Title: DRUG DELIVERY DEVICES AND METHODS AND APPLICATIONS THEREOF

Abstract: A drug delivery device (20) comprising, a conducting polymer element (22) and a substance incorporating element (24) containing a substance, wherein, when the device is placed within a surrounding environment (28) upon changing of an electric potential to the conducting polymer element, there is provided an initiation and/or control of a release of the substance from the delivery device. Also provided is a method for delivering a substance to a target location. Furthermore, an application of the device is provided.
Drug delivery devices and methods and applications thereof

Technical Field
The present disclosure relates to drug delivery devices, and methods for delivery of substances to a target location. Furthermore, the invention relates to applications of the drug delivery device.

Background
The present disclosure addresses the problem of delivering therapeutic agents on demand, at selected times and at precise locations in a body and more particularly to the problem of controlling the amount of therapeutic agent released, the release rate and the release schedule near a treatment site within the body.

It is often desirable to administer therapeutic agents such as drugs only to localized sites in the body and at selected times to alleviate widespread drug toxicity issues, to increase the efficacy of drug delivery, to decrease the risk of side-effects, and for selective treatment of localized ailments. Various alternatives have been proposed for controlled and localized drug delivery.

U.S. Pat No. 5545208 and European patent EP1 117351 describe drug coated intravascular stents capable of locally delivering a drug to a treatment site by passive diffusion of a drug from the stent surface. U.S. Pat. No. 5674192 describes a catheter with a PTCA balloon coated with a hydrogel layer. The hydrogel is filled with a biological agent before being inserted into the body. Upon expansion of the balloon at the treatment site, the biological agent is forced from the hydrogel layer due to compression forces between the balloon and the vessel wall. U.S. Pat. Nos. 6364856, 7048714, and 6149641 describe alternative forms of a drug eluting balloon to further improve drug delivery to the treatment site.

U.S. Pat. No. 6468304 describes a conducting polymer coating onto an implant, such as a stent, which is electrochemically loaded with charged bioactive molecules, attached through an ionic bonding process. U.S. Pat. Nos. 6309380 and 6326017 describe still further polymer coatings that incorporate a bioactive agent. In each of these cases, the bioactive agent is slowly released from the polymer coating due to passive diffusion and/or degradation of the host polymer.

U.S. Pat. No. 5735897 discloses the use of a drug containing layer that swells irreversibly when in contact with blood and squeezes drug out.

Such systems provide a means of delivering drug locally to a treatment site, but often suffer from poor overall delivery efficacy due to the loss of drug during travel to the treatment site, and/or washout of drug into the
blood stream. In addition, such systems often require the surgeon to handle toxic drugs during the surgical procedure. Moreover such systems feature little possibility for actively controlling the release profile and achieving short and rapid release at a desired time.

Another alternative method relates to the use of responsive gels have been considered for constructing devices for drug delivery. Often these gels swell and expand in response to pH or temperature. U.S. Pat. Nos. 5876741 and 5651979 describe systems for delivering active substances into an environment using cross-linked polymer gel networks. 5876741 discloses a container-enclosed hydrogel, which experiences an increase in volume upon exposure to a predetermined environmental condition, such as pH or temperature. The expansion of the hydrogel presses out drugs in an adjacent compartment through an orifice. U.S. Pat. No. 6394997 further describes the use of an electrorheological gel based drug delivery system that can be activated by an externally applied electrical field. Volumetric changes in the gel are used to mechanically pressurize a drug reservoir and force drug out into the surroundings.

Osmotic delivery mechanisms are also a known method of drug delivery. U.S. Pat. Nos. 3732865, 3987790, 5059423, 5137727, 5308348, 5413572, and 5985305 all describe variations on osmotic drug delivery devices. Such prior art generally includes a chamber having at least a portion of a wall that selectively passes water into the interior of the chamber containing an osmotic agent. The absorption of water into the chamber results in its expansion. Mechanical means are provided between the chamber and a drug reservoir such that the expansion of the chamber releases the drug into the surroundings.

Although such systems can controllably initiate drug delivery, they are generally very slow to react to stimuli, thus limiting their use during surgical procedures. They are also rather bulky which limits their ability to be used internally to a body in conjunction with minimally invasive techniques. In addition, their response to stimulus is very pH and temperature dependent. Thus variation of environmental conditions in the vicinity of the treatment site can significantly affect the release rate and overall dosage of drug delivered from such devices. They must also be stored in a solvent bath, thereby limiting their practical use and complicating packaging, storage, delivery and integration of such solutions into products.

U.S. Appl. No 2004/0037050 describes a medical device having drug loaded microcapsules arranged on its outer surface. As the medical device expands against a lumen wall, the microcapsules are fractured and drug is released from the device. One embodiment mentions using an electroactive polymer actuator to displace the outer surface of the medical device and thus break the microcapsules.
It may be difficult to control the overall dosage released from such systems, especially when biasing directly against the lumen wall, as it would be difficult to assure that the same fraction of microcapsules are ruptured in any given release condition.

It is also known to deliver drugs in a controlled manner using mechanical pumping devices. U.S. Pat. No. 4360019 describes an implantable infusion device including actuating means (a solenoid driven miniature pump) for delivery of drug through a catheter.

Such devices often comprise many moving parts and compartments, which complicate device miniaturization and thus inhibit precision placement of the devices near a treatment site. In an attempt to further miniaturize mechanical pumping devices, recent efforts have focused on electroactive materials.

Electroactive polymers (EAP) are a comparatively novel class of materials that have electrically controlled properties. U.S. Appl. No. 2004/0068224 describes an implantable infusion pump whereby an EAP actuator compresses a drug chamber that subsequently pumps a drug into the surroundings. U.S. Pat. No. 6663615 describes utilizing EAP valves to open and close an outlet of a drug reservoir.

Even with the inclusion of EAP actuators into traditional mechanical drug delivery systems, miniaturization remains an outstanding issue along with dosage control and efficacy of the delivery of the therapeutic agent to the treatment site.

EAP can also be used to deliver ionic therapeutic agents by means of electrochemical and/or electrokinetic transport. U.S. Pat. No. 4585652 describes the use of polymers with charged redox sites, such as polypyrrole, for controlled delivery of ionic bioactive chemicals that are ionically bound to the EAP. WO0213785 describes an improvement on this method by using a burst type release profile. WO0125406 describes the use of electroactive polymers as drug release pads by the same principle.

Instead of using the redox properties of conducting polymers directly, WO9833552 discloses a different, indirect mechanism for electro release. Generation of protons by electrochemical oxidation at a second functional group, such as a cysteine group, causes breakage of the ionic bond that binds the charged species to the matrix, thereby releasing the electro-releasable species.

U.S. Pat. No. 6049733 discloses the incorporation of ion exchange materials, for which their definition includes polypyrrole, into a drug reservoir of an electrotransport system to assist with competitive ion immobilization to enhance traditional electrokinetic drug delivery.
Such drug delivery approaches are limited in that they are only applicable to delivery of drugs that can participate in electrochemical redox reactions. This requires that the drug is charged and available in a particular ionic form. Furthermore, special design considerations exist for each drug variant that is to be delivered, thereby making them unsuitable for general drug delivery. Furthermore the inventors have found that many ionic drugs cannot be incorporated into conducting polymers by common fabrication techniques, such as during electropolymerization processes. Moreover electrochemical reactions have been found to interfere with and/or alter the sensitive and important chemical structure of some drug species that have been bound to conducting polymers through ionic interactions.

Summary

In light of the aforementioned respects of known devices, a general object of the present disclosure is to provide an alternative and/or improved device and method, in particular which overcome at least some of the disadvantages of the prior art.

Another object of the present disclosure is to provide an alternative and/or improved device and method for controlled delivery of chemical substances, in particular for pharmacologically active substances.

Another object of the invention is to provide a means of delivering a wide range of therapeutic agents without excessive regard for the chemical properties of the therapeutic agent.

The objects are wholly or partially achieved by devices and methods according to the appended independent claims. Embodiments are set forth in the dependent claims and in the following description and drawings.

According to a first aspect, there is provided a drug delivery device comprising, a conducting polymer element and a substance incorporating element containing a substance. When the device is placed within a surrounding fluid, upon changing of an electric potential to the conducting polymer element, the conducting polymer element provides an electrically controllable flux of a fluid, an ion and/or the like between the surrounding environment and the device. The elements are adjacently arranged to enhance transfer of the flux provided there between. The flux is directed into and/or out of the conducting polymer element and into and/or out of the substance incorporating element, thereby providing an initiation and/or control of a release of the substance from the delivery device by mobilizing, convective, and/or diffusive processes.

By a conducting polymer element is meant an element of an essentially continuous material containing a conducting polymer material. There may be two or more of such elements containing the same or different conducting polymer material (-s).
By substance incorporating element is meant an element of an essentially continuous material containing a substance. There may be two or more of such elements containing the same or different substance(s).

The conducting polymer element or elements may be arranged in a layer or layers, for example. If several elements are arranged within one layer, for example, they may be arranged so as to provide cavities between them. The substance incorporating element may then be arranged in a similar way, wherein the substance incorporating element or elements may be arranged within the same layer as the conducting polymer element(s) or elements. For example, a substance incorporating element may be arranged within the above-mentioned cavity. The opposite arrangement may also be the case. Cavities may also be disposed within an element of one kind, in which cavities elements of the other kind may be arranged. Each element may also form a layer within a sheet structure.

By adjacently arranged is meant that the elements are arranged in close proximity and perhaps arranged in contact. This arrangement is advantageous for enhancing the magnitude of the flux as well as the concentration of a constituent within the flux as such effects are reduced at increased distances from the conducting polymer element. Furthermore, being adjacently arranged also reduces the distances over which a constituent of the flux must travel within the delivery device upon changing of the electric potential applied to the conducting polymer element, thereby reducing the overall size of the device, improving release rate of the drug and improving the precision with which the drug may be delivered to a particular treatment site.

The device can provide the possibility to release a wide range of substances. Different types of substances that may be released range from hydrophobic, polar, non-polar, charged or neutral materials to drugs or a biologically active substance. Some classes of therapeutic agents that may be released from the delivery device include antiproliferative agents, anti-inflammatory agents, anti-migratory agents, antineoplastic agents, anti-mitotic agents, anti-thrombotic agents, anti-restenotics, antibiotics, vascular cell growth promoters, vascular cell growth inhibitors, vasodilating agents, neuro-transmitters, immunosuppressive agents and neuro-modulators. The device may release substances provided in the form of a fluid, a gel or even a solid.

By flux of a fluid, ion and/or the like is meant a flow of a species, be it a continuous fluid or ionic species, with a flow vector indicative of the direction of flow. The flux may comprise multiple species and the concentrations of the species and/or the species themselves comprising the flux may change during the substance release process depending on the local conditions under which the flux is provided. The flux may be directed from the surroundings into the device or vice versa and may be directed into or out of the substance incorporating element and into or out of the conducting polymer element. The flux may also pass by the substance incorporating
element wherein the convective transfer processes between the substance incorporating element and the flux are enhanced under such conditions.

Such a device provides an electrically controllable release of a substance contained in the substance incorporating element (s), such as a drug. For example, the fluid uptake or removal can be controllable, and not necessarily on or off regulated, but rather controlled to a desired level, e.g. fluid uptake to a level of 20%, 50% or 75% (w/w). Accordingly, the substance release may be controlled to a desired level as well as controlled in time as a single release or repetitious release (pulsed/oscillated release) of the substance. The device provides a general release mechanism provided for a wide range of drugs, wherein the substance is provided alone or along with agents such as a carrier.

By mobilizing, convective and/or diffusive processes is meant the general processes by which the substance is released in this invention. Mobilizing processes refer to processes of disintegration or breakup of a substance or substance incorporating element. Mobilizing processes include physical erosion (in combination with convective processes), degradation, decomposition, disintegration or dissolution. Convective processes refer to processes involving mass transport along with and assisted by the flux. Diffusive processes refer to mass transport based on concentration gradients of material within and around the drug delivery device.

According to one embodiment, the conducting polymer element may have an electrically controllable swelling coefficient for providing the flux.

By swelling coefficient is meant the fractional change in the weight of a structure, such as the conducting polymer element, when it is placed in a swelling agent (solvent, solution etc.) divided by the density of the swelling agent into which the device is placed.

By electrically controllable swelling coefficient is meant that the swelling coefficient can be effectively increased or decreased by applying an electrical potential to the device, and in particular to the conducting polymer containing element (s). An electrically induced increase of the swelling coefficient causes fluid to flow into the conducting polymer containing element (s), i.e. the conducting polymer material sorbs the fluid. An electrically controlled decrease of the swelling coefficient may be used to provide a flow out of the conducting polymer containing element (s), when the conducting polymer element is already provided or imparted with a swelling coefficient greater than zero, i.e. the conducting polymer containing material desorbs the previously imbibed fluid. Furthermore, the conducting polymer element may reversibly swell in an electrically controlled manner. Thus, the flow of a fluid caused by an increase or decrease in swelling may be used to provide a flow of fluids and/or substances to and from the substance incorporating element, so as to provide an electrically controlled release of a substance contained in the at least one substance incorporating element into the surrounding environment.
According to another embodiment, the device may have a storage state, in which the swelling coefficient is approximately zero, and an electrically activated state, in which the swelling coefficient is significantly higher than zero. The electrically activated state is provided upon the application of an electric potential to the conducting polymer element.

According to one embodiment, the conducting polymer element may be arranged substantially between the substance incorporating element and the surrounding environment.

According to another embodiment, the conducting polymer element may have an electrically controllable morphology for providing the flux.

By *electrically controllably morphology* is meant that the shape, internal microscopic structure, and/or form of the conducting polymer material can be reversibly or irreversibly changed by applying an electrical potential to the device. In this way the permeability through the conducting polymer material can be changed in an electrically controlled manner, wherein a morphological change, for example, may provide a more open structure for a passage or diffusion of fluids or substances through the conducting polymer material, for example. Based on the present disclosure, the skilled person will appreciate how to provide the material (-s) with such an effect.

According to one embodiment, the conducting polymer element may comprise an electrically formable pore.

In general, the term *porous material* refers to a material having pores, or tiny openings.

By *electrically formable pore* is meant that the porous formation of the conducting polymer element can be effectively activated or deactivated by applying an electrical potential to the device. By forming the pores disposed within the conducting polymer element, the diffusion and/or passage of a fluid, ion and/or the like through the conducting polymer element (-s) can be provided in a controlled manner.

Such a formable pore is provided by a morphological change in the conducting polymer. In this way, a change in the shape, internal microscopic structure, and/or form of the conducting polymer material can provide such a formable pore.

The formed porous structure disposed within the conducting polymer element may form channels or passages that allow movement of ions, fluids and/or substances between the side facing the surrounding environment of the device with the side facing the interior part of the device, in which the interior part the substance comprising element (-s) is arranged. The substance incorporating element (-s) may also be in the form of a solution.
The solution may contain substances that may pass through any of the electrically formed pores thereby providing the release of the substance. Alternatively, the substance incorporating element (-s) may be disposed within an encapsulated cavity or cavities disposed within the conducting polymer element (-s). This cavity (-s) may be connected to the electrically formed channels.

Such a device provides the possibility of substance delivery in environments with limited solvent access. Moreover, there is provided a possibility of employing a very thin layer (-s) of a conducting polymer element (-s), which in turn provides an alternative for rapid initiation of the substance delivery process. Due to the primary release process being diffusion through a conducting polymer material, the release may be slower than a device having a controllable swelling coefficient as mentioned above. Therefore, there is provided a way of electrically controlling the release initiation and sustained release.

Based on the present disclosure, the skilled person will appreciate how to provide the conducting polymer element with such an effect of forming pores in an electrically controlled manner.

According to yet another embodiment, the drug delivery device may comprise, a support layer, arranged so as to separate the substance incorporating element from the surrounding environment. The drug delivery device may further comprise a channel, arranged through the support layer. The conducting polymer element may be arranged within and around the channel and the conducting polymer element may have a surface that is electrically controllable between a hydrophobic and a less hydrophobic or a hydrophilic state for providing the flux.

The skilled person will appreciate that the fluid motion due to changes in surface energy may be related to the so-called Marangoni effect. Basically, that localized gradients in surface tension between a fluid and its container walls, on the micro scale, is sufficient to cause localized flow of fluid at the wall. The channel (-s) may be provided as a structural feature of the support layer.

Such a drug delivery device provides an increase in convective processes locally around the device and the drug. In addition, an increase of the influx of fresh surrounding solution into the vicinity of the drug is provided and an enhancement of the mixing on the micro scale between the drug and solution is also provided. The device can also be used as a switchable barrier layer, whereby a polar solvent (such as water) is kept from passing by the support layer until the conducting polymer element is switched to a more hydrophilic state and the water can enter and mix with the drug.

According to another embodiment, the conducting polymer element may be a conducting polymer, optionally containing a dopant.
According to another embodiment, the conducting polymer may be selected from a group consisting of polypyrroles, polyanilines, polythiophenes, poly(ethylene dioxythiophenes), poly(phenylenes), poly( paraphenylenes), polyvinylenes, and copolymers thereof, including substituted forms of the different monomers.

