt (or cation) may be selected for different purposes. Examples of cationic stabilized polymers are L-PEI-NO-Na, i.e. L-PEI diazeniumdiolate stabilized with
sodium, and L-PEI-NO-Ca, i.e. L-PEI diazeniumdiolate stabilized with calcium.

Three important factors in controlling and regulating the elution of nitric oxide from a nitric oxide eluting polymer are how quickly a proton donor comes in contact with the nitric oxide releasing polymer, such as a diazoliumdiolate group, the acidity of the environment surrounding the nitric oxide eluting polymer, and the temperature of the environment surrounding the nitric oxide releasing polymer (higher temperature promotes elution of nitric oxide).

In one embodiment of the present invention a nitric oxide eluting polymer, such as L-PEI-NO, is mixed with a carrier polymer to slow down or prolong the elution of nitric oxide. Also, in another embodiment, the nitric oxide eluting polymer may be mixed with more than one carrier polymer, whereby be elution or release may be tailor made to fit specific needs. Such a need may for example be a low elution during a first period of time, when the environment of the nitric oxide eluting polymer is hydrophobic, and a faster elution during a second period of time, when the environment of the nitric oxide eluting polymer has been altered to be more hydrophilic. This may for example be accomplished by using biodegradable polymers, whereby a low elution during a first period of time is obtained, after which, when the hydrophobic polymer has been dissolved, the hydrophilic polymer provides a higher elution of nitric oxide. Thus, a more hydrophobic carrier polymer will give a slower elution of nitric oxide, since the activating proton donor, such as water or body fluid, will penetrate the carrier polymer slower. On the other hand, a hydrophilic polymer acts the opposite way. One example of an hydrophilic polymer is polyethylene oxide, and one example of an hydrophobic polymer is polystyrene. These carrier polymers may be mixed with the nitric oxide eluting polymer
and then electrospun to suitable fibers. The skilled person in the art knows which other polymers may be used for similar purposes. Fig. 9 illustrates two elution profiles (NO concentration vs. time) for two different polymer mixtures; a nitric oxide eluting polymer mixed with a hydrophilic carrier polymer in an acidic environment (A), and a nitric oxide eluting polymer mixed with a hydrophobic carrier polymer in a neutral environment (B).

In one embodiment this carrier polymer is substituted by another material with hydrophobic or hydrophilic properties. Therefore, the term “carrier material” in the present context should be interpreted to include carrier polymers and other materials with hydrophilic or hydrophobic properties.

In another embodiment of the present invention the elution of nitric oxide from a nitric oxide eluting polymer, such as L-PEI-NO, is influenced by the presence of protons. This means that a more acidic environment provides a quicker elution of nitric oxide. By activating the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, with an acidic fluid, such as an ascorbic acid solution, the elution of nitric oxide may be accelerated.

The carrier polymers and carrier materials mentioned above may affect other characteristics than the regulation of nitric oxide elution. An examples of such characteristic is mechanical strength.

In respect of the carrier polymers or carrier materials, the NO-eluting polymer may be integrated in, spun together with, or spun on top of, any of these materials in all of the embodiments of the present invention. This spinning includes electro spinning, air spinning, dry spinning, wet spinning, melt spinning, and gel spinning. In this way, one may manufacture fibers of a polymer mixture, comprising a nitric oxide eluting polymer
and a carrier polymer, or a carrier material, with predefined nitric oxide eluting characteristics. These characteristics may be tailor made for different elution profiles in different applications.

The polymers may be manufactured by electro spinning, gas spinning, air spinning, wet spinning, dry spinning, melt spinning, and gel spinning. Electro spinning is a process by which a suspended polymer is charged. At a characteristic voltage a fine jet of polymer releases from the surface in response to the tensile forces generated by interaction by an applied electric field with the electrical charge carried by the jet. This process produces a bundle of polymer fibres, such as nano-fibres. This jet of polymer fibres may be directed to a surface to be treated.

Furthermore, US 6,382,526, US 6,520,425, and US 6,695,992 disclose processes and apparatuses for the production of such polymeric fibres. These techniques are generally based on gas stream spinning, also known within the fiber forming industry as air spinning, of liquids and/or solutions capable of forming fibers.

Other example for NO eluting polymers are given in US-5,770,645, wherein polymers derivatized with at least one -NOX group per 1200 atomic mass unit of the polymer are disclosed, X being one or two. One example is an S-nitrosylated polymer and is prepared by reacting a polythiolated polymer with a nitrosylating agent under conditions suitable for nitrosylating free thiol groups.