According to yet another embodiment, the conducting polymer may be polypyrrole.

According to another embodiment, the conducting polymer may be polypyrrole, doped with dodecylbenzene sulfonate, octylbenzene sulfonate and/or polystyrenesulfonate.

According to another embodiment, the conducting polymer element may be electrically controllably degradable.

By electrically controllably degradable is meant that degradation of the structure can be effectively activated or deactivated by applying an electrical potential to the device. Based on the present disclosure, the skilled person will appreciate the material (-s) that may provide the element with such an effect.

By such controlled degradation of the conducting polymer element, the passage or diffusion of a fluid, ion or the like into the substance incorporating element (-s) can be effectively initiated and controllably increased to expedite the delivery of the substance.

According to yet another embodiment, the device may further comprise a second conducting polymer element arranged to separate the conducting polymer element and the surrounding fluid, and provide at least a portion of the flux.

The second conducting polymer element is provided so as to control the flow of fluid between the conducting polymer element and the surroundings. The second conducting polymer element is suitable for providing a barrier layer during storage and transport of the delivery device, prior to the application of an electrical potential to the device.

According to another embodiment, at least one substance incorporating element may further comprise a carrier.

By carrier is meant any material that is added to a chemical or formulation, i.e. the substance, to facilitate its preparation, storage or use. In particular, carriers are substances that serve as mechanisms to improve the
delivery and the effectiveness of the substance. Here, the substance may be a biologically active substance like a drug.

By such a carrier there is provided a way to compatibilize the drug for use with the conducting polymer element, and alternatively create a substance release dynamic of the drug from the carrier that passively or actively controls the release process, e.g. by limiting premature release or providing a fast release. Furthermore, the carrier may provide means that eases the manufacturing, improves storage/aging characteristics of the delivery device, limits contact between the conducting polymer and the drug, and/or protects the drug during electrochemical operations.

The carrier can be selected based on the specific drug properties/chemistry. Examples of a carrier include polymers, non-polymers, fluid disintegratable materials, capsules, micelles, a solvent or a liquid dispersion medium or a combination thereof. The carrier may also be an excipient such as a preservative, a lubricant, a filler, a binder and the like.

According to another embodiment, the carrier may be a fluid disintegratable carrier.

By *fluid disintegratable carrier* is meant a material that degrades, decomposes, disintegrates or dissolves in contact with fluid, and in particular the carrier material is disintegratable upon fluid contact in vivo. In this way a controlled release of the substance is facilitated.

According to yet another embodiment, the carrier may be a hydroactivated carrier.

By *hydroactivated carrier* is meant a material that degrades, decomposes, disintegrates or dissolves in contact with an aqueous solution.

According to another embodiment, the carrier may be a polymer material.

According to another embodiment, the carrier may be a non-polymeric material.

According to yet another embodiment, the substance may be a solid drug substance.

In this way a controlled release of the substance may be facilitated while the substance incorporating element takes up a little space within the drug delivery device. By providing the substance as a solid, the drug may be provided in a very concentrated a form, thereby providing a further miniaturized device.
According to another embodiment, the drug delivery device may comprise a film. The film may comprise the conducting polymer element and the substance incorporating element.

By *film* is meant a thin single-layered or multilayered sheet structure, i.e. a single-layer film or a multilayer film being as thin as or thinner than 500 μm. The elements may be comprised in one layer or in several layers. Furthermore, each element may constitute one layer of the film. Preferably, the thickness of the film is 500 μm or thinner, 250 μm or thinner, 100 μm or thinner, 50 μm or thinner or 10 μm or thinner.

According to yet another embodiment, the film may comprise at least one more conducting polymer element according to the invention and/or at least one more substance incorporating element according to the invention.

According to another embodiment, the film may be a multilayered film.

According to a further embodiment, the drug delivery device may further comprise a semipermeable membrane to provide a selective passage of the flux and/or the substance between the surrounding environment and the device.

Such semipermeable membranes are able to retain selected substances while transmitting alternative substances while simultaneously providing means for transmitting or retaining selected fluids. Based on the disclosure, the skilled person will appreciate the choice of material for providing such a semipermeable membrane.

According to another embodiment, the drug delivery device may further comprise an impermeable membrane or element. The impermeable membrane or element may be substantially impermeable to fluids, gas and substances.

Such a membrane or element may form a barrier within the drug delivery device or between the drug delivery device and the surrounding environment of the drug delivery device.

According to yet another embodiment, the drug delivery device may further comprise a substrate.

The substrate may provide a rigid support for the conducting polymer element (-s) and the substance incorporating element (-s). Any one of the elements may be adhered to a surface of the substrate. The elements may also be arranged within the substrate structure. The substrate may form a layer within a film.

Such a substrate may improve robustness and provide a means of connecting the drug delivery device to an electrical power source.
Furthermore, the substrate may control the direction of drug release or flux and provide mechanical constraints. In general, the substrate simplifies the fabrication and arrangement of the drug delivery device, as, for example, layers may be directly synthesized onto this substrate providing a film device.

According to a further embodiment, at least one through opening may be arranged in the substrate.

By providing the substrate with such a through opening or an equivalent pore, there is provided a pathway for a substance or an electrolyte to exchange between the surroundings and the conducting polymer element and/or the substance incorporating element through the substrate. Such a substrate may also be suitable for two directional delivery of a substance such as a drug from the delivery device.

According to another embodiment, at least a portion of the substrate may be an electrode.

According to yet another embodiment, the substrate may be a medical device, or part of a medical device, for providing an additional medical action other than the drug delivery action. The medical device may preferably be a catheter, a guidewire, a stent, a balloon, a lead or an aneurysm coil.

According to a further embodiment, a conducting polymer element and/or a substance incorporating element may be arranged on at least a portion of the medical device as a film.

According to another embodiment, the drug delivery device may comprise a controllable electroporation device.

According to another embodiment, a conducting polymer element may be arranged between the substrate and a substance incorporating element.

According to yet another embodiment, a substance incorporating element may be arranged between the substrate and a conducting polymer element.

According to another embodiment, a substance incorporating element may be enclosed in a cavity defined by a conducting polymer element and the substrate.

According to a further embodiment, one or more cavities may be comprised within a conducting polymer element or between two or more conducting polymer elements. A substance incorporating element may be substantially arranged within such a cavity.
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By arranging the substance incorporating element (-s) within a conducting polymer element (-s), the entire film may be more easily processed. Furthermore, the conducting polymer element (-s) may improve isolation of the substance incorporating elements from the surrounding environment during storage, before application of an electric potential to the device.

According to another embodiment, one or more cavities may be comprised within a substance incorporating element or between two or more substance incorporating elements. A conducting polymer element may be substantially arranged within such a cavity.

This approach can provide an alternative approach to the fabrication of the device and may further improve flux transfer between the substance incorporating elements and the conducting polymer elements.

According to another embodiment, the medical device may comprise a chamber and a housing with the chamber being defined by the housing. A substance incorporating element may be arranged within the chamber and the housing may comprise a conducting polymer element.

According to yet another embodiment, the medical device may comprise a chamber and a housing, with the chamber being defined by the housing. A fluid may be contained within the chamber. The housing may comprise a substance incorporating element and a conducting polymer element arranged to separate the substance incorporating element from the surroundings.

According to another embodiment, the fluid may be an aqueous infusate liquid comprising at least one of saline, a sugar solution, a contrast agent, whole blood, or blood plasma.

Such fluids are utilized in many surgical procedures and may provide both a medium for the transfer of the substance, but may also provide suitable ionic species for activation of the conducting polymer element.

According to yet another embodiment, the housing may further comprise an inner layer facing the chamber. The layer may be a fluid permeable membrane.

According to another embodiment, a plurality of outwardly protruding elements may be arranged on an outer facing surface of the drug delivery device.

According to a further embodiment, a bonding layer may connect at least one of the outwardly protruding elements to the delivery device.
According to another embodiment, the device may comprise a cup-like cavity. The cup-like cavity may be defined by the surface of the delivery device and two or more of the outwardly protruding elements and have an opening for accessing at least a portion of the surrounding environment.

A cup-like cavity is a precursor element arranged on the outside of the delivery device that can be used to form a cell during a treatment. The cup-like cavity is generally a recess in the medical device with an open face so as to hold fluid from the surrounding electrolyte. Furthermore, it can be arranged so that the enclosed fluid is retained even when the drug delivery device is biased against a treatment site.

According to yet another embodiment, the device may be provided with an electrical isolation between at least one of the outwardly protruding elements and the conducting polymer element and the outwardly protruding element may provide a counter electrode or a reference electrode for the drug delivery device.

Suitable electrical isolation between an outwardly protruding element and the conducting polymer element can be achieved by providing a bonding layer of an electrically insulating material, or by strategically patterning the conducting polymer element on the housing and suitably arranging the outwardly protruding elements. Based on the disclosure, the skilled person will appreciate suitable techniques for providing electrical isolation of an outwardly protruding element from the delivery device. Furthermore, the skilled person will appreciate the benefit of having a counter electrode or reference electrode situated in the vicinity of the working electrode upon reading the disclosure.

According to a second aspect, there is provided a drug delivery device comprising, a conducting polymer element, a substance incorporating element containing a substance, and a film. The conducting polymer element and the substance incorporating element are adjacent arranged within the film. When the device is placed in a surrounding environment, upon changing of an electric potential to the conducting polymer element, the conducting polymer element provides a mechanical work on the substance incorporating element, thereby providing a release of the substance from the delivery device by fracturing, pressurizing, and/or tensioning processes.

By mechanical work on is meant a movement and/or force provided by the conducting polymer element, such as expansion and/or contraction of the conducting polymer element or the biasing towards or away of a surface of the conducting polymer element so as to act upon a structure, such as a substance incorporating element. The mechanical work may be provided as a single unit or a rapid succession of units, as desired for a rapid release of drug, or as a succession of increments or slowly varying quantity for providing an electrically controlled release of the drug over a longer time period.
Such a device may provide a local bulk expansion or contraction within the film for directly releasing the drug. Such a device may provide an electrically controllable release of a substance, such as a drug, contained in the substance incorporating element (-s). For example, the release of the substance may be controlled and adjusted as discussed above for other aspects. Thus, there is provided a possibility of miniaturization of the drug delivery device, allowing for more pure and concentrated drug forms to be incorporated in the drug delivery device as well as released. Also provided may be reliable release profiles due to the controlled and repeatable nature of the interaction of the elements. Furthermore, there is provided a possibility of releasing the substance, such as a drug, without altering the position or shape of the overall film, which provides efficacy, and reliability of the drug release process. The device can provide the possibility to release a wide range of substances as mentioned for the device according to the first aspect.

According to a group of embodiments, many of the embodiments mentioned above may also be combined with the second aspect instead of the first aspect. More specific embodiments of the second aspect are depicted below.

According to one embodiment, the conducting polymer may be polypyrrole, doped with dodecylbenzene sulfonate and/or octylbenzene sulfonate.

According to another embodiment, the thickness of the film may be 500 ūm or thinner, 100 ūm or thinner, 50 ūm or thinner, 10 ūm or thinner, or 1 ūm or thinner.

According to yet another embodiment, the film may comprise at least two layers.

According to a further embodiment, the film may comprise at least one more conducting polymer element and/or at least one more substance incorporating element.

According to another embodiment, the film may comprise a layer comprising a conducting polymer element and a substance incorporating element.

According to yet another embodiment, one or more cavities may be comprised within a conducting polymer element or between two or more conducting polymer elements. A substance incorporating element may be substantially arranged within such a cavity.

Such an arrangement may provide more intimate interconnection between the conducting polymer element (-s) and the substance incorporating element (-s) which may provide more localized stress
heterogeneity for improving the transfer of the mechanical work and hence the efficacy of the device.

According to another embodiment, one or more cavities may be comprised within a substance incorporating element or between two or more substance incorporating elements. A conducting polymer element may be substantially arranged within such a cavity.

This is an alternative arrangement to the one described above that may provide an improved fabrication option while still providing the advantage of improved efficacy.

According to another embodiment, the conducting polymer element may be electrically controllably expandable and/or contractible in a direction (s) that is substantially in plane with the film to provide the mechanical work.

According to yet another embodiment, the conducting polymer element may be electrically controllably expandable in a direction substantially towards the substance incorporating element to provide the mechanical work.

According to a further embodiment, the conducting polymer element may be electrically controllably contractible in a direction substantially away from a substance incorporating element to provide the mechanical work.

According to another embodiment, the delivery device may further comprise a semipermeable membrane. The semipermeable membrane may be selectively permeable to the substance or a fluid.

Such semipermeable membranes are able to retain selected substances while transmitting alternative substances, while simultaneously providing means for transmitting or retaining selected fluids. Based on the disclosure, the skilled person will appreciate the choice of material for providing such a semipermeable membrane.

According to a further embodiment, the device may further comprise a sealing element or layer being substantially impermeable to fluids and/or substances. The sealing element may be arranged to separate at least a portion of the drug delivery device from the surrounding environment.

According to yet another embodiment, the sealing element or layer may be an at least partially releasable element or layer that is releasable by the mechanical work.

According to another embodiment, the substance incorporating element may comprise a sealing element or layer being substantially impermeable to fluids and/or substances. The sealing element or layer may partly or fully encapsulate a substance.
According to another embodiment, the sealing element or layer may be a breakable element or layer that is breakable via the mechanical work. This may provide a pathway to enhance the release of the substance by diffusive processes or subsequent mechanical work.

According to another embodiment, the sealing element or layer may be arranged in contact with the film.

According to another embodiment, at least one constraint element or layer may be arranged so as to protrude from an outer surface of the film.

According to another embodiment, a constraint layer may be arranged so as to fully or partially cover an outer surface of the film.

According to a further embodiment, a substance incorporating element may be a breakable element that breaks or fractures via the mechanical work.

According to another embodiment, the conducting polymer element and the substrate may be arranged in contact to form a gas sealed interface therebetween. The drug delivery device may further comprise an enclosed conducting element arranged along the gas sealed interface. The enclosed conducting element may provide the formation of gas upon application of an electric potential to the device for enhancing the mechanical work.

Such an arrangement may provide a movement of the conducting polymer containing structure towards a substance-containing element, or provide back pressure to the conducting polymer, which in turn may increase expansion and/or stress levels of or on the substance-containing element. This provides the possibility of very rapid expansion and therefore rapid release of the substance such as a drug. There is also provided a possibility for very heterogeneous stress formation in the film when the electrode is suitably featured.

According to another embodiment, a substance incorporating element may be enclosed in a region defined by a conducting polymer element and the substrate.

According to yet another embodiment, at least one constraint element or layer may provide the at least one outwardly protruding element.

According to another embodiment, the substance may be selected from anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, antineoplastic agents, anti-mitotic agents, anti-thrombotic agents, anti-restenotics, antibiotics, vascular cell growth promoters, vascular cell growth inhibitors, vasodilating agents, neurotransmitters, immunosuppressive agents and neuro-modulators.
According to yet another embodiment, the substance may be an antineoplastic agent, including paclitaxel or its analogs or derivatives.

According to a further embodiment, the substance may be an immunosuppressive agent, including sirolimus, tacrolimus, pimecrolimus and everolimus or its analogs or derivatives.

According to yet another embodiment, the substance may be an anti-inflammatory agent including a dexamethasone or prednisolone compound or its analogs or derivatives.

According to a third aspect, there is provided a method for delivering a substance to a target location comprising bringing at least a part of the drug delivery device as described above in contact with the target location and delivering the substance by providing an electrical potential to the device.

According to another embodiment, the method may utilize the delivery device according to the first aspect for providing a flux of a fluid, an ion and/or the like.

According to yet another embodiment, the step of providing a flux may be repeated.

According to yet another embodiment, the method may utilize the delivery device according to the second aspect for providing a mechanical work.

According to another embodiment, the step of providing a mechanical work may be repeated.

According to another embodiment, the method may further comprise forming a cell when the delivery device comprises at least one cup-like cavity. The cell may be defined by the cup-like cavity and the target location.

A cell is and enclosure formed when a cup-like cavity as previously described is abutted against the surface of a treatment site or target location. A cell provides an alternative environment for the release of a drug towards the surface of a treatment site or target location. The surrounding fluid within the cell may provide sufficient ions for activation of the conducting polymer elements without the need for further access to the surrounding fluid. The cell also provides stagnation of the fluid contained therein. In many cases, where the treatment site is a lumen wall, the lumen will generally be subject to flows of bodily fluids. The cell generally separates the enclosed fluid from the primary fluid flow within the lumen. This reduces washout of the released drug and thereby enhances delivery of the drug to the lumen wall.
According to a fourth aspect, there is provided a surgical method utilizing the drug delivery device according to the first or second aspects for delivering a substance to a target site by providing an electrical potential to the device; wherein the surgical procedure is a percutaneous transluminal angioplasty procedure, a percutaneous transluminal coronary angioplasty procedure, treatment of emboli or thrombi, treatment of aneurysms or an implantation procedure.

Brief Description of the Drawings

All figures are schematic and not to scale. In addition, some details, such as electrical leads or wires to and from the actuators, electrodes, etc. have been omitted from the drawings for clarity.

Fig. 1 is a schematic overview of an electrochemical system.