Akron University has developed NO-eluting L-PEI molecule that can be nano-spun onto the surface of permanently implanted medical devices, such as implanted grafts, showing significant improvement of the healing process and reduced inflammation when implanting such devices. According to US-6,737,447, a coating for medical devices provides nitric oxide delivery using nanofibers of
linear poly(ethylenimine)-diazoniumdiolate. Linear poly(ethylenimine)diazoniumdiolate releases nitric oxide (NO) in a controlled manner.

However, the meaning of "controlled" in the context of US 6,737,447 is only directed to the fact that nitric oxide is eluted from the coating during a period of time, i.e. that the nitric oxide not is eluted all in once. Therefore, the interpretation of "controlled" in respect of US 6,737,447 is different from the meaning of "regulating" in the present invention.

In one embodiment of the present invention an NO eluting polymer, such as polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine) B-PEI (Branched PolyEthyleneImine), PEI-C (PolyEthyleneImine Cellulose), is provided, and/or combined, with microencapsulated liquid, such as water or water containing liquid, according to Fig. 1. Fig. 1 shows a microcapsule 100, comprising a shell 101 and a microencapsulated liquid 102, such as water or water containing liquid.

This may for example be done by first manufacture micro capsules, containing water or water containing liquid, in a state of the art manner. These micro capsules may then be formed into a film, tape, sheath, etc. These micro capsules, in form of a film, tape, sheath, etc., are then applied on the NO eluting polymer, according to Fig. 6, which is a planar view of an NO eluting polymer and a film, etc., of micro capsules, and Fig. 7, which is a cross section of the configuration in Fig. 6. The application of the micro capsules on the NO eluting polymer may for example be done by gluing, such as pattern gluing, or instead spinning the NO eluting polymer onto said micro capsules. In this way a device or a system, comprising NO eluting polymer and micro encapsulated water or water containing liquid is manufactured. Said device may for example be any device selected from the group; patches,
ointments, tapes for cosmetic treatment; tapes, condoms, patches, sheets for treatment of wounds or infections in the oral cavity; patches, socks, condoms for treatment of onychomycosis; patches, socks, tapes, sheets for treatment and/or prevention of neuropathy, such as diabetic neuropathy, diabetic ulcers, vaso-constrictive disorders and macro-angiopathy; condoms, sheets, patches for treatment of rectal disorders, such as fissures, ulcers, haemorrhoids, and levator spasm; devices for target treatment of gastric and gastrointestinal complications, such as gastric ulcer; condom/sheath, tape/coating, fibres, nano-particles, or micro-spheres for wound care; devices for prevention of infection and obtainment of anti-thrombotic effect; feedstuff or food; and patches etc., for pre-treatment of an area before insertion of a catheter, venflone etc. Said device may for example be any of which are mentioned in the pending European patent applications; 04029796.2, 05006474.0, 05002937.0, 05002935.4, 05002934.7, 05002933.9, 05006495.5, 05006489.8, 05011785.2, and 05011786.0, which pending European patent applications are based on inventions made of the present inventor, and which pending applications hereby are integrated as references in the present application.

Of course, in other embodiments of the present invention, the liquid contained in the micro capsules may be any other proton donor, such as water, body fluids (blood, lymph, bile, etc.), alcohols (methanol, ethanol, propanols, butanols, pentanols, hexanols, phenols, naphtols, polyols, etc.), aqueous acidic buffers (phosphates, succinates, carbonates, acetates, formats, propionates, butyrates, fatty acids, amino acids, etc.), or any combinations of these, or any other polar solvent, with the ability to initiate and produce elution of NO from said NO eluting polymers.
In another embodiment a substance that changes color when it comes in contact with water can be incorporated in the device. Thus when the water capsules or water bag breaks the material changes color, thereby indicating that the material is activated.

In another embodiment of the present invention the device or system only allows NO-elution in one direction. In this kind of embodiment one side of the device has low permeability, or substantially no permeability, to nitric oxide. This may also be accomplished by applying a material on one side of the device according to the invention that is not permeable to NO. Such materials may be chosen from the group comprising common plastics, such as fluoropolymers, polyethylene, polypropylene, polycrylonitrile, polyurethane, polyvinylacetates, polylactic acids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. This embodiment is also easy to manufacture as the NO eluting polymer, e.g. L-PEI (or nitric oxide eluting polymer and carrier material, which will be explained in more detail below) may be electro or gas-jet spun onto the surface of the device according to the invention of e.g. the mentioned plastics, latex, or cotton.

In still another embodiment the device is provided with one membrane, which is permeable to nitric oxide, on a first side of the device, and another membrane, which has low permeability or substantially no permeability to nitric oxide, on a second side of said device. This embodiment provides the possibility to direct the elution to said first side of the device, while the elution of nitric oxide is substantially prevented from said second side. Thereby,
a greater amount of nitric oxide will reach the intended area to be treated.

The activation of the nitric oxide eluting polymer may be accomplished by contacting said polymer with a suitable proton donor. In one embodiment the proton donor may be selected from the group comprising water, body fluids (blood, lymph, bile, etc.), alcohols (methanol, ethanol, propanols, butanols, pentanols, hexanols, phenols, naphtols, polyols, etc.), aqueous acidic buffers (phosphates, succinates, carbonates, acetates, formates, propionates, butyrates, fatty acids, amino acids, etc.), or any combinations of these.

By adding a surfactant in the proton donor one can facilitate the wetting of the device. The surfactant lowers the surface tension and the activating fluid is easily transported throughout the device.

Another embodiment of the present invention comprises mixing the nitric oxide eluting polymer, or a mixture of the nitric oxide eluting polymer and a carrier material, with an absorbent agent. This embodiment provides the advantage of an accelerated elution of nitric oxide since the polymer, or polymer mixture, via the absorbent agent, may take up the activating fluid, such as water or body fluid, much faster. In one example 80 % (w/w) absorbent agent is mixed with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and a carrier material, and in another embodiment 10 to 50 % (w/w) absorbent agent is mixed with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material.

Since the elution of nitric oxide is activated by a proton donor, such as water, it may be an advantage to keep the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material, in contact with said proton donor. If an indication requires an elution of
nitric oxide during a prolonged period of time, a system is advantageous, which presents the possibility to keep the proton donor in contact with the nitric oxide eluting polymer, or mixture of nitric oxide eluting polymer and carrier material. Therefore, in still another embodiment of the present invention, the elution of nitric oxide may be regulated by adding an absorbent agent. The absorbent agent absorbs the proton donor, such as water, and keeps the proton donor in close contact with the nitric oxide eluting polymer during prolonged periods of time. Said absorbent agent may be selected from the group comprising polyacrylates, polyethylene oxide, carboxymethylcellulose, and microcrystalline cellulose, cotton, and starch. This absorbent agent may also be used as a filling agent. In this case said filling agent may give the nitric oxide eluting polymer, or mixture of said nitric oxide eluting polymer and a carrier material, a desired texture.

The device or system may then be applied on a target area on which exposure of NO is desired. Such a target area may for example be located on an animal organ, such as the skin, mucous membrane etc, or any other area mentioned and/or described in the pending European patent applications mentioned above.

When the device or system is applied on the target area the device or system is compressed or squeezed. Said compression or squeezing results in breakage of the micro capsules. The NO eluting polymer is thus exposed to said water or water containing liquid, and the elution of NO from the NO eluting polymer is initiated on the target area.

In other embodiments of the present invention the liquid inside the micro capsules is released by heating or shearing the micro capsules until the micro capsules are ruptured.
The elution of NO from said polymer may be used for any conceivable purpose, such as to obtain anti microbial and/or viral effect, vasodilating effect, anti fungal effect, etc.

In another embodiment of the present invention microcapsules, containing water or water containing liquid, are manufactured in a manner according the state of the art. These micro capsules are then covered with an NO eluting polymer, according to above. The covering of the micro capsules is for instance done by spinning the NO eluting polymer onto the micro capsules, containing water or water containing liquid, according to Fig. 2, in which an NO eluting polymer 103 encloses a microcapsule 101. When the combined particle 200 is compressed, or in any other way ruptured, the liquid, such as water or water containing liquid, will get in contact with the NO eluting polymer 103, and thus the elution of NO is initiated. The particles 200 may for example constitute a film, sheath, tape, etc., such as illustrated in Fig. 4.

The spinning may for example be done by air spinning, electro spinning, gas spinning, wet spinning, dry spinning, melt spinning, or gel spinning. In this way microcapsules covered with NO eluting polymer may be manufactured.

In other embodiments of the invention, the NO eluting polymer may be mixed and manufactured together with other suitable materials, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylactic acids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. The NO-eluting polymer may be integrated in, spun together with, or spun on top of, any of these materials in all of
the embodiments of the present invention. In these embodiments the elution of NO is regulated, such as by decreasing the elution rate, by the admixed materials.