Fig. 2 shows the result from an experiment of repeated and reversible volume change with associated water and ion influx/outflux during cyclical activation of a conducting polymer (CP).

Fig. 3 shows the result from an experiment of the electrically controlled initiation of volume change of a conducting polymer and the resulting influx of water and ions into the conducting polymer thereafter.

Figs. 4a-4c schematically illustrate, in longitudinal cross section, the drug release process of a drug delivery device with electrically controllable swelling power.

Figs. 5a-5c schematically illustrate the drug release process of an alternative embodiment of a drug delivery device with electrically controllable swelling power for delivering a substance in close proximity to the wall of a body lumen.

Figs. 6a-6b schematically illustrate, in longitudinal cross section, the drug release process of a further embodiment of a drug delivery device with electrically controllable swelling power.

Figs. 7a-7c schematically illustrate, in longitudinal cross section, the drug release process of another embodiment of a drug delivery device with electrically controllable swelling power further comprising a semipermeable membrane.

Figs. 8a-8c schematically illustrate, in longitudinal cross section, the drug release process of an embodiment of a multilayered drug delivery device with electrically controllable swelling power.

Figs. 9a-9b schematically illustrate, in longitudinal cross section, the drug release process of a drug delivery device with electrically controllable permeability.
Figs. 10a-10c schematically illustrate, in longitudinal cross section, the drug loading and drug release processes of another embodiment of a drug delivery device with electrically controllable swelling power further comprising a porous conducting polymer element.

Figs. 11a-11b schematically illustrate, in longitudinal cross section, the drug release process of an embodiment of a drug delivery device comprising a hydroactivated disintegrating carrier material.

Figs. 12a-12b schematically illustrate, in longitudinal cross section, the drug release process of a drug delivery device with an electrically controllable degradable conducting polymer for drug release.

Figs. 13a-13b schematically illustrate, in longitudinal cross section, the drug release process of a drug delivery device with a CP element and a disintegrative drug carrier whereby the release process is governed by electrically controlling the surface energy of the CP element.

Figs. 14a-14f schematically illustrate the drug release processes of further embodiments of a drug delivery device that is incorporated into the surface of a medical device whereby the release process is governed by electrically controlling the permeability of the CP element.

Figs. 15a-15b schematically illustrate in longitudinal cross section, the drug release process from a drug delivery device with at least one region of CP and at least one region of drug incorporated into a film whereby the release process is governed by electrically controllable in-plane expansion of the CP.

Figs. 16a-16b illustrate the drug delivery device of Figs. 15 further comprising a barrier layer facing the surrounding electrolyte.

Figs. 17a-17b illustrate the drug delivery device of Figs. 15 further comprising a barrier layer forming the outer layer of the device against the surrounding electrolyte.

Figs. 18a-18b illustrate the drug delivery device of Figs. 15 further comprising a constraint element for improved drug delivery.

Figs. 19a-19b schematically illustrate, in longitudinal cross section, the drug release process from a drug delivery device with at least one region of CP and at least one region of drug incorporated into a film whereby the release process is governed by electrically controllable in-plane contraction of the CP.

Figs. 20a-20b illustrate a plane view of two embodiments of the drug delivery device as described in Figs. 15-19 where both the CP and the drug
regions are strategically micro-patterned to enhance the drug delivery process.

Figs. 21a-21b illustrate, in longitudinal cross section, the drug release process of a drug delivery device with a layered arrangement of drug and CP regions that further comprises a porous constraint layer facing the surrounding electrolyte.

Figs. 22a-22b schematically illustrate an alternative embodiment of the drug delivery device in Fig. 21 for delivering a substance in close proximity to the wall of a body lumen.

Figs. 23a-23c schematically illustrate, in longitudinal cross section, the deposition and drug release processes to form and use a drug delivery device with a porous host polymer and drug into which CP regions are arranged whereby the release process is governed by electrically controllable expansion and/or contraction of the CP.

Figs. 24a-24c schematically illustrate, in longitudinal cross section, the drug loading and drug release processes of another embodiment of a drug delivery device with porous CP regions into which the drug is arranged whereby the release process is governed by expansion and/or contraction of the CP.

Figs. 25a-25b schematically illustrate, in longitudinal cross section, the drug release process from a drug delivery device with multiple layers whereby the drug release process is governed by the in-plane expansion and/or contraction of the CP.

Figs. 26a-26b schematically illustrate, in longitudinal cross section, the drug release process from an alternative embodiment of the drug delivery device of Fig. 25 further comprising a constraint layer arranged over the outer surface of the multilayered structure.

Figs. 27a-27b schematically illustrate, in longitudinal cross section, the drug release process from a further embodiment of the drug delivery device with an electrically conducting electrode region, encapsulated by the CP region whereby the drug release process is governed by the production of gas at the interface between the electrode and the CP.

Figs. 28a-28b schematically illustrate, in longitudinal cross section, the drug release process from a further embodiment of the drug delivery device with an electrode region encapsulated by CP and an adhesive arranged around the perimeter of this region whereby the drug release process is governed by the production of gas at the interface between the electrode and the CP.
Figs. 29a-29b schematically illustrate, in longitudinal cross section, the drug release process from yet another embodiment of the drug delivery device with an CP region that encapsulates an electrode region comprising features whereby the drug release process is enhanced due to gas production near features at the interface between the electrode and the CP.

Figs. 30a-30b schematically illustrate, in longitudinal cross section, the drug release process from another embodiment of the drug delivery device with pockets of substance arranged within a layer of CP and a porous substrate whereby the drug release process is governed by contraction of the CP and expulsion of the drug through the porous substrate.

Figs. 31a-31c schematically illustrate, in longitudinal cross section, the drug release process from yet another embodiment of the drug delivery device with drug loaded capsules embedded into an CP layer whereby during expansion and/or contraction of the CP the capsules are fractured and the drug is released into the surroundings.

Figs. 32a-32b schematically illustrate, in longitudinal cross section, the drug release process from a further embodiment of the drug delivery device with a substance coated directly onto an CP layer whereby during in-plane expansion and/or contraction of the CP the drug layer is broken up and released into the environment.

Figs. 33a-33b schematically illustrate, in longitudinal cross section, the drug release process from yet another embodiment of the drug delivery device with a layered arrangement of CP, substance and a barrier layer whereby the barrier layer is broken during expansion and/or contraction of the CP and drug is released into the environment.

Detailed descriptions of embodiments

Electroactive polymers (EAP) are a comparatively novel class of materials that have electrically controlled properties. An overview on electroactive polymers can be found in "Electroactive Polymers (EAP) Actuators as Artificial Muscles - Reality, Potential, and Challenges" 2nd ed. Y. Bar-Cohen (ed.) ISBN 0-8194-5297-1.

One class of EAPs is conducting polymers (CP). These are polymers with a backbone of alternating single and double bonds. These materials are semiconductors and their conductivity can be altered from insulating to conducting with conductivities approaching those of metals. Polypyrrole (PPy) is one conducting polymer and may throughout the present disclosure be taken as a non-limiting example of such CP materials. Other examples are polyanilines, polysulfones, polythiophenes, polyacetylenes, polyethylenedioxythiophenes, poly(p-phenylenes), poly(p-phenylene vinylene), polypyrrolidines, polypyrroloquinoxalines, polyanthraquinones, poly(n-vinylcarbazole) and derivates or copolymers of these. The CP material described in the present invention is preferably PPy and may be doped with
at least one of the following dopants: dodecylbenzene sulfonate, octylbenzene sulfonate and polystyrenesulfonate, other dopants are not excluded.

PPy can be electrochemically oxidized and reduced by applying an appropriate potential to the material. The oxidation or reduction leads to a charge imbalance that, in turn, results in a flow of ions into or out of the material in order to balance charge. The oxidation and reduction is also accompanied with the transport of solvents (often water) into and out of the PPy. This redox reaction changes the properties of PPy, such as the conductivity, volume and water content.

The redox reaction is typically driven in an electrochemical cell that comprises a working electrode (e.g. PPy) and a counter electrode, optionally a reference electrode, and an electrolyte. Fig. 1 schematically illustrates such an electrochemical system 10 with a 3-electrode set-up, which comprises a control device 11, a container 12 containing an electrolyte 13, a working electrode 14, a counter electrode 15 and a reference electrode 16.

PPy can be electrochemically or chemically synthesized from a solution of pyrrole monomers and a salt as is known to those skilled in the art. After synthesis PPy is in its oxidized, or also called doped, state. The polymer is doped with an anion from the salt in the electrolyte.

Two different schemes of redox are possible. If PPy is doped with a large, immobile dopant anion A- scheme 1 occurs, which schematically can be written as:

\[
\text{PPy}^+(\text{A-}) + \text{M+}(\text{aq}) + \text{e-} \leftrightarrow \text{PPyO(A-M+)} \quad (1)
\]

OV, Oxidised -1V, reduced

When PPy is reduced to its neutral state cations M+ including their hydration shell and solvent are inserted into the PPy and the material swells. When PPy is oxidized again the opposite reaction occurs, M+ cations (including hydration shell and solvent) leave the PPy and it decreases its volume. If on the other hand PPy is doped with small, mobile anions a-, scheme 2 occurs:

\[
\text{PPy}^+(\text{a-}) + \text{e-} \leftrightarrow \text{PPyO() + a-(aq)} \quad (2)
\]

OV, Oxidised -1V, reduced

In this case the opposite behavior of scheme 1 occurs. In the reduced state the anions leave the material and it shrinks. The oxidized state is now the expanded state and the reduced state the contracted. Non-limiting examples of suitable ions for the various types described include A- dodecylbenzene sulfonate (DBS-), a- perchlorate (ClO4-), and M+ sodium (Na+) or lithium (Li+).

Usually, these can be exchanged for active species such as drugs. These charged drugs are then incorporated into the polymer as dopants (e.g. a-, in scheme 2) or charge-compensating ions inserted or expelled during redox reactions (e.g. M+ in scheme 1). The release of such charged species in response to electrical potentials is described in the prior art as indicated above. However many drugs are uncharged and/or hydrophobic thereby preventing them from being applicable in the above examples where drugs are directly released from the CP due to electrorepulsive forces and breaking of ionic bonds. Moreover, it can often be desirable to incorporate the drug in another material rather than in the CP to prevent electrochemical interactions during redox that interfere with drug stability and chemical integrity. In these aspects CP has a number of features that may be applied for improved drug delivery devices. The present invention presents novel solutions using the electrically controllable properties of CP such as large volume change and incorporation/expulsion of solvents such as water for drug delivery of a wide range of drugs irrespective of their charge, size, stability or other properties.

Conducting polymers such as PPy have the advantage that, under potential control, they can be reversibly switched between an oxidized and a reduced state or any intermediate state. The electrochemical redox reactions of CP (scheme 1 or 2) are associated with a significant reversible volume change as exhibited in Fig. 2. A large portion of this volume change is due to solvent (in most cases water) influx/outflux into/out of the CP. As these volume changes can be repeated for hundreds, or thousands of cycles, a significant volume of solvent and associated ions can be dragged in and out through the CP. The response time and time for reaching a significant volume change can be very fast (few seconds) as also seen in Fig. 2. The amount of solvent transferred as well as the direction of the solvent flow is controlled by the level of the applied electric potential to the CP and degree to which the redox reaction is allowed to complete.

An example of the significant amount of reversible solvent flow is shown in Fig. 2. Here PPy(DBS) was deposited on a silver metal wire through galvanostatic electropolymerization at 0.4 mA/cm². The PPy(DBS) was deposited to a thickness in dry state of approximately 45 μm. Using a potentiostat the sample was subsequently activated in 0.15 M NaCl (aq) with a Ti/Pt mesh counter electrode through application of 0.2 V(oxidation) and -0.4 V(reduction) vs. an Ag/AgCl reference electrode until the maximum volume change had stabilized. The volume change was continuously monitored using a laser scanmeter as is known in the art. As is seen in Fig. 2 the PPy(DBS) volume change and its direction representing water influx/outflux was
controlled by the applied potential level and was reversible for a large number of cycles. Moreover, the volume change was fast and a significant volume change was obtained in a few seconds. Similar results were obtained for PPy doped with octylbenzensulfonate or polystyrenesulfonate.

In addition, water influx or passive absorption into a CP such as PPy will not occur until an electric potential is applied. This property is depicted by the constant thickness of the sample shown in Fig. 3 prior to application of an electric potential and hence the initiation of swelling. The same degree of water flow control is maintained during water outflux.

An example of the controlled initiation of solvent inflow is shown in Fig. 3. Here PPy(DBS) was deposited on a silver metal wire through galvanostatic electropolymerization at 0.4 mA/cm². The thickness in dry state was approximately 45 µm, the same thickness was maintained when the dry, unactivated sample is immersed in 0.15 M NaCl(aq) as seen from the initial flat part of the curve in Fig. 3. A Ti/Pt mesh counter electrode was used and once a reduction potential of -0.1 V vs. an Ag/AgCl reference electrode was applied the PPy(DBS) coating was electrochemically reduced (according to scheme 1) and momentarily starts drawing in water and ions and hence begins to swell. The final swelling was substantial and amounts to ca 30% change in volume. Once applying an oxidation potential of 0.2 V the process was reversed and water and ions are expelled and the PPy contracts (not shown).

Thus the CP can be used as a controllable solvent flow reservoir and regulator, wherein an electric potential can be used to start drawing water into the initially empty reservoir, and subsequently controllably expel water from the reservoir upon reversal of the applied electric potential. This process can be used to enhance and control drug release in a variety of ways and enables new possibilities for controlling when and at what location in the body that drug release is to be initiated and the speed and total amount of drug release.

This property of the CP can be further clarified by considering its swelling coefficient. Swelling coefficient, in the context used herein, is meant as the fractional change in the weight of a structure, such as the conducting polymer element, when it is placed in a swelling agent (solvent, solution etc.) divided by the density of the swelling agent into which the device is placed. In this context, the CP essentially has an electrically controllable swelling coefficient.

An electrically induced increase of the swelling coefficient of the conducting polymer causes fluid to flow into the conducting polymer containing, i.e. the conducting polymer material sorbs the fluid. An electrically controlled decrease of the swelling coefficient may be used to provide a flow out of the conducting polymer, when the conducting polymer is already provided or imparted with a swelling coefficient greater than zero, i.e. the
conductive polymer containing material desorbs the previously imbibed fluid. Furthermore, the conducting polymer element may reversibly swell in an electrically controlled manner. Thus, the flow of a fluid caused by an increase or decrease in swelling may be used to provide a flow of fluids and/or substances to and from the substance incorporating element, so as to provide an electrically controlled release of a substance contained in the at least one substance incorporating element into the surrounding environment.

The description will now focus on embodiments of a drug delivery device that takes advantage of these general properties of CP to improve the drug delivery process as compared with the prior art.

Fig. 4a shows a cross sectional view of an embodiment of a drug delivery device 20 where a drug is incorporated in a separate drug/carry layer 24 on top of an element 22 consisting of CP. The drug/carry layer 24 serves as a reservoir for the drug. An optional substrate 26 is provided to complete the delivery device 20. The drug/carry layer 24 does not absorb water or release drug in any significant proportion prior to activation of the CP element 22. The CP element 22 is activated by applying an appropriate electric potential during process A. Then a solvent, such as an aqueous solvent, from surrounding electrolyte 28 is drawn into the CP element 22 along with ions as a water and ion flux F1. The water and ion flux F1 then passes through drug/carry layer 24 and into the CP element 22. This process of imbibing solvent initiates the release of drug from drug/carry layer and is depicted in Fig. 4b. The water and ion flux F1 can be electrically controlled both in magnitude and direction to generate solvent flow repeatedly into and out of the drug/carry layer. Subsequently a reversed electrical potential is applied to CP element 22 in process R. This initiates and controls a water and ion flux expulsion process F2 that is shown in Fig. 4c where the associated drug release is also shown. The insertion of water into drug/carry element 24 will initiate drug release through dissolution of drug and subsequent diffusion and convection that will result in released drug 30 in surrounding electrolyte 28. Moreover, since the water and ion fluxes F1, F2 can repeatedly pass in and out through the drug/carry layer 24, drug is actively released into the surroundings through diffusion (due to concentration gradients), convection (due solvent flow and drag), and ion drag (transports associated drug molecules).

The surrounding electrolyte 28 may be of biological body fluids such as blood, gastric fluids, urine, ocular fluid, amniotic fluid, bile, chyle, lymph, pleural fluid. The surrounding electrolyte 28 may also be a liquid that is infused externally during a surgical procedure, for example saline solution, contrast solution etc. Generally the CP elements 22 and their incorporated dopant ions are selected so as to operate favorably in such an electrolyte and also to demonstrate suitable biocompatibility.
To construct a delivery device 20 as depicted in Fig. 4, the CP element can be deposited by any of several known methods. Often the CP is deposited in the form of a layer. It is preferable that the CP layer is relatively impermeable to the drug and/or drug and carrier. At least one separating element (not shown) may be applied between the CP element 22 and the drug/carrier material 24. Such at least one separating element substantially prevents direct contact as well as mixing or diffusion of different chemical species (and therefore prevents undesired chemical reactions) between the CP element 22 and the drug/carrier material 24. Moreover, according to one embodiment, the at least one separating element may generally comprise a permeable nonreactive polymer. Examples of polymers include acrylonitrile polymers; halogenated polymers such as polytetrafluoroethylene, polychlorotrifluoro-ethylene, copolymer tetrafluoroethylene and hexafluoropropylene; polyimide; polysulfone; polycarbonate; polyethylene; polypropylene; polyvinylchloride-acrylic copolymer; polycarbonate-acrylonitrile-butadiene-styrene; polystyrene; polyether ether ketone (PEEK). Permeability of these polymers can be adapted by any methods known to those skilled in the art such as incorporation of pores by mechanical or chemical means.

The term "impermeable" intends that the material is sufficiently impermeable to an agent. Hereby migration of such agents into or out of the device through the impermeable material is so low as to have substantially no adverse impact on the function of the device during the delivery period.

The drug/carrier layer 24 can be deposited subsequently on top of the deposited CP layer 22. The drug/carrier layer 24 generally comprises at least one type of therapeutic agent and optionally at least one carrier material, which assists in the handling and containment of the therapeutic agent, for example. A wide range of drug loading levels or combinations of different drugs in the drug/carrier can be used in connection with the various embodiments of the present invention, depending, for example, upon the condition to be treated and the nature of the therapeutic agent itself. The carrier material may be selected from a large array of polymers or non-polymeric materials that are known by those skilled in the art and as described below. In a preferred embodiment, it is possible that the drug/carrier material comprises only a drug, if it, for example is applied to the delivery device in a solvent carrier that is evaporated during the deposition process to provide a layer of drug in a crystalline state.

In another preferred embodiment, the drug/carrier layer 24 can be applied to the delivery device in layers or by non-equilibrium deposition processes, thus creating a composite film on the surface of the delivery device. Such a film may preferentially have varying physical and/or chemical properties through its thickness. In one example of such an embodiment, the outermost surface of the drug/carrier layer 24 can be made hydrophobic so as to prevent water uptake into the drug/carrier layer before water and ion uptake is actively initiated by activation of the CP element 22. This is
especially applicable in cases when the carrier material is not substantially hydrophobic and faces a risk to significantly absorb water prematurely during insertion and transport of the delivery device through to a treatment site.

The drug/carrier described in the previous as well as the following embodiments may be formed by many methods known in the art. Often the carrier is a polymer. Solvent is added to from an initial polymer/solvent mixture and then the drug is metered and added to the polymer/solvent mixture. Alternatively, the polymer, solvent, and drug can be added simultaneously to form the mixture. The polymer/solvent mixture may take the form of a dispersion, a suspension or a solution. The drug may also be mixed with the polymer in the absence of a solvent. The therapeutic agent may be dissolved in the polymer/solvent mixture or in the polymer to form a true solution with the mixture or polymer, be dispersed into fine or micronized particles in the mixture or polymer, be suspended in the mixture or polymer based on its solubility profile, be combined with micelle-forming compounds such as surfactants or be adsorbed onto small carrier particles to create a suspension in the mixture or polymer.

Numerous carrier materials appropriate for the practice of the present invention exist in the art. Representative examples are nondegradable or degradable polymer materials. More specific examples include polyvinyl alcohol polymers, such as ethylene vinyl alcohol copolymers; polyfluoro copolymers; cellulosic polymers, including cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellulose propionate, and cellulose ethers; polycarboxylic acids; polyphosphoesters; polyphosphoester urethanes; polyanhydrides including maleic anhydride polymers; polyvinylpyrrolidones; polyamides; polysaccharides; polydioxanone; polyesters; polycrylamides; polyesteramides (e.g. hyperbranched); polyethers; polyether sulfone; polyalkylene oxalates; polyphosphazenes; polyalkylenes; polyolefins such as polyisobutylene; halogenated polyalkylenes including polytetrafluoroethylene; polyurethanes (including dispersions); polyorthoesters; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl acetates; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers and olefins, such as ethylene-methyl methacrylate copolymers, polycaprolactam; alkyd resins; polycarbonates; polyoxymethylene; polyimides; epoxy resins; polybutylmethacrylate; rayon; rayon-triacetate; silicones; siloxane polymers; polylactic acid; polylactic acid; polycaprolactone; poly(lactide) and polyglycolic acid; polycaprolactone; poly(oxazolidone); polyhydroxybutyrate. Copolymers, such as ethylene-vinyl acetate copolymers; styrene-isobutylene copolymers; copolymers of polylactic acid and polylactic acid; copolymers of polylactic acid and polycaprolactone; polyethylene glycol/polyethylene oxide copolymers; polyethyleneoxide/poly(butylene terephthalate copolymers; copolymers of poly(ethylene-co-vinyl acetate) and poly(butyl methacrylate) such as disclosed in U.S. Patent No. 20070038667; protein-based coatings and derivatives; amino-acid based coatings; polymers bearing pendant
zwitterionic, for example phosphorylcholine, groups such as disclosed in U.S Pat. No 6924338. Derivatives, copolymers and blends of the above are also contemplated. Inorganic, non-polymeric materials such as hydroxyapatite based materials or nanoporous ceramics, made of aluminium oxide, titaniumoxide or iridiumoxide, may also be used as a suitable carrier material.

The drug/carrier may be applied by a range of common methods. Examples of suitable methods are spraying, laminating, pressing, brushing, swabbing, syringe deposition, dipping, soaking, rolling, electrostatic deposition, vapor deposition etc. Due to the advantageous configuration of the present invention, loading of the drug/carrier into the CP can be achieved using non-electrochemical methods as opposed to the electrochemical methods described by the prior art. This simplified and versatile approach to fabrication also lends itself to the sequential deposition of CP and drug/carrier, thereby facilitating the production of multilayered delivery devices.

In the previous embodiment described in fig.4 a-c as well as in the figures to follow, the drug delivery device might comprise a substrate 26, onto which the CP and drug/carrier are applied. The substrate might comprise one or several electrode regions that are electrically conducting thus providing a means for electrically connecting the device to a control unit. Alternatively, the electrode regions may form part of the electrochemical cell (i.e. a working electrode together with the CP, a counter electrode or a reference electrode). Methods and materials for the application and patterning of electrodes onto a substrate are well known to the skilled person.

An alternative embodiment is described in Figs. 5a, 5b, and 5c. Fig. 5a shows a delivery device 40 comprising a CP element 42 arranged in a substantially thin layer onto which is located a drug/carrier material 44 in the form of a deposited layer. The delivery device 40 may also comprise a porous or perforated substrate 46 that is attached to the bottom surface of the CP element 42. The optional porous substrate 46 allows passage of solvent and ions from a surrounding electrolyte 50 located to the backside of the delivery device 40. The delivery device 40 of this type may be positioned in close proximity to a lumen wall 48 or an equivalent treatment site such that the drug/carrier material 44 is in contact or near contact with the lumen wall 48. Upon activation of the CP element 42 by application of an electric potential in process A2, water and ion uptake will occur from the surrounding electrolyte 50 through the back side of the delivery device 40. The result of this action is shown in Fig. 5b. The water and ion uptake flux F3 can occur through the optional porous substrate 46. The CP element 42 may be provided such that it is impermeable to the drug/carrier material. In this case, during the water and ion uptake process, the drug and/or carrier is not substantially drawn into the CP element 42 and generally remains in close proximity with the lumen 48.
After the water and ion uptake process F3 is sufficiently completed, a water and ion expulsion process is initiated. This process can be initiated by reversing the electric potential applied to the CP element 42 in process R2. Repeated water uptake and expulsion steps can be performed to further enhance the drug delivery process. Fig. 5c depicts the result of the simultaneous water and ion uptake and/or expulsion processes F4, F5. As indicated by the flux F5, these processes release drug towards the lumen wall 48, while flux F4 indicates that water and ions (primarily free from drug species if the CP element 42 is impermeable to drug) are expelled from the CP element 42 and back towards the surrounding electrolyte 50 through the optional porous substrate 46. The net result of these processes is the delivery of released drug 52 to a treatment site 48.

If the CP element 42 is provided such that it is permeable to the drug and or drug/carrier material and the substrate is porous or perforated, a bidirectional delivery of drug by both flux F4 and F5 can be achieved both towards the lumen wall 48 as well as towards the lumen interior.

Some examples of lumens 48 where the disclosure can be applied are lumens of the cardiovascular system such as the heart, arteries (e.g. coronary, femoral, aorta, ilial, carotid arteries), lumens of the genitourinary system (e.g. the urethra, bladder, ureters, vagina), the nasolacrimial duct, the eustachian tube, lumens of the respiratory tract (e.g. the trachea, bronchi), lumens of the gastrointestinal tract (such as the esophagus, gut, small intestines, colon), lumens of the lymphatic system, the major body cavities (peritoneal, pleural, pericardial), and so forth.

Figs. 6a and 6b depict an alternative embodiment of a delivery device 60. Fig. 6a shows an embodiment where the drug/carrier layer 64 is arranged between a CP-comprising layer 62 and a substrate 66. When the CP layer 62 is activated by applying an electric potential, water and ions are drawn into the CP layer from the surrounding electrolyte 68. The uptaken water and ions subsequently enter the underlying drug/carrier layer 64. The release of the drug begins once water and ions from the surrounding electrolyte 68 have come into contact with the drug and/or drug carrier. Subsequently, released drug 70 is delivered from the delivery device 60 into the surroundings through diffusion, convection and other mechanisms as previously described. The result of this process is shown in Fig. 6b. The application of reduction and oxidation potentials can be repeatedly applied in process AR1 to further aid in releasing drug 70 by generating repeated influx/outflux out of device 60 as represented by the flux F6.

In this case, the drug/carrier layer 64 may substantially consist of drug i.e. no carrier material. This might be achieved by first depositing drug to the substrate in a solvent carrier material such as a liquid which is subsequently evaporated during the fabrication process. When water, upon activation of the CP layer 62 reaches the drug layer 64, the drug is dissolved, mobilized and subsequently released from the delivery device 60 by flux F6.
Illustrative examples of the carrier material used in layer 64 are polymers and non-polymeric materials. Although such materials may be generally selected from the previously described list, preferred materials are polymers that are at least partially water absorbing such as including for instance: polysaccharides such as gelatin, starch; polyacrylate; polyamides; copolymers containing acrylic acid such as a starch-acrylic acid graft copolymer, a vinyl acetate-acrylic acid copolymer and the like; polyethylene glycol/polyethylene oxide copolymers; polyactic acid and polyglycolic acid, copolymers, polycaprolactone; copolymers containing acrylonitrile such as a cellulose-acrylonitrile graft copolymer, a starch-acrylonitrile graft copolymer, a hydrolyzed product of polyacrylonitrile and the like; polyvinyl alcohol; copolymers containing vinyl alcohol such as a vinyl alcohol-maleic anhydride copolymer, a vinyl alcohol-vinylacetate copolymer and the like; polyvinylpyrrolidones; copolymers containing maleic anhydride such as an isobutylene-maleic anhydride copolymer, a styrene-maleic anhydride copolymer, a methylvinylether-maleic anhydride copolymer and carboxymethylated cellulose products such as a carboxymethyl cellulose, a carboxymethyl rayon and the like.

Another alternative embodiment is shown in Figs. 7a, 7b, and 7c. A delivery device 80 is shown in Fig. 7a where a drug/carryer layer 84 is arranged between an CP-comprising layer 82 and a membrane 86. The membrane 86 is provided with semi-permeable properties and will prevent significant water influx into the drug/carryer layer 84 until the CP layer 82 is controllably activated. Semi-permeable membranes (e.g. reverse osmosis, nanofiltration, ultrafiltration, and microfiltration membranes) have a long history of use in separating solution components. Such membranes are able to retain certain substances while transmitting others. In this case the membrane is permeable to the passage of drug but has a lowered permeability towards the passage of water in the inwards direction. Upon activation of the CP layer 82 by application of an electric potential in process A3, a flux of water F7 is drawn into the delivery device 80 from the surrounding electrolyte 88 and reaches the drug/carryer layer 84. This process is shown in Fig. 7b. The drug and/or drug/carryer is dissolved, or otherwise put in a mobile form, in the presence of water and ions, thereby initiating transport of the drug through the membrane 86 and into the surroundings according to same transport mechanisms as previously stated. Although the membrane 86 may be applied as a distinct and uniform layer, another option for providing semi-permeability is to modify the properties of the outermost surface of the membrane 86. The outermost surface of the membrane 86 can be made additionally hydrophobic (e.g. using plasma deposition of a hydrophobic layer) so as to prevent water uptake into the drug/carryer layer before water and ion uptake is actively initiated by the CP activation.

Although, the drug and/or drug/carryer may passively diffuse through the membrane after controlled activation of the CP layer 82 during process A3, further activation of the CP layer 82 by applying a reversed electrical potential in process R3 generates an outflow of water and ions F8, F9 which
can be used to enhance the drug release process. Fig 7c illustrates the effects of further activation of the CP layer 82 and the release of drug 90 into the surroundings. In this case, it is desirable that the CP layer 82 is significantly impermeable to the drug or drug/carrier such that the flow of drug or drug/carrier is substantially directed through the membrane 86 by flux F9. This can be achieved by addition of another semi-permeable membrane (not shown) between the CP layer 82 and drug/carrier layer 84. In this case the membrane is chosen to be permeable to the passage of water but is substantially impermeable to the passage of the drug. Examples of suitable materials for the membrane 86 include cellulose nitrate, cellulose acetate, polyamides, polyimides, polytetrafluoroethylene, poly-(vinyl chloride) and polysulfone.

Another embodiment of a delivery device 100 is shown in Figs. 8a, 8b and 8c. As depicted in Fig. 8a a layered structure is shown where a series of drug/carrier layers 104a, 104b and layers incorporating CP 102a, 102b, and 102c are alternately stacked onto an optional substrate 106. It is preferable that a CP layer 102c is arranged at the top of the layered structure facing the surrounding electrolyte 108 to prevent premature water absorption and to electrically initiate water absorption. The CP layers 102a, 102b, and 102c are electrically connected to an external power supply and an optional control unit (not shown) such that they can be controllably activated. When the CP layers 102a, 102b and 102c are activated by the application of an electric potential in process A4, water and ions are drawn into the CP layers from the surrounding electrolyte 108 and into or through the underlying drug/carrier layers 104a, 104b. The result of the water and ion uptake process F10 is shown in Fig. 8b. The water and ion flux can be electrically reversed by applying a reversed electrical potential in process R4 to generate an outflux F11 of water ions and also drug 110. Repeated cycling of steps A4 and R4 can thereby generate an oscillating flow of water in and out of the drug/carrier layers. This results in enhanced and/or oscillating flux F11 and, as depicted in Fig. 8c, the release of drug 110 into the surroundings. In an alternative embodiment, the drug/carrier layers 104a, 104b may in this case comprise drug without a carrier material i.e. no carrier material such as polymer, gel etc. The CP layers 102 a-c and drug/carrier layers 104 a-b can be provided with perforations or slots along both/either the thickness or plane directions to facilitate more rapid release of drug into the surrounding electrolyte 108. Such perforations or slots are especially useful for enhancing drug release from layers that are arranged deep within the layered structure. Moreover similar function to the perforations or slots is provided by use of a porous CP material in the CP layers 102a-c. Optionally, on top of the layered structure or between selected drug/carrier layers, another coating (not shown) can be applied. This coating might be used to modify the release rate of drug into the surroundings. Such release rate modifications may include a delayed release coating. The coating might also provide other desirable features such as a porous coating to prevent direct mechanical contact with external objects, a semi-permeable membrane to prevent contact between CP and drug/carrier layer and/or a biocompatible coating facing the external electrolyte.
Figs. 9a and 9b depict another alternative delivery device. Fig 9a shows a delivery device 120 comprising a drug/carrier layer 124 arranged between a substrate 126 and a CP layer 122. In the embodiment shown, the drug/carrier layer 124 is fully encapsulated by the CP layer and substrate. The CP layer 122 may be grown or deposited onto a previously deposited drug/carrier layer 124. The CP layer 122 is connected to an external power supply and an optional control unit (not shown) and can thus be controllably activated to initiate the drug delivery process. Prior to activation, the delivery device 120 is generally positioned in close proximity to a treatment site and a surrounding electrolyte 128. Upon activation, during the process A5, the properties of the CP layer 122 are controllably changed so as to affect the drug delivery process. In one case, the diffusion properties of substances in the CP layer 122 are controlled based on the applied potential. During activation, the CP layer 122 alters it morphology and structure hence becoming more microporous with micropores 130 forming though the CP layer 122 and thereby creating conduits between the drug/carrier 124 and the surrounding electrolyte 128. This increases the diffusion coefficient of both water and drug through the CP layer and hence increases the permeability of CP layer 122 to allow water and drug to be exchanged between the device 120 and the surrounding electrolyte 128 by a flux F12 that is composed of water, ions and drug and that can be reversibly switched back and forth to further improve drug release. This process is depicted in Fig. 9b, where released drug 132 in the surroundings is shown. By controlling the diffusion coefficient of substances such as drugs in the CP layer, the rate of drug release from the delivery device can also be controlled.