In an embodiment of the invention the NO eluting polymer is in form of nano-particles, or micro spheres. These nano-particles, or micro-spheres, may be formed from the NO-eluting polymers by grinding or in any other way divide the spun polymeric fibres into small parts.

In another embodiment of the device or system, said device or system may be manufactured in the form of a polyurethane, or polyethylene, tape or coating. This polyurethane tape or coating may easily be wrapped around, or applied on, the target area to be treated. At least the side facing the body may be covered with NO-eluting nano-particles, or micro-spheres, or nano-filament of NO-eluting polymer. The covering of NO-eluting nano-particles, or micro-spheres, or nano-filament of NO-eluting polymer is in turn covered with the micro capsules, containing water or water containing liquid. When these particles or filaments get in contact with the water, moisture or water containing liquid inside the micro capsules, after the micro capsules have been compressed or squeezed until the micro capsules break and the water or water containing liquid inside the micro capsules is let out, the NO eluting polymer starts to elute NO.

The increased blood perfusion and vasodilatation, that may obtained from the device or system may in another embodiment of the present invention, result in an improved effect when combined with other products, comprising active components. Thus, the synergistic effect from NO and other wound healing, or anti-microbial, anti-inflammatory, or anti-viral, components is within the scope of the present invention.

These fibres, nano-particles, or micro-spheres, may in one embodiment be formed from the NO-eluting polymers
comprised in the present invention, for example polyalkyleneimines, such as L-PEI (Linear PolyEthyleneImine), B-PEI (Branched PolyEthyleneImine), and PEI-C (PolyEthyleneImine Cellulose), which polymers have the advantage of being biocompatible. They may also be encapsulated in any suitable material, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylacticacids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these. In the context of this embodiment the term “encapsulate” is intended to be interpreted as fixating the nitric oxide eluting polymer in a three dimensional matrix such as a foam, a film, a nonwoven mat of nano-fibers, fibers, or other materials with the capability to fixate the NO eluting polymer, or enclosing the nitric oxide eluting polymer in any suitable material. Thus, the term “encapsulate” in this embodiment should not be confused with the terms “micro encapsulate” or “micro encapsulation” used in the description of the present invention.

In a further embodiment fibres, nano-particles, or micro-spheres of an NO eluting polymer are mixed with micro capsules, containing water or water containing liquid, according to Fig. 3, wherein fibres, nano-particles, or micro-spheres 200 of an NO eluting polymer are mixed with micro capsules 100. The mixture 300 is then for example applied on a carrier material, such as a tape of polyethylene or any other suitable carrier material. From this tape patches, sheets, or the like, are constructed, which patches, sheets, or the like then are applied on the target area to which elution of NO is desired. It is also
possible to produce a film, tape, etc., directly from a mixture of fibres, nano-particles, or micro-spheres 200 and the micro capsules 100.

In still another embodiment, according to Fig. 6 and 7, the micro capsules, containing water or water containing liquid, are formed into a film, tape, or sheath 602. Thereafter, a film, tape, or sheath of an NO eluting polymer 601 is glued onto the film, tape, or sheath of micro capsules 602, containing water or water containing liquid. Preferably the film, tape, or sheath of the NO eluting polymer 601 is glued onto the film, tape, or sheath of the micro capsules, containing water or water containing liquid, in patterned way. The obtained pattern includes spaces where there is no glue, in which spaces the water or water containing liquid will be transported to the NO eluting polymer once the micro capsules are broken from compression or squeezing. When the water or water containing liquid gets in contact with the NO eluting polymer the elution of NO starts. Thus, the combination of film, tape, or sheath of micro capsules, containing water or water containing liquid, and NO eluting polymer may be applied on a target area, such as in Fig. 8. Thereafter the combination is compressed or squeezed, which results in that the target area is exposed to NO.

In yet another embodiment the NO eluting polymer is spun directly onto the film, tape, or sheath of micro capsules, containing water or water containing liquid, according to Fig. 5, in which fibres 501 of an NO eluting polymer are spun onto the micro capsules 100. The combination of film, tape, or sheath of micro capsules, containing water or water containing liquid, and spun NO eluting polymer may be applied on a target area. Thereafter the combination is compressed or squeezed, which results in that the target area is exposed to NO.
In still another embodiment of the present invention the device or system is provided with an activation indicator. This activation indicator indicates when the micro capsules are satisfactorily broken, hence when the NO eluting polymer is subjected to enough water or water containing liquid to elute an efficient amount of NO. This activation indicator may for example be obtained by coloring the water or water containing liquid that is trapped inside the micro capsules. When the micro capsules are broken the colored water or water containing liquid escapes the microcapsules and the color gets visualized while efficiently wetting the NO eluting polymer. Another way of obtaining an activation indicator is to choose a manufacture the micro capsules in a material, or choose a wall thickness of said micro particles, that creates a sound when the micro capsules break. It is also possible to admix a scent in the water or water containing liquid, contained in the micro capsules. This results in that the user of the device or system may smell the scent when the water or water containing liquid escapes from the micro capsules after breakage thereof. The released NO may even synergetically augment this scent impression, by itself or by influencing the smell sensing organs, e.g. by vasodilation thereof.

In another embodiment of the present invention the device or system only allows NO-elution in one direction. In this kind of embodiment one side of the device according to the invention is non-permeable to NO. This may be accomplished by applying a material on one side of the device according to the invention that is not permeable to NO. Such materials may be chosen from the group comprising common plastics, such as polyethylene, polyurethane etc. This embodiment is also easy to manufacture as the NO eluting polymer, e.g. L-PEI nano fibres may be electro or gas-jet spun onto the surface of the device according to
the invention of e.g. the mentioned plastics, latex, or cotton.

In yet another embodiment of the present invention the NO-eluting device or system is acting as a booster for drug eluting patches, e.g. pharmaceuticals, vitamins, nicotin, nitroglycerin, Non-Steroidal Anti-Inflammatory Drugs (NSAID), such as diclofenac, ibuprofen, aspirin, naproxen, COX-2 inhibitors, choline magnesium trisalicylate, diflunisal, salsalate, fenoprofen, flurbiprofen, ketoprofen, oxaprozin, indomethacin, sulindac, tolmetin, meloxicam, piroxicam, meclofenamate, mefenamic acid, nabumetone, etodolac, ketorolac, celecoxib, valdecoxib, and rofecoxib; steroids, such as cortisone, prednisone, methylprednisolone, prednisolone, vitamin D, estrogen, cholestrol, beclomethasone, flunisolide, fluticasone, triamcinolone, desonide, clobetasol, alclometasole, desoximetasone, betamethasone, halcinonide and dexamethasone; pain reliefs, such as motrin, feldene, naprosyn, lidocaine, and prilocaine; and other substances, such as indinavirsulfate, finasteride, aprepitant, montelukast sodium, alendronate sodium, rofecoxib, rizatriptan benzoate, simvastatin, finasteride, ezetimibe, caspofungin acetate, ertapenem sodium, dorzolamide hydrochloride, timolol maleate, losartan potassium, and hydrochlorotiazide; etc. This embodiment presents a device with the advantage of combining two treatments, of significant value, in one treatment.

Hence, when the device or system is used as a medical application, such device or system may achieve a synergetic effect, when NO is eluted from said device or system. NO has a vasodilatory effect on the region where the device having the combination compound actuates. Vasodilated tissue is more susceptible to certain medications and thus more easily treated by the medical preparations and still NO has in addition to that the anti-inflammatory, anti-
bacterial etc. effect. Hence, an unexpected surprisingly effective treatment is provided.

The device or system elutes nitric oxide (NO) from said eluting polymer in a therapeutic dose, such as between 5
The device elutes nitric oxide (NO) from said eluting polymer in a therapeutic dose, such as between 0.001 to 5000 ppm, such as 0.01 to 3000 ppm, such as 0.1 to 1000 ppm, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 ppm. The concentration may vary widely depending on where the concentration is measured. If the concentration is measured close to the actual NO eluting polymer the concentration may be as high as thousands of ppm, while the concentration inside the tissue in this case often is considerably lower, such as between 1 to 1000 ppm.

In the embodiments of the present invention it may be suitable to control or regulate the time span of NO release from the device according to the invention. This may be accomplished by integrating other polymers or materials in said device. These polymers or materials may be chosen from any suitable material or polymer, such as polyethylene, polypropylene, polyacrylonitrile, polyurethane, polyvinylacetates, polylactic acids, starch, cellulose, polyhydroxyalkanoates, polyesters, polycaprolactone, polyvinylalcohol, polystyrene, polyethers, polycarbonates, polyamides, polyolefins, poly(acrylic acid), Carboxy Methyl Cellulose (CMC), protein based polymers, gelatine, biodegradable polymers, cotton, and latex, or any combinations of these.
The NO-eluting polymers in the device or system may be combined with silver, such as hydroactivated silver. The integration of silver in the devices gives the healing process an extra boost. Preferably the silver is releasable from the devices in the form of silver ions. The integration of silver in the device may present several advantages. One example of such an advantage is that the silver may keep the device in itself free from bacteria or viruses, while the nitric oxide eluting polymer elutes the therapeutic dosage of nitric oxide to the target site.