More intimately arranged composites of drug or drug/carrier and CP are also possible (as opposed to layered composite structures). As an example it is possible to form a composite by first depositing a porous CP and subsequently filling up voids/enclosures in the CP with the drug/carrier or drug. In one case, the CP may be porous PPy. Porous CP can be fabricated by a variety of methods known to those skilled in the art. One approach, applicable to polypyrrole (PPy) based CP, is to use suitable dopant ions during the electropolymerization of the PPy (see e.g. Hara, 2004, Gel-like Polypyrrole Based Artificial Muscles with Extremely Large Strain, Polymer Journal, Vol. 36, Issue 11, pp. 933—936). The porous CP might also be fabricated as a composite e.g. a hybrid material with CP deposited into a porous host material such as meso-porous carbon (see e.g. Fuertes, 2007,
Encapsulation of Polypyrrole Chains Inside the Framework of an Ordered Mesoporous Carbon, Macromolecular Rapid Communications, Volume 26, Issue 13, p 1055-1059) or porous membranes such as alumina or nylon (see e.g. Seung Lee, 2000, Chemical synthesis and characterization of polypyrrole coated on porous membranes and its electrochemical stability, Synthetic metals, Volume 113, Issue 1, p 115-119). Another approach for achieving a porous CP is to use some kind of sacrificial template that is removed e.g. a microsized polymer particle such as polyesterene that can be dissolved (see e.g. Yang, 2004, Microporous conducting polymers on neural microelectrode arrays I Electrochemical deposition, Sensors and Actuators B, Volume 101, Issue 1-2, p 133-142).

The drug loading process into the porous CP can be achieved by a number of methods. One method is to soak or dip the CP in a solution of the drug/carrier possibly dissolved in a solvent. This process might be step-wise divided by first dipping in drug solution and then dipping in a carrier solution, possibly with drying steps in-between. Alternative methods for the drug loading process include spraying (e.g. ultrasonic), painting (air brush), syringe application, printing, or molding, among others, to apply a drug or drug/carrier into the CP. Such application processes can proceed under the assistance of vacuum, pressure or temperature so as to expedite absorption. After the drug/carrier is absorbed or pushed into the CP it remains with minimal leakage until use.

During activation of the CP, a flux of water and ions is generated in and out of the drug containing pores and the drug is expelled into the surroundings. It is also possible that a carrier is not needed and that the drug is provided in a concentrated crystallized form, without a polymer, gel, or liquid carrier. In this case, a solvent may have been used to assist in the deposition of the drug into the CP and then been removed by evaporation in order to prevent the drug from leaking during transport and storage. Upon rehydration when the water flux reaches drug layer, the drug will again mobilize and be transported from the delivery device with the flux.

Figs. 10a, 10b and 10c describe an embodiment of a delivery device. Fig. 10a shows a porous CP layer 142 as deposited onto a substrate 144 forming a host layer 141. A drug/carrier is deposited into cavities 146 of the CP layer 142 during a drug loading process DL1, which may involve a solvent removal step as mentioned previously. The resulting delivery device 140 is shown in Fig. 10b. After the delivery device 140 is transported to the treatment site, the CP layer 142 is activated under potential control during process A6 which generates a flux F13 of water and ions into and/or out of the delivery device 140 from surrounding electrolyte 150. The water and ion flux through the drug loaded pores 148 transports drug from the delivery device into the surrounding electrolyte 150. This process is shown in Fig 10c, which shows released drug 152. Further activation cycles of the PPy host polymer generate repeated influx/outflux F13 of water and ions can be used to release more drug from the delivery device.
Besides a porous CP other composite structures of CP and drug/carrier are also possible. The drug/carrier can be initially deposited onto the optional substrate. CP is subsequently deposited into the drug/carrier material and penetrates into this layer substantially making mechanical and/or electrical contact with the substrate. The resulting structure is a composite structure where drug/carrier material and CP material are dispersed and mixed with each other.

It is also possible to utilize the CP as a gate-keeping means controlling access of and mixing of the surrounding electrolyte to the drug/carrier material within the delivery device. Once the CP allows and/or generates electrolyte in-flow to the drug/carrier layer this initiates a degradation, decomposition, disintegration or dissolution process whereby, the drug is transformed into a releasable form and can be released into the surroundings. In these examples, the CP initiates these secondary processes that further drive the drug release process. The following embodiments describe this form of functionality in further detail.

Figs. 11a and 11b depict an alternative embodiment of a delivery device, where the drug-containing materials may comprise a hydroactivated or water-soluble carrier material. Fig. 11a shows a delivery device 160 where a drug/carrier material 164 is arranged between a layer consisting of CP 162 and a substrate 166. In one example, the substrate 166 is provided as a semipermeable membrane that is permeable to the drug while being impermeable to water. When the CP layer 162 is activated by applying an electric potential during process A6, water from surrounding electrolyte 168 is drawn into the CP layer 162 as a flux of water and ions. Water and ions drawn into the CP layer 162 come into contact with the interface between the CP layer 162 and the drug/carrier layer 164. This process is depicted in Fig. 11b. Once in this configuration, the penetration of water into the drug/carrier layer 164 proceeds by diffusive and osmotic processes. In addition, the activation process A6 can be reversed. During this reverse process, water and ions will be driven in all directions from the CP layer 162, thereby forcefully driving further quantities of water into the underlying drug layer 164.

The drug/carrier material generally comprises a drug containing carrier. The drug containing carrier is activated by the presence of water and begins releasing drug when the carrier material starts, dissolving, degrading, fragmenting, eroding etc. Suitable breakdown mechanisms for the drug containing carrier include, but are not limited to, water dissolution, hydrolyzing or enzymatically catalyzed reactions. After release from the drug containing carrier, the drug is then released into the surroundings, either through the CP layer 162 or through the substrate 166 if it is chosen to be substantially permeable to drug. The passage of drug generally occurs by the processes of diffusion and optional forced convection if further activation processes A6 are applied to the CP layer 162 during the release process. The influx of water and ions and outflux of water, ions and drug is depicted as a flux F14 in Fig. 11b. By reversing the applied potential it is possible to repeatedly
generate influx and outflux of water and ions that further facilitates drug release by flux F14. It is also possible to provide a drug/carrier layer 164 comprising only a therapeutic agent, present in a crystalline form. In this case the drug is dissolved when CP 162 enables water access to the drug layer 164, the drug becomes mobilized and subsequently reaches the surrounding electrolyte 168 as released drug 170.

Hydroactivated or water-soluble materials used as carriers in drug/carrier layer 164 may be a number of materials known to those skilled in the art and medical device and drug delivery systems. Some examples are biodegradable polymers, water soluble polymers and bio erodible hydrogels. Non-limiting examples of biodegradable polymers include: poly(amides) such as poly(amino acids) and poly(peptides); poly(esters) such as poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and poly(caprolactone); poly(anhydrides); poly(orthoesters); poly(carbonates); polyethylene oxide; copolymers of polyethylene oxide and polypropylene oxide; other water dispersible ethylene oxide copolymers, water dispersible blends of polyethylene oxide, water degradable grades of polyvinyl alcohol, blends of polyvinyl alcohol, polyvinyl pyrrolidone, polyethyleneazoline water degradable branched polyesters and copolyesters, water dispersible polyurethanes, water degradable acrylic acid based copolymers, water dispersible polyvinyl methyl ether, cellulose derivatives such as methyl cellulose, hydroxypropyl cellulose, methylated hydroxypropyl cellulose; collagen; agar; fibrin; polysaccharides such as alginate, pectin, chitosan; dextran; malt; gelatin; talc and chemical derivatives or copolymers and mixtures thereof. The degradation rate of the biodegradable coating can be controlled by the ratio of different constituents, or by the thickness or density of the coating. A possible embodiment is to not have any carrier at all but only drug, for example in crystalline state. The drug/carrier material may also contain additional species such as excipients or disintegrants to further improve drug delivery.

The CP comprising material 22, 42, 62, 82, 102, 122, 142, 162 described in the above (and following) embodiments related to generation of flow of solvent and ions may be fabricated to have material properties adapted for this purpose. Preferred CP materials are CP that may be doped with dopants that are known to generate large water influx and outflux. Such large water influx and outflux can be but is not necessarily associated with significant volume changes. This might be the case if the CP is manufactured to be very porous as previously discussed. Some preferred examples used in the previous and upcoming embodiments employing water fluxes are polypyrrole doped with polystyrenesulfonate, and dodecylbenzene sulfonate but other dopants are not excluded.

Figs. 12a and 12b describe another alternative embodiment of a delivery device. Fig. 12a shows a delivery device 180 comprising a drug/carrier 184 deposited onto an optional substrate 186. In this example, the drug delivery device comprises a series of fully encapsulated drug regions 184 (e.g. in the form of cavities) and a continuous region of
degradable CP 182. Prior to degradation of the degradable CP 182, the drug regions 184 are sufficiently isolated from the surroundings such that minimal diffusion of drug occurs during transport of the delivery device to the treatment site. Upon delivery to the treatment site and a suitable surrounding electrolyte 188, an electric potential is applied to the degradable CP 182. This electrochemical activation process EA1 draws water into the CP 182 and initiates degradation of the CP. This process is shown in Fig. 12b. As the degradable CP 182 is degraded, the drug is exposed to the surrounding electrolyte 188 and is subsequently released from the delivery device 180 as released drug 190. The release can be expedited by generating an outflux of water and ions F15 by applying another potential. Various forms of degradable CP useful for the CP 182 are known in the art. Degradable electrically conducting polymers are for example disclosed in US6696575 and US 7291693.

It is also possible that the degradable CP 182 with incorporated drug/carrier 184 as depicted in Fig. 12 is combined with an additional outermost layer of non-biodegradable CP element (not shown). Upon application of a potential this CP layer allows and generates electrolyte in-flow to the degradable CP layer 182. This initiates the degradation process of the underlying degradable CP 182 after it is exposed to water and applied potential. Subsequently the drug is released into the surroundings.

It is also possible to enhance and control initiation of mixing of the electrolyte solution with the degradable or dissolvable drug/carrier material previously described. An embodiment suitable for this form of enhanced mixing type delivery device is described in Figs. 13a and 13b. Fig. 13a shows a delivery device 200, in cross section and with symmetry lines SS, that comprises a substrate 210 onto which a drug/carrier layer 208 is applied. The drug/carrier layer is placed in close proximity (and possibly mechanically attached to) a substantially open CP layer 202. This CP layer 202 can be spatially separated from the drug/carrier layer 208. The CP layer 202 is further comprised of a series of CP regions 204 coated over optional electrode regions 206. Throughout the CP layer 202, there are a substantial number of channels 214 that cross fully through the CP layer 202. The channels 214 in the CP layer 202 have characteristic length L and characteristic channel width W. It is preferable that the channels 214 are sufficiently small in characteristic width W compared with their length L such that, when the CP regions 204 are not activated, any flow within the channels 214 is limited and flow stagnation readily occurs. This minimizes exchange of fluid between the surrounding electrolyte 212 and the drug/carrier 208 prior to activation of the CP regions 204. The CP regions 204, or alternatively the optional electrode regions 206, are attached to an external power supply and an optional control unit (not shown) such that they can be controllably activated. When the delivery device 200 is placed into a surrounding electrolyte 212 and transported to the treatment site, the CP regions 204 can be activated. The CP regions 204 are activated by applying an electric potential and this alters the surface energy of the CP which in turn creates
local surface tension gradients around the CP layer 202 and draws water and ions from the surrounding electrolyte 212 into the channels 214 and the drug/carrier 208. The result of this process is depicted in Fig. 13b. When fresh electrolyte 212 makes contact with the drug/carrier layer 208 a disintegration or dissolution process takes place, as discussed previously. This process releases drug from the drug/carrier layer 208 and it is subsequently transported into the surroundings as released drug 216. The activation process AR2 can be reversed and repeated. These create an oscillatory influx and outflux of water and ions F16 through the channels 214. The oscillating flow F16 enhances micro-scale mixing of fresh electrolyte and drug rich electrolyte thereby enhancing delivery of released drug 216 from the delivery device 200 into the surroundings. It is preferable that the CP regions 204 are substantially hydrophobic in the un-activated state and even more preferable if the CP layer 204 becomes more hydrophilic when switched to the activated state. Such a CP layer 204 would prevent the surrounding electrolyte 212 from coming into contact with the drug/carrier layer 208 during transport of the delivery device 200 to the treatment site. Instead exceedingly small air bubbles would remain within the channels 214 and would not be removed until the CP layer 204 is activated. Upon activation (process AR2) of the CP layer 204, fresh electrolyte is forced into the channels 214, displaces the entrapped air, and makes contact with the drug/carrier layer 208. Causley et al. showed that solvent flow in small channels could be initiated, generated and controlled using a conducting polymer (Causley et al. Electrochemically-induced fluid movement using polypyrrole, Synthetic Metals 151 (2005) 60-64).

An example of the control of surface energy of the CP is now described. A PPy(DBS) layer was deposited onto a Si/Cr/Au wafer using potentiostatic electropolymerization at 0.575 V for. The surface energy of the PPy layer is then changed during activation as follows. In the deactivated state, the surface of a PPy(DBS) sample was placed into contact with a droplet of water. Using a goniometer (in air measurements) the advancing contact angle of water on the surface of the PPy layer is measured at several spots and the mean value was approximately 65 degrees (more hydrophobic). After application of an electric potential of -1V vs. an Ag/AgCl reference electrode the contact angle of the water droplet was changed to approximately 50 degrees (more hydrophilic). This is a large change in surface energy that is sufficient to control flow through a microchannel as disclosed in Fig. 13.

The delivery device 100,120,140,160,180, 200 described herein can be incorporated into or onto a range of surgical tools. The delivery device can be integrated into the surgical tool or applied as a coating onto the tool surface. The delivery device can be selectively applied on areas of the tool to fit the application and desired treatment site. Often a coating can be applied on the outside of a tool such as a balloon to readily deliver drugs to a lumen wall. However, it is also possible to apply coatings to the inside of a tool such
as a catheter, if desiring to deliver drugs to a lumen interior. Examples of surgical tools where the invention can be incorporated include catheters (urinary catheters, in-dwelling catheters, aspiration catheters, injection catheters, infusion catheters, drainage catheters, venous catheters, arterial catheters, central line and peripheral line catheters, balloon catheters), guide wires, electrodes, coated or uncoated stents (including coronary vascular stents, peripheral vascular stents, cerebral, urethral, ureteral, biliary, tracheal, gastrointestinal and esophageal stents), vascular grafts, stent grafts, aneurysm fillers (including Guglielmi detachable coils), devices for rotational atherectomy or thrombectomy, temporary occlusion devices, embolic protection devices, filters (for example, vena cava filters), baskets and snare e.g. for retrieval, cardiac pacemaker leads or lead tips, leads or parts of implanted devices (for example in spinal stimulation, peripheral nerve stimulation, deep brain stimulation or neuromonitoring), vascular patches, electroporation devices, iontophoresis devices, in-dwelling access ports, devices for cardiac mapping or ablation, introducers, sheaths, intraluminal paving systems, heart valves, annuloplasty rings and bands, sewing rings and cuffs, cannulas, trocars, endoscopes, probes, laparoscopes, sutures, staples, myringotomy tubes, wound or nasal packings, dressings, gauze, bone screws, halo screws, total joints, hernia meshes, needles, wound drains, contact lenses, peristaltic pump chambers, arteriovenous shunts, gastroenteric feed tubes, endotracheal tubes, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, shunts, tissue adhesives and sealants, tissue scaffolds, various types of dressings, extravascular wraps and bone substitutes; joint prosthesis or part thereof, such as a hip prosthesis, a knee prosthesis, a vertebral or spinal disc prosthesis, a spinal cage as well as many other devices that are implanted or inserted into the body and from which therapeutic agent is released.

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The delivery device 100,120,140,160,180, 200 may be operated in conjunction with other functions of the surgical tool as part of a surgical operation. In such surgical procedures, the drug delivery device may be required to deliver a therapeutic agent to the treatment site rapidly and on demand, or sustain constant delivery rate of a therapeutic agent during a prolonged or short surgical procedure. The delivery device may also be required to deliver a plurality of therapeutic agents in a simultaneous or sequential fashion.

Alternatively, the delivery device 100,120,140,160,180, 200 may also be part of an implantable device. In this case, the drug delivery from the delivery device may be controlled over longer periods of time so as to sustain a constant delivery rate of a therapeutic agent, or to provide timed delivery of the therapeutic agent (perhaps based on the time of day or the physiological state of the patient).

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Figs. 14a - 14f describe a delivery device that has been incorporated into a surgical tool in form of an angioplasty balloon. Although Figs. 14a -14f show a delivery device with controllable diffusion properties, similar to the
embodiments described in Fig. 9, the main aspects described herein can be suitably applied to the application of any of the delivery devices described in Figs. 1-13 to a surgical tool.

Fig. 14 depicts multiple delivery devices incorporated into a surgical tool 1000 shown here as an angioplasty balloon. Generally, the surgical tool has a housing 207 which is reflective of the outer surface of the surgical tool 1000. The surgical tool may also have an interior chamber 205, 224, which may contain a drug in the form of a solution with a carrier fluid containing saline, water and/or a solution of sugar. The interior chamber 205, 224 is generally defined by the housing 207 of the surgical tool 1000. The surgical tool 1000 is inserted into a body lumen 203. The surgical tool 1000 is transported to the treatment site and a series of procedures may be performed. The surgical tool 1000 may be configured so as to bias the delivery device 220 towards a lumen wall 201, preferably towards a desired treatment site. Once into position, the delivery device 220 can be activated and the drug delivery process proceeds as described earlier.

Figs. 14a and 14b focus now on the detailed region 220 of Fig. 14. Figs. 14a and 14b describe more particularly how a delivery device 220 can be incorporated into a surgical tool 1000. Fig. 14a shows a delivery device 220 comprising at least a CP element 222 and at least one electrode 228a-c. The electrode 228a can provide electrical contact to the CP working electrode. The electrode, if sufficiently isolated from the CP element, may also function as counter electrode 228b or reference electrode 228c in the electrochemical cell. In another embodiment, the electrodes 228a-c may be electrically connected together and patterned so as to minimize mechanical influence of the electrode materials on the electrochemomechanical processes occurring within the CP element during activation. The delivery device 220 is generally arranged as a wall in or coating on the surgical tool 1000. The delivery device 220 can extend substantially over the complete surface area of the surgical tool. In the embodiment shown, the interior region of the surgical tool 1000 is filled with a drug/carrier solution 224 that it is to be delivered to a treatment site. The CP element 222 prevents passage of the drug/carrier solution 224 in the interior of the surgical tool prior to activation. Upon application of an electric potential to the CP element 222, optionally via the at least one electrode 228a-c, the CP element 222 is activated as indicated by process A7. Once activated, the drug and or drug/carrier material can more easily diffuse through the CP element 222. Released drug 236 is then delivered to the lumen interior 203 in close proximity to lumen wall 201. Drug release is improved if drug/carrier is actively transported with the solvent and ion flow F17 that can be generated back and forth over the delivery device (between lumen and tool interior) if repeated activations are performed. This process is depicted in Fig. 14b. Hence, drug is delivered to the treatment site. It is preferable in this type of arrangement that the balloon be a double walled balloon so that a minimal amount of drug/carrier solution 224 is transported within the surgical tool during the delivery procedure.
An improvement to the delivery device 220 shown in Figs. 14a and 14b is now described so as to further elucidate how other embodiments of the delivery device 100, 120, 140, 160, 180, 200 can be incorporated into a surgical tool 1000. Figs. 14c and 14d demonstrate an alternative delivery device 220 comprising an optional membrane 230 which may be provided by the original surface of the surgical tool 1000. The membrane 230 may be permeable to a solvent or tracing solution 205 that is passed through the surgical tool interior during a surgical procedure. A concentrated drug/carrier material 226 is deposited onto the outside of the membrane 230. An arrangement of at least one CP element 222 and at least one electrode 228a-c are deposited onto the drug/carrier material 226. The CP element 222 is connected to an external power supply and an optional control unit (not shown), possibly via the at least one electrode 228a-c, such that it can be controllably activated during the surgical procedure. The CP element 222 is provided such that, prior to activation, the drug/carrier material 226 is substantially contained by the CP element 222. Upon application of an electric potential, in process A8, to the CP element 222, possibly via the at least one electrode 228a-c, the permeability and/or porosity of the CP element 222 is significantly altered and/or water is drawn into the CP. Thus a flux F18 through drug/carrier 226 is generated. In the presence of the flux F18, the drug/carrier material 226 can pass through the CP element 222 as released drug 236 and be delivered to the treatment site i.e. lumen interior 203 and/or lumen wall 201. The electrolyte required for activation of the CP element 222 can be provided by fluids injected during the surgical procedure or liquids provided a priori in the lumen interior 203.

It is also possible to enhance the drug delivery process by providing a solvent such as saline that is passed through the surgical tool during the surgical procedure. Here, the surgical tool interior may be filled with a solvent 205 such as saline during the inflation of a balloon. In this case, the CP element 222 can be provided so as to contain both the drug/carrier material 226. Upon activation, the CP element is made more permeable and/or porous and both solvent and drug/carrier are delivered through the CP element 222 towards the treatment site.

Figs. 14e and 14f describe a further enhancement to improve delivery of a therapeutic agent to a treatment site. Fig. 14e depicts a delivery device 220 comprising a membrane 230, that may or may not be permeable to solvent 205 contained in the interior of a surgical tool 1000, onto which is deposited a drug/carrier layer 226. Onto the drug/carrier layer is deposited an arrangement of at least one CP element 222 and at least one electrode 228a-c. Onto the CP element 222 is patterned at least two structural elements, each structural element comprising a bonding layer 234a-b, which may be electrically insulating or non-insulating, and a structural feature 232a-b.

The structural features 232a-b may act as spacer elements forming a suitable gap between the CP element 222 and the lumen wall 201. Thus
sufficient electrolyte is available within the gap defined by the CP element 222, the lumen wall 201 and the structural features 232a-b to fully activate the CP element 222. When an electric potential is applied to the CP element 222, as indicated by the activation process A9, a flux of solvent and drug F19 is generated through the delivery device 220.

The structural features 232a-b may also provide a means of containment for the drug/carrier material after it is released from the delivery device into the lumen interior 203 as released drug 236. In this case, the structural features may shield the local fluids from blood flow around the surgical tool. This enhances the overall efficacy of delivery of the therapeutic agent to the delivery site since it minimizes the amount of therapeutic agent that is washed away by the flow of bodily fluids.

The structural elements may also comprise a bonding layer 234a that is electrically insulating and a structural feature 232a that is conducting. In this case, the structural feature 232a may act as a counter electrode since it is electrically isolated from working electrode as defined by the CP element 222. The close positioning of such counter electrodes enhances the design of the electrochemical cell for the activation and deactivation of the CP element 222 and allows for more rapid and efficient operation of the delivery device 220. In yet another embodiment, the structural feature 232b may act as an electric field shaping element. This is useful for enhancing the drug delivery process by allowing for simultaneous use of electroporation, iontophoresis, and/or electro osmosis. Electroporation is a technique used for introducing molecules across a cell membrane and into a cell. In a typical application, an a brief electrical field is applied over cell membranes. The electrical field causes a transient porosity of the cell membranes, allowing molecules to enter. Thus the features of the delivery device 220 may provide this enhanced capability with minimal extra hardware.

The structural features 232a-b may also comprise a micro-needle or micro-blade element suitable for penetrating the lumen wall 201. In this case, the penetration of the lumen wall 201 both anchors the delivery device and facilitates easier penetration of the released drug 236 into the lumen wall 201.

The membrane 230, being a membrane in the medical device 1000, may be considered equivalent to a general substrate, as depicted in the previous figures. In this way, the previously discussed embodiments may be suitably incorporated onto the surface of a medical device (such as a balloon as in this case) for delivering a therapeutic agent during to a treatment site during a surgical procedure.

In another aspect of the invention it is also possible to design drug delivery devices that employ the force output generated by volume change of CPs to transport a substance such as a therapeutic agent. Conducting polymers such as PPy have the advantage that, under potential control, they can be reversibly switched between an oxidized and a reduced state or any
intermediate state. The reactions follows scheme 1, for example and as depicted in Fig. 1 is associated with a significant reversible volume change that can be very fast. The amount of volume change and the speed is controlled by the applied potential. Furthermore, by controlling the applied potential any intermediate volume change can be reached and held. The prior art such as U.S. Pat. No. 5876741 describes crosslinked polymer gels that change volume in response to a pH variation. Such gels are well known to have limited response rate and it may take many minutes for such a material to reach full expansion during activation. In comparison, the CP materials described in this application require only a few seconds to achieve such volume change. This process is shown in Fig 1 as has been already described. Moreover the prior art systems feature little control of the overall volume change or control over stopping or reversing the volume change process. This is not case for the present invention where CP such as PPy(DBS) can be in reversibly change or hold its volume at any selected point when applying an appropriate potential. Moreover, gels often need to be stored in swelled states such as exemplified in U.S. Pat. No. 6394997. Volume change upon activation of CPs such as PPy(DBS) is independent of whether it was stored and transported to the treatment site in a swelled, contracted or dry state as seen in Figs. 1 and 2. Moreover, in the present invention, highly integrated layers or patterned coatings are possible. Thus the present invention is especially suited for integration of such delivery devices directly into other medical devices as thin and easily producible coatings.

The volume change, consists of both out-of-plane and in-plane deformation. The out-of-plane volume change of PPy(DBS) is depicted in Figs. 2 and 3. This volume change is generally accompanied by significant force generation measured to be greater than 1 MPa in the in-plane direction. The deformation of a CP element is typically highly anisotropic. For example, in-plane strains may be roughly 2-5% while at the same time the out-of-plane strains may be 20-30%. The volume change and force generation of CP can be applied for drug delivery in a number of ways as described below.

Figs. 15a and 15b show an embodiment of the present invention provided as a delivery layer 500. Figs. 15a and 15b show a cross section of a part of this delivery layer 500. The delivery layer 500 is constructed using at least one element 502 substantially consisting of CP that is deposited onto an optional substrate 506 with substantially vertical voids situated within individual or between adjacent CP elements. The substantially vertical voids are filled by a drug/carrier material 504. Although the substantially vertical voids are shown in Fig. 15 as penetrating through the entire delivery layer 500, they may also partially penetrate through the delivery layer 500. The drug/carrier material may include the therapeutic agent along with an optional carrier, which will be described in more detail later. As depicted schematically in Fig. 15b, upon expansion of the CP elements (by oxidation or reduction) during process E1 the CP elements 502 quickly reach an expanded state and compress the regions of the delivery layer that contain the drug/carrier
material 504. This expels all or a fraction of the drug/carrier material that was previously contained therein. The drug and potentially also the carrier material are forcefully expelled from the voids into the surrounding electrolyte 508 as a flux M1. The direction in which the drug/carrier material is expelled is determined by the local geometry of the delivery layer and the substrate.

Although not depicted in Fig. 15, the CP elements 502 can be repeatedly contracted and expanded to further release drug/carrier material from the voids. This process can be continued until a desired amount, perhaps all, of drug/carrier is released from the delivery layer. The expansion and contraction processes of the CP elements 502 are governed by an external power supply and an optional control unit (not shown) and as such, can be easily controlled as desired.

Figs. 16a and 16b show an alternative embodiment similar to Fig. 15 where a layer 530 is applied over a drug/carrier material 524. The barrier layer 530 possibly extends substantially over CP elements 522. The barrier layer 530 is preferably impermeable and prevents any water influx to the drug/carrier material during storage and transport to the treatment site. This prevents premature absorption of water from the surrounding electrolyte 528 that might induce swelling of the drug/carrier material 524 and cause premature release of the drug/carrier material. The barrier layer 530 might also prevent diffusion of drug molecules from drug/carrier material 524 into surroundings. Upon actuation through application of electrical potential, CP element 522 is brought to an expanded state in process E2. The barrier layer is forcefully displaced and/or released allowing the drug/carrier material to be expelled from the delivery layer 520 into the electrolyte 528. This release process M2 is indicated in Fig. 16b, wherein the released barrier layer 530 is shown after it is released from the delivery layer 520. The barrier layer 530 may also be fixed to the CP elements 522 or optional substrate 526 at least in one point and thus be only partially releasable. In this case the barrier layer 530 is displaced from the void by CP expansion and drug/carrier 524 is subsequently expelled.

In a similar embodiment schematically represented in Figs. 17a and 17b a barrier layer 550 may also completely cover the CP elements 542 and the drug/carrier elements 544 and possibly be attached to an optional substrate 546. In this case the barrier layer 550 is porous and also functions as a constraint layer. Electrically activating CP elements 542 by applying an electrical potential will expand the CP elements 542 as indicated by process E3. This compresses the drug/carrier element 544 and expels drug from delivery layer 540 into surrounding electrolyte 548. The resulting flux M3 is indicated in Fig. 17b.

The barrier layer 530, 550 is preferably biocompatible and/or biostable. It may be selected from a range of polymeric or inorganic materials. Suitable polymers include numerous examples that are known in the art such as polyolefins, polypropylenes, and polybutylenes and copolymers thereof;
ethylenic polymers such as polystyrene; ethylenic copolymers such as ethylene vinyl acetate (EVA); polyacetal; chloropolymers such as polyvinylchloride (PVC); fluoropolymers such as polytetrafluoroethylene (PTFE); polyesters such as polyethylene terephthalate (PET); polyethers; polyethers; polyamides such as nylon 6; polyamide ethers; polyesters; elastomers such as elastomeric polyurethanes and polyurethane copolymers; silicones; polycarbonates; polyacrylonitril; polyvinylidene chloride; parylene. Suitable inorganic materials for use within the barrier include, but are not limited to metals such as aluminum, chromium, gold, platinum, and alloys of metals, as well as inorganic compounds, such as inorganic suicides, oxides, nitrides, and carbides. Even though a biostable, non-biodegradable barrier may be a preferable embodiment of a barrier layer, some biodegradable materials may be used in the barrier layer.

Further structural re-enforcement of the delivery layer can be provided to enhance the expulsion of drug or drug/carrier. In Figs. 18a and 18b, constraint elements 570a-b are integrated into the delivery layer 560 and provide a substantially vertical rigid support against which the CP elements 562 can push during the actuation and expansion process E4. As a result, more of the volume expansion in the CP elements 562 is directed towards the drug/carrier material 564 and more substantial ejection of drug/carrier material is possible. This process is depicted in Fig. 18b. Therein, the expanded CP elements 562 have caused expulsion of a fraction of the drug/carrier material 564 as a flux M4 from the delivery layer 560 into surrounding electrolyte 568. The constraint elements 570a-b may be arranged in the form of ribs, ridges, columns, or other such structures. The constraint elements 570a-b may be comprised of metals, rigid polymers or inorganic materials. They may be added to the substrate 566 before CP element deposition process and thereby provide a means for patterning and spacing of the CP element(s). The constraint elements 570a-b may also serve dual functions as counter electrodes, and/or field shaping elements (for enhancement of secondary electroporation, electroporation, or electropermeabilization, or iontophoresis related to the delivery of drug). Moreover, the constraint elements may be outwardly protruding as indicated by the constraint element 570b and serve a function as a spacer element to prevent contact between the delivery layer and the delivery site. The inventors have found that such intimate contact between a drug delivery layer, as disclosed in several of the preceding embodiments for example, and delivery site will lead to limited activation of the CP and limited drug release. This is due to limited electrolyte access and release volume. Such spacers 570b will ensure that a sufficient electrolyte volume is available adjacent to the CP element 562 for the actuation and expansion process. Moreover, spacer elements 570a-b may be arranged so as to provide a confined volume in close proximity to the delivery site preventing unwanted wash-out and dilution of the released drug.

Separating elements (not shown) may be applied between the CP elements 502, 522, 542, 562 and the drug/carrier material 504, 524, 544, 564. Such separating elements prevent mixing or diffusion of chemical species.
between the CP elements and the drug/carrier material. Thus, the separating elements can prevent unwanted chemical reactions and/or mixing of the drug/carrier material and the CP elements. Suitable separating elements generally comprise a membrane of nonreactive polymer or a thin layer of metal or alloy. Examples of polymers include acrylonitrile polymers; halogenated polymers such as polytetrafluorethylene, polychlootrifluoroethylene, copolymer tetrafluoroethylene and hexafluoropropylene; polyimide; polysulfone; polycarbonate; polyethylene; polypropylene; polyvinylchloride-acrylic copolymer; polycarbonate-acrylonitrile-butadiene-styrene; polystyrene; polyether ether ketone (PEEK).

The release of the drug from the delivery device can also be facilitated by contraction of the CP elements. Fig. 19a and 19b show such an alternative embodiment of a delivery layer 580. A void filled with drug/carrier material 584 is surrounded by CP elements 582. By applying an appropriate potential a process 51 is initiated resulting in in-plane contraction of the CP elements 582. This process is shown in Fig. 19b and demonstrates the release of the drug/carrier material 584 from the void into the surrounding electrolyte 588 through as a flux M5. The releasable drug/carrier material 584 may be a portion of drug dispersed in a carrier such as a polymer or non-polymer material. The releasable element might also be a microcapsule, microparticle or granule containing the drug.

The above exemplified embodiments comprise at least one CP element, and at least a drug/carrier portion comprising a controllably releasable drug. Keeping true to the preceding descriptions, multiple CP elements and drug/carrier portions can be patterned in regions so as to further enhance the drug delivery process. Individual portions or regions can then be selectively activated to expel the therapeutic agent stored within that region of the layer. To this effect, a delivery layer comprising a plurality of drug/carrier material combinations and CP elements can, during delivery of drugs to the treatment site, release multiple drug/carrier combinations simultaneously or in sequence as desired.