The device or system may be manufactured by, for example electro spinning of L-PEI or other polymers comprising L-PEI or being arranged in combination with L-PEI. L-PEI is the charged at a characteristic voltage, and a fine jet of L-PEI releases as a bundle of L-PEI polymer fibres. This jet of polymer fibres may be directed to a surface to be treated. The surface to be treated may for example be any suitable material. The electro spun fibres of L-PEI then attach on said material and form a coating/layer of L-PEI on the device according to the invention.

It is of course possible to electro spin the other NO-eluting polymers, according to above, on the device according to the invention while still being inside the scope of the present invention.

In one embodiment the NO-eluting polymers are electro spun in such way that pure NO-eluting polymer fibres may be obtained.

It is also within the scope of the present invention to electro spin an NO-eluting polymer together with other suitable polymer/polymers.

Gas stream spinning, dry spinning, wet spinning, melt spinning, gel spinning, or air spinning, of said NO-eluting polymers onto a film of microencapsulated water or water containing liquid or a combination of microencapsulated
water or water containing liquid and any suitable NO eluting or non NO eluting polymer is also within the scope of the present invention.

The manufacturing process presents the advantages of large contact surface of the NO-eluting polymer fibres with the area to be covered with NO eluting polymer, effective use of NO-eluting polymer, and a cost effective way of producing the device or system.

Hereinafter, some potential uses of the present invention are described:

A method of treating an animal organ, comprising applying a device or system, that comprises a nitric oxide (NO) eluting polymer configured for eluting a therapeutic dosage of nitrogen oxide (NO) when used for said treatment and micro capsules, containing water or water containing liquid, rupturing said micro capsules to set said water or water containing liquid in contact with said NO eluting polymer, and thereby exposing said organ to said nitric oxide when said polymer in use elutes nitrogen oxide (NO) by eluting a therapeutic dose of nitric oxide from said nitric oxide eluting polymer to said treatment site.

The method according to above, wherein said site of said at least one wound is a head, face, neck, shoulder, back, arm, hand, stomach, genital, thigh, leg, or foot of an animal, such as a human, of a body, and wherein said method comprises applying a device, according to above, to said head, face, neck, shoulder, back, arm, hand, stomach, genital, thigh, leg, or foot, for said exposure.

Use of nitric oxide (NO) in a therapeutic dose for therapeutically treating and/or preventing at least one part of an organ.

The invention may be implemented in any suitable form. The elements and components of the embodiments according to the invention may be physically, functionally,
and logically implemented in any suitable way. Indeed, the functionality may be implemented in a single unit, in a plurality of units, or as part of other functional units.

Although the present invention has been described above with reference to specific embodiments, it is not intended to be limited to the specific form set forth herein. Rather, the invention is limited only by the accompanying claims and, other embodiments than the specific above are equally possible within the scope of these appended claims.

In the claims, the term "comprises/comprising" does not exclude the presence of other elements or steps. Furthermore, although individually listed, a plurality of means, elements or method steps may be implemented.

Additionally, although individual features may be included in different claims, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms "a", "an", "first", "second" etc do not preclude a plurality. Reference signs in the claims are provided merely as a clarifying example and shall not be construed as limiting the scope of the claims in any way.
AMENDED CLAIMS 2007-11-22

1. A medical device, comprising a nitric oxide (NO) eluting polymer configured for elution of nitric oxide (NO) therefrom upon contact between a proton donor and said nitric oxide (NO) eluting polymer,

   wherein said device is adapted to be applied on a target area on which exposure of nitric oxide (NO) is desired, and wherein said device is chosen from a patch, ointment, tape, sock, condom, or sheet;

   characterized in that said device is provided with a proton donor configured for said contact, and which is microencapsulated in micro capsules, and wherein said micro capsules, in which said proton donor is contained, are arranged to release at least a part of said proton donor after breakage of said micro capsules, and said micro capsules are arranged such that said proton donor, when released after said breakage, at least partly contacts said nitric oxide (NO) eluting polymer such that elution of nitric oxide (NO) from said nitric oxide (NO) eluting polymer is initiated, whereby said elution of nitric oxide (NO) from said nitric oxide (NO) eluting polymer in use of said device is provided on said target area.