Figs. 20a and 20b depict planar top views of two embodiments of a drug delivery device. The embodiments demonstrate examples of general patterning and integration possibilities of CP and drug/carrier into thin single layered coatings. For reasons of clarity, the previously indicated constraint, separating or barrier elements are not shown, but can be incorporated as previously described. Fig. 20a shows a planar top view of a part of a drug delivery device 600. A patterned layer of continuous drug/carrier region 604 is applied onto an optional substrate 606 with inter-dispersed CP regions 602. Another possibility is depicted in Fig. 20b which shows a planar top view of a part of a delivery device 620. A continuous CP layer 622 with at least one cavity is applied on a substrate 626. Drug/carrier regions 624 are inter-dispersed within the cavities of the CP layer 622. The drug/carrier elements 624 such as pictured in Fig. 20b may be provided with key dimensions (element thickness, width, length spacing etc.) in the microscale thus enabling
a large number of drug/carrier elements to be applied over a reasonably small area.

The tightly organized interconnection of drug/carrier regions 604, 624 and CP regions 602, 622 improve the efficacy of the drug delivery process. Such morphologies minimize the volume change of the CP required to release drug from the drug/carrier region(s). The effective integration of the CP and drug/carrier into a single layer also provides a means of further miniaturizing the delivery device and allow it to be precisely located in close proximity to the treatment site. It is also conceived that the drug/carrier regions 624 depicted in Fig. 20b may comprise different drug species, so as to more optimally deliver a range of drug species to the treatment site.

Such thin coatings as depicted in Figs. 20a and 20b featuring a large number of drug/carrier elements and CP elements can completely or partially cover the surface of a medical device. Thus, the aliquot of drug released during the delivery process can be provided uniformly over the area of the medical device and hence uniformly to the intended treatment site. This is a major improvement over the prior art which often features large and bulky devices with a single drug release outlet, often through an orifice and cannot provide uniform delivery of a drug over a wide treatment site.

Although not depicted in the Figs. 20a and 20b, in the above exemplified embodiments the drug/carrier material regions 604, 624 can be further patterned onto the substrate 606, 626 in a variety of shapes such as circular, elliptical, or rectangular columns, rows, zig-zags, hatching, concentric rings, and other geometric shapes.

The cavities between adjacent CP elements described in the above exemplified embodiments may be formed by selectively depositing CP elements on the substrate e.g. using photolithographic techniques or by depositing the CP elements over previously deposited drug/carrier regions. The cavities may also be formed through deposition of a continuous CP layer where CP material is then selectively removed to form cavities, e.g. using laser ablation or reactive ion etching techniques. Although not shown, the cavities need not protrude through the entire CP layer, but rather may penetrate through a fraction of the thickness as need be. In other words, the cavities may be provided as pits, indentations or pivots formed into the CP elements. Such cavities can be created using known microforming technologies such as laser ablation, micromolding, hydroforming, cutting, abrasion, etc.

Numerous materials that are suitable for the CP elements 502, 522, 542, 562, 582, 602, 622 as well as embodiments to follow include polypyrroles, polyanilines, polysulfones, polythiophenes, polyacetylenes, polyethylene dioxythiophenes, poly(p-phenylenes), poly(p-phenylene vinylene), polypyrrolines, polyquinolines, polyanthaquinones, poly(n-vinylcarbazole) and derivates or copolymers of these. A preferred conducting
polymer is polypyrrole due to its ease of manufacture, stability in aqueous solutions and biocompatibility and large volume change.

Conducting polymers may be doped with dopants that are known to generate large volume change and/or forces. For large in-plane volume change octylbenzene sulfonate is an example that would preferably used in the case of the embodiment described in Fig. 15-20, (other dopants may also be used to produce similar behavior). It is also possible to adapt other external parameters to make the CP elements generate a large volume change and force generation to improve drug delivery. Examples are supplying a suitable electrolyte containing ions and having a temperature that improve volume change and speed of volume change such as a lithium ion containing electrolyte of high concentration and increased temperature above room temperature. The control of such external parameters is disclosed in PCT application No PCT/SE2007/000813 that is hereby incorporated in its entirety.

The drug/carrier material 504, 524, 544, 564, 584, 604, 624 as well as in embodiments to follow may comprise a drug and a carrier. In some cases, it may also comprise only a drug. In the case of the drug/carrier material comprising a carrier, the carrier may be any material selected from of a large array of polymers and non-polymeric materials, that are known by those skilled in the art to be suitable for housing drugs (as described below). The carrier may also comprise excipients that are inactive substances used to complement the active drug. Examples of excipients are preservatives, lubricants, fillers, binders etc. The drug/carrier material should not release drug to any significant degree prior to CP actuation. Moreover, the carrier in the drug/carrier material may be a gel electrolyte that provides at least a portion of the ions needed to the CP elements during actuation.

Numerous carrier materials appropriate for the practice of the present invention exist in the art. Examples of materials are preferably polymer materials, such as polycarboxylic acids, including polyacrylic acid; cellulotic polymers, including cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ethers, carboxymethyl cellulose; gelatin; polyvinylpyrrolidone; cross-linked polyvinylpyrrolidone; polyanhydrides including maleic anhydride polymers; polyamides; polyesteramides (e.g. hyperbranched); polyvinyl alcohols; polyesters including polyethylene terephthalate; polyacrylamides; polyethers; polyether sulfone; polydioxanone; polyoxyesters; polyalkylene oxalates; polyphosphazenes; polyalkylenes including polypropylene, polyethylene; polyolefins such as polyisobutylene; polystyrenes; halogenated polyalkylenes including polytetrafluoroethylene; polyurethanes (including dispersions); polyorthoesters; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylimide halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers
with each other and olefins, such as ethylene-methyl methacrylate copolymers; polypeptides; polycaprolactam; alkyd resins; polycarbonates; polyoxymethylene; polyimides; polyethers; epoxy resins; polybutylmethacrylate; rayon; rayon-triacetate; silicones; siloxane polymers; polyactic acid; polyglycolic acid; polycaprolactone; poly(hydroxyvalerate); polyhydroxybutyrate valerate; fibrin; collagen and derivatives thereof; polysaccharides such as starches, dextrins, alginates and derivatives. Copolymers, such as ethylene-vinyl acetate copolymers; styrene-isobutylene copolymers; copolymers of polyactic acid and polyglycolic acid; copolymers of polylactic acid and polycaprolactone; polyethyleneoxide/poly(butylene terephthalate) copolymers; polyethylene glycol/polyethylene oxide copolymers; copolymers of poly(ethylene-co-vinyl acetate) and poly(butyl methacrylate), such as disclosed in U.S. Pat. No 7008667; polyolefin polymers; protein-based coatings and derivatives; amino-acid based coatings and hydrogel polymers, including natural hydrogels, such as fibrin, collagen, hyaluronic acid, proteoglycan, elastin, laminin, alginate and agarose, as well as synthetic hydrogels, such as polyHEMA and acrylate hydrogels; polymers bearing pendant zwitterionic, for example phosphorylcholine, groups such as disclosed in U.S Pat. No 6924338. Derivatives, copolymers and blends of the above are also contemplated.

Non-polymeric materials are also possible, for example hydroxyapatite based materials or nanoporous ceramics, made of aluminium oxide, titanium oxide or iridium oxide.

In the case the carrier is provided as a liquid, it can be a solvent or liquid dispersion medium comprising, for example, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof.

The volume change and force generation of the CP elements may also be employed in designs where the drug/carrier element is applied as a layer that is placed upon or in between a layer or layers of CP. A description of such an embodiment follows.

Figs. 21a and 21b show an embodiment of a delivery device 640 comprising a porous constraint layer 650. The delivery device 640 comprises a substrate 646 whereupon a CP layer 642 is arranged. A drug/carrier material 644 is arranged as a layer on top of the CP layer 642 and a porous constraint layer 650 is provided as an outer element around both the drug/carrier material 644 and CP layer 642. The porous constraint layer 650 acts as a mechanical constraint during actuation of the CP layer 642 from an unexpanded state to an expanded state during process E5 when an electrical potential is applied. During actuation of the CP layer 642 the CP expands, the drug/carrier material 644 is compressed between the CP layer 642 and the porous constraint layer 650. This releases the drug/carrier material 644 to be pushed through the porous constraint layer into the surrounding electrolyte 648 as a flux M6. The drug release is depicted in Fig. 5b. In this figure, the
released drug/carrier 652 is indicated after having passed through the porous constraint layer 650. In this case the CP material 642 is preferably PPy which may be doped with dopant ions that are known to generate large volume change and force generation in the out-of-plane direction; a preferred example of dopant is dodecylbenzene sulfonate.

The drug/carrier material need not be arranged as a substantially flat layer, as depicted in Fig. 21, but may also be applied so as to cover the sides of the CP layer i.e. forming substantially vertical layers over CP that are pushed and compressed against the substantially vertical sides of the constraint.

The porous constraint layer 650 may also function as a barrier to prevent premature water influx from the environment that might induce premature swelling and/or disintegration of drug/carrier material 644 and thus undesirable drug release from the delivery device 640. The barrier properties of the porous constraint layer might also prevent premature diffusion of drug species from the drug/carrier material, thus behaving as a semipermeable membrane. The porous constraint layer may also comprise a hydrophobic material that further prevents water influx or prevents drug from passing through into the surroundings until the drug/carrier material is placed under compression by the CP layer.

The porous constraint layer 650 may be selected from a group of materials including a range of polymeric or inorganic materials. Some examples are semipermeable membranes including cellulose nitrate, cellulose acetate, polyamides, polyimides, polytetrafluoroethylene, poly-(vinyl chloride) and polysulfone. The materials previously described under Fig. 16 for the barrier layer 530 may also be used as constraint layers 650. The appropriate material must be porous or made porous using any technique commonly known by those skilled in the art to make materials porous. Such non-limiting techniques include laser ablation, etching techniques, or the use of elutable particulate materials that give porosity. Examples of porous polymeric materials are disclosed in US. Pat. No 7291 165.

For some particular arrangements, a lumen wall or target tissue may also act as a constraint layer (or reinforce a constraint layer) upon which the CP presses and expels drug from drug/carrier layer. Figs. 22a and 22b show an embodiment of a delivery device 660 comprising a CP element 662 which can be actuated to an expanded state by application of a potential in process E6. A layer of drug/carrier material 664 is deposited onto the CP element 662. During the expansion process, drug/carrier material 664 is pushed into contact with a lumen wall 672, which may be, for example, the wall of a blood vessel. Hence the drug is expelled as a flux M7. The released drug and/or carrier material 674 is shown in Fig. 22b. The substrate 666 is optionally perforated with holes allowing passage of the surrounding electrolyte 668 through the substrate 666 to the CP element 662 during the actuation process. Without the holes it is possible that ion depletion can occur around
the CP element 662 due to limited access to the surrounding electrolyte 668, thereby slowing or inhibiting the delivery of the therapeutic agent. The delivery device 660 may also feature an optional constraint layer 670 such as is discussed in Fig. 21a and 21b but in this case, the constraint layer 670 may assist more with constraining the CP element 662 in-plane with the substrate 666 and thereby increase expansion of the CP element 662 towards the lumen wall 672.

Furthermore, in the case where the delivery device 660 is in or on the wall of a balloon, an internal pressure may be generated in the balloon to further assist in holding the delivery device 660 in close contact with the lumen wall 672, and therefore enhance the delivery of the therapeutic agent. By maintaining tight contact between the delivery device 660 and the lumen wall 672, minimum drug/carrier material will be released into the blood stream and washed away from the treatment site.

Some examples of lumens where the disclosure can be applied are lumens of the cardiovascular system such as the heart, arteries (e.g. coronary, femoral, aorta, ilial, carotid arteries), lumens of the genitourinary system (e.g. the urethra, bladder, ureters, vagina), the nasolacrimal duct, the eustachian tube, lumens of the respiratory tract (e.g. the trachea, bronchi), lumens of the gastrointestinal tract (such as the esophagus, gut, small intestines, colon), lumens of the lymphatic system, the major body cavities (peritoneal, pleural, pericardial), and so forth.

The CP elements and drug/carrier elements need not be structured in separate and distinct layers or regions but may also be constructed as integrated composites where the CP and therapeutic agent or CP, therapeutic agent, and carrier are substantially dispersed, integrated, or admixed with each other.

An example of one such embodiment is shown in Figs. 23a, 23b and 23c. Fig. 23a shows a host layer 681 into which a CP will be deposited. The host layer 681 comprises a drug/carrier material 684 and an optional substrate 686. The drug/carrier material 684 comprises a therapeutic agent and a carrier material as discussed previously. As depicted in Fig. 23b, through a deposition process ED1, CP 682 is deposited into the drug/carrier material 684 and penetrates into the host layer 681 substantially making mechanical and/or electrical contact with the substrate 686. The resulting structure is referred to as a composite structure 683. After being placed into a surrounding electrolyte 688, upon application of electrical potentials an expansion process EC1 is initiated. During the expansion process EC1, the CP portions 682 of the composite 683 expand, and apply large internal stresses on the drug/carrier material 684 portions of the composite structure 683. This in turn causes the expulsion and release of drug (and possibly carrier) from the drug/carrier material 684 portion of the drug delivery layer 680 into the surrounding electrolyte 688. Optionally the CP portions 684 can be repeatedly contracted and expanded during process EC1. This process,
be it a single incidence or cyclical, releases a flux M8, comprising released
drug 692, from drug delivery device 680 as shown in Fig. 23c. Optional
porous and substantially vertical channels 685 can be formed into the
drug/carrier material 684 of the host layer 681 so as to enhance the fraction of
the substrate 686 with which the CP 682 can make contact during the
deposition process ED1. Such channels 685 can also enhance the structural
integrity of the composite structure 683.

Furthermore, pores 687 with substantially vertical channels may also
be formed subsequently in the CP portions 682 of the composite structure
683 so as to increase the number and area fraction of passageways from
which drug and/or drug/carrier can be transported and released into the
surrounding electrolyte 688. Such channels are shaped into structures
suitable for releasing/transporting the drug through diffusion, migration etc.
from a drug/carrier layer through the CP layer and into the surroundings. The
channels 687 can include the following: an aperture, orifice, bore, hole, or
porous element, hollow fibers, capillary tubes, cracks, and the like through
which drug can be transported. These holes may be generated by a number
of methods such as laser ablation, drilling, bombardments with high energy
ion sources and addition of elements such as fibers and tubes into a layer or
a combination of these methods.

The carrier component of the drug/carrier material 684 used as a host
layer 681 could be made from a number of different materials that are able
to house drugs. Furthermore, it is preferable that the drug/carrier material 684
provide a suitable host for the subsequent deposition of CP inside its matrix.
Some non-limiting examples of suitable carrier materials for this embodiment
are polymers, hydrogels, polymer electrolytes, biodegradable polymers, and
ionic conducting polymer such as naflon or flemion into which the drug is
mixed/dispersed/dissolved.

Since CP deposition is often performed using electropolymerization in
a liquid solvent, the host material 684 should be substantially penetrable to
the solvents used during this process. Electropolymerization is often
performed in aqueous solvents and in this case the carrier is preferably
substantially hydrophilic and gel-like in nature to allow CP inclusion.
Examples of suitable hydrophilic monomers used for forming such polymers
include, but are not limited to; (meth)acrylic acid; (meth)acrylamide;
(meth)acrylonitrile; 2-hydroxyethyl (meth)acrylate and 2-hydroxypropyl
(meth)acrylate. Other hydrophilic polymers also include polyvinyl alcohol
polysaccharides and related cellulosic polymers; polyalkylene glycols and
oxides such as the polyethylene oxides; polymerized ethylenically
unsaturated carboxylic acids such as acrylic, methacrylic and maleic acids
and partial esters derived from these acids and polyhydric alcohols such as
the alkylene glycols; homopolymers and copolymers derived from acrylamide;
and homopolymers and copolymers of vinylpyrrolidone.
As an alternative to the previous example it is also possible to form a composite by first depositing a porous CP and subsequently applying the drug/carrier filling up voids/enclosures in CP. This embodiment will now be described in more detail while referring to Figs. 24a, 24b and 24c.

A porous CP host polymer 702 is shown in Fig. 24a as deposited onto an optional substrate 706. Collectively this structure is referred to as a host layer 701. It is also possible to retain the capability of the embodiment without the substrate 706 being present, but in general, the substrate helps in directing the flow of drug during the release process. A drug/carrier material 704 is deposited into the pores 703 by a drug loading process DL2. The resulting composite structure 700 is shown in Fig. 24b. After being placed in a suitable electrolyte 708 and being transported to a treatment site, the CP host polymer 702 is actuated. This actuation process is indicated by process EC2. This process begins with the application or change of an applied electrical potential. This results in deformation of the CP host polymer 702 which in turn causes the drug loaded pores 704 to experience a combination of compressive, shear and tensile loading which expels the drug and/or carrier. Further drug and possible carrier release can be achieved with subsequent actuation cycles of the CP host polymer 702. During the actuation process EC2, the pores 704 can undergo a combination of expansion and contraction. Fig. 24c demonstrates the result of such an expansion/contraction process. As shown, some regions of the CP host polymer 702 cause expansion of local drug loaded pores 707 while other regions of the CP host polymer 702 cause contraction of local drug loaded pores 705. The result of this process is a flux M9 of released drug 710 into the surrounding electrolyte 708. The optimization of the porous structure of the CP host polymer 702 may further improve the drug release process.