2. The medical device according to claim 1, wherein said nitric oxide (NO) eluting polymer comprises diazeniumdiolate groups, S-nitrosylated groups, and O-nitrosylated groups, or any combination of these.

3. The medical device according to claim 1 or 2, wherein said nitric oxide (NO) eluting polymer is L-PEI (linear polyethyleneimine), loaded with nitric oxide (NO) through said diazeniumdiolate groups, S-nitrosylated groups, or O-nitrosylated groups, or any combination of these.
4. The medical device according to claim 1, 2, or 3, wherein said nitric oxide eluting polymer is selected from the group comprising amino cellulose, amino dextrans, chitosan, aminated chitosan, polyethyleneimine, PEI-cellulose, polypropyleneimine, polybutyleneimine, polyurethane, poly(buthanediol spermate), poly(iminocarbonate), polypeptide, Carboxy Methyl Cellulose (CMC), polystyrene, poly(vinyl chloride), and polydimethylsiloxane, or any combinations of these, and these mentioned polymers grafted to an inert backbone, such as a polysaccharide backbone or cellulosic backbone.

5. The medical device according to claim 1, 2, 3, or 4, wherein said proton donor is selected from the group comprising water, blood, lymph, bile, methanol, ethanol, propanols, butanols, pentanols, hexanols, phenols, naphtols, polyols, phosphates, succinates, carbonates, acetates, formates, propionates, butyrates, fatty acids, and amino acids, or any combinations of these.

6. The medical device according to claim 1, wherein said microencapsulated proton donor is microencapsulated in formaldehyde and gelatine microcapsules.

7. The medical device according to claim 1, wherein said device comprises a film comprising said proton donor microencapsulated in said microcapsules, wherein said NO eluting polymer is spun onto said film.

8. The medical device according to claim 1, wherein said device comprises said NO eluting polymer mixed with said microcapsules containing said proton donor.

9. The medical device according to claim 8, wherein said NO eluting polymer, configured to elute NO, is
provided in form of fibres, nano-particles and/or micro-spheres.

10. The medical device according to claim 1, wherein said NO eluting polymer is provided in form of a film, sheath or tape, which is attached onto a film, sheath, or tape comprising said proton donor, microencapsulated in said microcapsules.

11. The medical device according to claim 1, wherein said NO eluting polymer comprises a secondary amine in a backbone or a secondary amine as a pendant.

12. The medical device according to claim 11, wherein a positive ligand is located on a neighbor carbon atom to the secondary amine.

13. The medical device according to claim 1, comprising an absorbent agent.

14. The medical device according to claim 13, wherein said absorbent agent is selected from the group comprising polyacrylate, polyethylene oxide, Carboxy Methyl Cellulose (CMC), microcrystalline cellulose, cotton, or starch, or any combinations thereof.

15. The medical device according to claim 1 or 13, comprising a cation for stabilizing the nitric oxide eluting polymer.

16. The medical device according to claim 15, wherein said cation is selected from the group comprising Na⁺, K⁺, Li⁺, Be²⁺, Ca²⁺, Mg²⁺, Ba²⁺, and/or Sr²⁺, or any combinations thereof.

17. The medical device according to claim 10, wherein said attachment is performed with glue.
18. The medical device according to claim 17, wherein said glue is applied in a pattern allowing for the proton donor inside said micro capsules to get in contact with said NO eluting polymer after breakage of said micro capsules.

19. The medical device according to claim 1, wherein said device is supplied with an activation indicator.

20. The medical device according to claim 19, wherein said activation indicator is in form of a color, scent, and/or sound indicator.

21. The medical device according to claim 1, wherein one side of the device has low permeability, or substantially no permeability, to nitric oxide.

22. The medical device according to claim 21, wherein the device is provided with one membrane, which is permeable to nitric oxide, on a first side of the device, and another membrane, which has low permeability or substantially no permeability to nitric oxide, on a second side of said device.

23. A manufacturing process for a medical device according to claim 1, comprising:
   selecting a plurality of nitric oxide (NO) eluting polymeric particles, including nano fibres, nano particles or micro spheres,
   microencapsulating a proton donor to form micro capsules containing said proton donor,
   applying said micro capsules on said nitric oxide (NO) eluting polymer, to form said device.

24. The manufacturing process according to claim 23, further comprising
selecting said nitric oxide (NO) eluting polymer such
that it is configured to elute a therapeutic dosage of
nitric oxide (NO),

selecting a carrier material, which carrier material
is configured to regulate and control the elution of said
therapeutic dosage of nitric oxide (NO),

incorporating the NO-eluting polymer with said
carrier material into an nitric oxide (NO) eluting
material, such that said carrier material, in use of said
device, regulates and controls the elution of said
therapeutic dosage of nitric oxide (NO), and

deploying said nitric oxide eluting material into a
suitable form, or as a coating onto a carrier, to form at
least a part of said device, such that said device is
configured to expose a therapeutic target site to said
nitric oxide when said NO-eluting polymer in use elutes
nitric oxide (NO).

25. The manufacturing process according to claim 24,
wherein said selecting said nitric oxide (NO) eluting
polymer comprises selecting a plurality of nitric oxide
(NO) eluting polymeric particles, preferably nano fibres,
nano particles or micro spheres.

26. The manufacturing process according to claim 24
or 23, wherein said incorporating said NO-eluting polymer
with said carrier material comprises integrating said NO-
eluting polymer in said carrier material, spinning said NO-
eluting polymer together with said carrier material, or
spinning said NO-eluting polymer on top of said carrier
material, in order to redefine nitric oxide eluting
characteristics of said device.

27. The manufacturing process according to claim 23,
further comprising integrating silver in said device.
28. The manufacturing process according to claim 23, further comprising microencapsulating said proton donor in said micro capsules, prior to deploying said nitric oxide (NO) eluting polymer.

29. The manufacturing process according to claim 23, wherein said applying comprises pattern gluing, or spinning the NO eluting polymer onto said micro capsules.

30. The manufacturing process according to claim 23, comprising forming the micro capsules into a first film, tape, or sheath, forming a second film, tape, or sheath comprising said NO eluting polymer, and gluing the first film, tape, or sheath of micro capsules to said second film, tape, or sheath comprising said NO eluting polymer.

31. The manufacturing process according to claim 30, wherein said gluing comprises patterned gluing, such that a pattern is obtained including glue free spaces.

32. The manufacturing process according to claim 23, comprising forming the micro capsules into a first film, tape, or sheath, and directly spinning a material comprising the NO eluting polymer onto the film, tape, or sheath of micro capsules, containing a proton donor.

33. The manufacturing process according to claim 23, comprising providing an activation indicator configured to indicate when the micro capsules are broken such that the NO eluting polymer is subjected to said proton donor to elute NO.

34. The manufacturing process according to claim 33, wherein said providing an activation indicator comprises providing a coloring agent inside the micro capsules.
35. The manufacturing process according to claim 33, wherein said providing an activation indicator comprises selecting a material for the micro capsules, or choosing a wall thickness of said micro capsules, that creates a sound when the micro capsules break.

36. The manufacturing process according to claim 33, wherein said providing an activation indicator comprises admixing a scent material into the micro capsules.

37. The manufacturing process according to claim 33, wherein said providing an activation indicator comprises providing a substance that changes color when it comes in contact with the proton donor.

38. A method of activating nitric oxide (NO) elution from a medical device according to claim 1, said device comprising a NO eluting polymer configured to elute nitric oxide (NO) therefrom upon contact with a proton donor, comprising arranging said NO eluting polymer in the vicinity of micro capsules containing said proton donor, and releasing said proton donor by rupturing said micro capsules for contacting said NO eluting polymer with said proton donor.

39. The method according to claim 38, wherein said rupturing is performed with pressure, shear, or heat.

40. A method of treating an animal organ, comprising applying a medical device or system, that comprises a nitric oxide (NO) eluting polymer configured for eluting a therapeutic dosage of nitrogen oxide (NO) when used for said treatment and micro capsules, containing a proton donor containing liquid, including water or water containing liquid, rupturing said micro capsules to set
said proton donor containing liquid in contact with said NO eluting polymer, and thereby exposing said organ to said nitric oxide when said polymer in use elutes nitrogen oxide (NO) by eluting a therapeutic dose of nitric oxide from said nitric oxide eluting polymer to said treatment site.

41. The method according to claim 40, wherein said site of said at least one wound is a head, face, neck, shoulder, back, arm, hand, stomach, genital, thigh, leg, or foot of an animal, such as a human, of a body, and wherein said method comprises applying a device, according to above, to said head, face, neck, shoulder, back, arm, hand, stomach, genital, thigh, leg, or foot, for said exposure.
Application number / numéro de demande: 7006/50902

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