The drug loading process DL2 can be achieved by a number of methods. One method is to soak or dip the host layer 701 in a solution of the drug/carrier possibly dissolved in a solvent. This process might be step-wise divided by first dipping in drug solution and then dipping in a solution of carrier solution, possibly with drying steps in-between. Alternative methods for the drug loading process DL2 include spraying (e.g. ultrasonic, thermal jetting), painting (air brush), syringe application, printing, or molding, among others, to apply a solution based drug/carrier into the host layer 701. Such application processes can proceed under the assistance of vacuum, pressure or temperature so as to expedite absorption. During the drug loading process, the drug/carrier is absorbed or pushed into the CP layer where it remains with minimal leakage until use. It is possible to follow-up the drug loading process with a complimentary process such as drying, etc in order to further alter or improve the properties of the drug/carrier material.

Porous CP can be fabricated by a variety of methods known to those skilled in the art. One approach, applicable to polypyrrole (PPy) based CP, is to use suitable dopant ions during the electropolymerization of the PPy (see e.g. Hara, 2004, Gel-like Polypyrrole Based Artificial Muscles with Extremely
Large Strain, Polymer Journal, Vol. 36, Issue 11, pp. 933—936). The porous CP might also be fabricated as a composite e.g. a hybrid material with CP deposited into a porous host material such as meso-porous carbon (see e.g. Fuertes, 2007, Encapsulation of Polypyrrole Chains Inside the Framework of an Ordered Mesoporous Carbon, Macromolecular Rapid Communications, Volume 26, Issue 13, p 1055-1059) or porous membranes such as alumina or nylon (see e.g. Seung Lee, 2000, Chemical synthesis and characterization of polypyrrole coated on porous membranes and its electrochemical stability, Synthetic Metals, Volume 113, Issue 1, p 115-119). Another approach for achieving a porous CP is to use a sacrificial template that is removed e.g. a collection of microsized polymer particle such as polystyrene that can be dissolved (see e.g. Yang, 2004, Microporous conducting polymers on neural microelectrode arrays 1 Electrochemical deposition, Sensors and Actuators B, Volume 101, Issue 1-2, p 133-142).

Other composite or multilayer designs are also possible. One embodiment is exemplified in Figs. 25a and 25b. Fig. 25a shows an arrangement of at least one CP layer 722 and drug/carrier layers 724a-b comprising drug 730 that are deposited in an alternating sequence to form a multilayered composite drug delivery layer 720. These layers can be free standing or combined with an optional substrate 726 as shown in Fig. 25a. Upon actuation through a process EC3 where an electrical potential is applied, the CP layer 722, expands or contracts which applies large internal stresses to the drug/carrier layers 724a-b. The result of this expansion process is shown in Fig. 25b. As the drug/carrier layers 724a-b are internally stressed during the CP expansion or contraction process, subsequently undergo volume changes and hence expel released drug 732 into the surrounding electrolyte 728 as a flux M10.

An alternative to this embodiment is shown in Figs. 26a and 26b. In addition to the features described in Fig. 25a and 25b, constraint layer(s) 752 may be optionally integrated into the multilayered composite structure 740 comprising at least one CP layer 742 and drug/carrier layers 744a-b comprising drug 750, and a substrate 746. Actuation of the at least one CP layer 742 is initiated and controlled via an electrochemical process EC4 by application and/or changing of an applied electrical potential. The electrochemical process EC4 results in the drug/carrier layers 744a-b being internally stressed as well as biased towards the constraint 752. This results in the expulsion of a flux M11 of released drug 754 into the surrounding electrolyte 748. The constraint layer(s) 752 may also be formed by the lumen wall or the tissue against which the device is situated.

It is possible that one drug/carrier layer 722a, 742a be provided as one therapeutic agent and carrier material, while the second drug/carrier layer 722b, 742b be provided as a second therapeutic agent and carrier material. In this case, the different therapeutic agents may be provided in different quantities and/or concentrations so as to alter their basic release profiles during the release process. In addition, the different therapeutic agents may
be provided in different layers of the delivery device 720, 740 such that each therapeutic agent is released in a substantially different direction from the other. In one case, the substrate 726, 746 is provided as a porous material such that upon activation of the CP layers 722, 742 the drug in drug/carrier layer 722b, 742b is released in a direction substantially away from the substrate 726, 746 while drug contained within the drug/carrier layer 722a, 742a is directed substantially through the substrate 726, 746. Thus it is possible for the delivery device 720, 740 to release therapeutic agents 732, 754 in a bidirectional manner e.g. both towards the lumen wall and the lumen interior (e.g. in a blood vessel).

It has been found that CP can be suitably combined with electrolysis to further enhance the drug delivery process. In this case, the CP provides a unique controllable permeable membrane for entraining reactive species (water molecules), a built-in enclosure for the produced gases, a host structure for carrying a therapeutic agent, and a means of combining mechanical actuation exhibited during redox cycling with gas formation based actuation. These contributions allow for the fabrication of simple, flexible, and thin drug delivery systems with minimal gas production requirements, gas bubble containment and enhanced delivery efficacy over the prior art. Various embodiments of this approach are described in Figs. 27, 28, and 29.

Figs. 27a and 27b show a substrate 766 with an optional electrode 772 covered with a CP layer 762. A drug/carrier layer 764 is deposited onto the CP layer 762. A porous constraint layer 770 is applied over the other layers to form a delivery device 760. The delivery device 760 is placed within a surrounding electrolyte 768 near a treatment site. Upon actuation of the CP layer 762 with sufficiently high electric potential, gas will form at the interface between the CP layer 762 and the substrate 766 or the optional electrode 772. This results in the creation of a gas bubble 774 under the CP layer 762. The result of this process G1 is shown in Fig. 27b. The gas is prevented from escaping through the CP layer 762 and can be further prevented from escaping through to the surroundings if the constraint layer 770 is provided as a non-gas permeable membrane. The gas bubble 774 will generate significant stresses within the drug/carrier layer 764 as it is biased against the constraint layer 770. Thus a flux M12 of drug will be forced from the drug/carrier 764 and released drug/carrier 776 will be delivered into the surrounding electrolyte 768.

Another embodiment is shown in Figs. 28a and 28b. Fig. 28a shows a delivery device 780 comprising a relatively porous CP element 782 that is deposited on a substrate 786 with an optional electrode 790 and preferably anchored to the substrate using a glue 792a-b. The glue is applied to the edges of the CP element 782 and prevents complete separation between the substrate 786 and the CP element 786 during actuation. The glue 792a-b further provides a mechanical constraint to the edges of the CP element 782. In another case, the glue 792a-b further electrically isolates sections of the substrate outside the vicinity of the CP element 782 from the surrounding
electrolyte 788. In some cases, an optional electrode 790 is patterned between the substrate 786 and the CP element 782. A drug or drug/carrier 784 is deposited into the CP layer 782 forming a composite. When the CP element 782 is actuated using a gas-generating potential (process G2), a gas bubble 794 forms and displaces the CP element 782 significantly. The result of this process M13 is shown in Fig. 28b. Thus significant stresses are generated in the CP layer 784. These stresses force drug 796 from CP/drug/carrier composite into the surrounding electrolyte 788.

Figs. 29a and 29b depict yet another alternative embodiment of a drug delivery device. Fig. 29a depicts a delivery device 800 comprising a substrate 806 onto which are patterned a series of electrodes 810a-b. The electrodes 810 may comprise a variety of electrode features 812 a-g. The morphology and placement location of the electrode features 812 a-g may be selected so as to provide preferable gas formation sites during the drug delivery process. A CP layer 802, potentially comprising both relatively porous regions and non-porous regions, is deposited onto the substrate 806 and electrodes 810a-b. The CP layer 802 is subsequently loaded with a drug/carrier 804. Upon insertion into a surrounding electrolyte 808 and placed near a treatment site, the CP layer 802 is actuated using a sufficiently high electric potential so as to produce gas. The results of this process G3 are depicted in Fig. 29b. A series of gas bubbles 814a-h are formed at the interfaces between the electrodes 810 and the CP layer 802. Preferential gas formation occurs near the electrode features 812 a-g and as such a series of local gas bubbles 814a-h are formed. Large heterogeneous stresses are generated within the CP layer 802 due to the formation of the gas bubbles 814a-h. This causes drug 816 and or drug/carrier to be released from the CP layer 802 and into the surrounding electrolyte 808 as a flux M14. The electrode features 812 a-g allow for the development of large heterogeneous stresses in the CP layer 802 with a minimum volume of gas bubbles, thereby improving the overall efficacy of the drug delivery process.

Thus far, the embodiments described have been configured to release therapeutic agent in a direction substantially away from the substrate as depicted in Figs. 15-29. Alternatively, the substrate may be perforated and thus provide a membrane through which a therapeutic agent can be delivered to a treatment site. Such embodiments can provide a means of separating the CP and therapeutic agent from the intended treatment site even when the delivery device is forcefully pushed into contact with the treatment site. Separation can be maintained until such time that the delivery of the therapeutic agent is desired.

Figs. 30a and 30b show a delivery device 820 comprising a substrate 826. Onto the substrate 826 is deposited a CP layer 822 with at least one cavity 830 that is filled with a drug/carrier material 824. Upon insertion into a surrounding electrolyte 828, the CP layer 822 can be actuated either via expansion, contraction or a sequence thereof. Upon actuation of the CP layer 822 by application of a suitable electric potential during a process C2, a
fraction of the drug/carrier material 824 is expelled from the cavity, through the pore(s) 831 in the substrate 826 and towards the treatment site. The result of this expulsion process M15 is shown in Fig. 30b. Further actuation cycles can be used to expel more drug/carrier material 824 from the delivery device 820.

In another embodiment volume change of CP is used to rupture or expel capsules containing therapeutic agents. An example is exhibited in Figs. 31a, 31b, and 31c. Fig. 31a shows a delivery device 840 comprising a substrate 846 and a composite of CP 842 and drug containing capsules 844. The actuation process EC5 of the CP 842 is initiated and controlled by the application and/or change of suitable electric potentials to the delivery device 840. This causes a fraction of the capsules 844 to break and take on the form of ruptured capsules 845. The result of this process is shown in Fig. 31b. Upon further actuation cycles the CP can repeatedly expand and contract. This causes the formation of more ruptured capsules 845. After a capsule 844 is ruptured, the drug is released into the CP 842 and the surrounding electrolyte 848 as released drug 850. This might occur through natural diffusion process NP1 and the result is shown in Fig. 31c where a flux M16 of released drug 850 is generated from the delivery device 840. It is also possible that unruptured capsules are expelled from CP element 842 into the surrounding electrolyte 848 where they eventually are degraded and ruptured based on the selected capsule material characteristics in relation to desired release rate.

The CP 842 is preferably electopolymerized around the drug containing capsules 844. The capsules will then be intimately linked with the CP 842. Such intimate contact will help maximize the fraction of capsules 844 that can be broken on each actuation cycle. Microcapsules are readily formed by a number of methods, including coacervation, interfacial polymerization, solvent evaporation, and physical encapsulation methods. Specific procedures for encapsulation of drugs are disclosed in U. S. Patent Application No. 20010033868.

Microcapsules typically refer to a reservoir of drug surrounded by a polymer shell. The capsules are preferably made from a material so that they are easily broken during actuation of the surrounding CP 842. Examples of capsule materials are polymeric or non-polymeric materials. The encapsulation of therapeutic agent into polymers may be achieved by various polymerization techniques known in the art, e.g. dispersion-, suspension- or emulsion-polymerization. Examples of encapsulating polymers are described in WO/2006/082221. Other examples of polymeric materials include, but are not limited to acrylic polymers such as polymethylmethacrylate (PMMA) or other latex-forming polymers, PVA, PLLA, copolymers of styrene and isobutylene, polyorthoesters, and polyanhydrid, semi-synthetic polyacryl starch, polyalkylcyanoacrylate, polymethylacrylate, monocarboxy cellulose. Examples of non-polymeric materials include cholesterol, glyceryl
monostearate, glycerol tristearate, stearic acid, stearic anhydride, glyceryl monooleate, glyceryl monolinoleate, and acetylated monoglycerides. The capsule may also be a liposome, colloid, aggregate, flocculate or microparticle which typically refers to a monolithic system where the therapeutic agent is dispersed throughout the particle or other such structure known in the art for encapsulation of drugs.

Another embodiment of a delivery device is shown in Figs 32a and 32b. Fig. 32a shows a delivery device 860 comprising a substrate 866 onto which are deposited a CP layer 862 and an outer layer of drug or drug/carrier material 864. The CP layer 862 is electrically connected to an external power supply and an optional control unit so that it can be controllably activated. The delivery device 860 is so arranged such that when the CP layer 862 is activated by the application of suitable electric potentials in process EC6, it undergoes expansion and/or contraction. This deformation creates large stresses within the layer of drug/carrier material 864. Such stresses cause fracture and delamination of the drug/carrier material 864 from the delivery device. Thus, the drug is released into the surrounding electrolyte 868 as released drug and or drug/carrier parts 870 depicted as a flux M17, which is shown in Fig. 32b. It is preferable that the drug/carrier material 864 be comprised of suitably brittle materials so as to enhance fracture when stressed by the CP expansion or contraction. Drug/carrier 864 might comprise substantially only drug in crystalline state that has been welded or dried to make a layer that does not readily dissolve in electrolyte 868. The carrier can also be a brittle polymer that for example can be produces a composite or blended material, where stiff polymers includes poly(lactic acid), poly(glycolide) and poly(lactide-co-glycolide), for example. Preferred materials for the matrix polymer are poly(lactic acid-co-glycolic acid) (95/5 and 85/15), which are usually stiff and brittle such as disclosed in US. Appl. No 20070202046.

Figs. 33a and 33b describe yet another embodiment of a delivery device. Fig. 33a shows a delivery device 880 that comprises a substrate 886 onto which a CP element 882 is deposited. A drug/carrier material 884 is deposited onto the CP element 882. Finally, a sealing layer 890 is deposited onto the drug/carrier material 884. The CP element 882 is electrically connected to an external power supply and an optional control unit (not shown) such that it can be controllably activated during the delivery process. The sealing layer 890 is provided so as to prevent uptake of water from the surrounding electrolyte 888 prior to activation of the CP element 882. Therefore, prior to the activation of the CP element 882 the delivery device 890 can be transported to the treatment site without releasing any significant levels of therapeutic agent. Upon activation of the CP element 892, by application of a suitable electric potential during process EC7, the sealing layer 890 is fractured due to stresses in the sealing layer 890 generated by the volume changes in CP element 882. The delivery device 890 in this activated state is shown in Fig. 33b. After the sealing layer 890 is fractured, water from the surrounding electrolyte 888 can enter into the delivery device.
and cause a degradation, decomposition, disintegration and/or dissolution reaction with the drug/carrier material 884. It is preferable that the drug/carrier material 884 is a hydroactivated or water soluble material as discussed previously. The drug 894 is then mobilized in the solvent that reaches the drug/carrier layer 884 and passes freely through the fractured sealing layer 890 and is released from the delivery device 880 as a flux M18.

Suitable materials for the sealing layer include thin layers of organic or inorganic materials such as pure metals (including aluminum, chromium, gold, hafnium, iridium, niobium, palladium, platinum, tantalum, titanium, tungsten, zirconium) and alloys of these metals or inorganic compounds, such as inorganic suicides, oxides (e.g. lindium tin oxide(ITO), nitrides, and carbides. The layers can be deposited by various methods such as sputtering or evaporation and typically have a thickness ranging from about 50 angstroms to about 20,000 angstroms. Preferred thicknesses are lower than 5000 A, preferably lower than 2000 A or even more preferably lower than 1000A. It is also possible to use polymers that can crack such as polyhydroxybutyrate.

In the case that the substrate described in the previous embodiments is not a medical device as previously mentioned, it may be formed from a range of suitable materials. In the case that the substrate is a medical device, it may optionally include a thin top coating of a suitable material to enhance adhesion between the other constituents of the delivery device and the substrate. The substrate material or thin top coat may be selected from the non-limiting groups of metals, ceramics and polymers. Examples of suitable metals and alloys include stainless steel, gold, silver, platinum, platinum alloy, and other alloys such as a wrought Cobalt-Chromium-Nickel-Molybdenum-Iron alloy. Other possible substrate materials include a wide range of synthetic polymeric and natural polymers used in medical devices such as a polyamide, polycarbonate, polyether, polyester, polyolefin, polyethylene, polypropylene, polystyrene, polyurethane, polyvinylchloride, polyvinylpyrrolidone, silicone elastomers, fluoropolymers, polycrylates, polyisoprenes, polytetrafluoroethylenes, rubber, or cellulose. In the case the substrates are not sufficiently conductive, various conductive materials may be applied on top (e.g. as coatings) to contact the CP elements. Examples of conductive materials are inks with conductive fillers (e.g. silver), conductive polymers (e.g. Baytron), or electroplated, sputtered or evaporated metal-containing coatings (e.g. gold).

When applied as a coating on a medical device in accordance with the present invention, the film thickness of the drug delivery layer is typically on the order of from about 1 to about 500 microns thick. The thickness is preferably about 1 to 50 microns thick, and more preferably about 2 to 20 microns. Very thin polymer coatings, e.g., of about 0.2-1 microns and much thicker coatings, e.g. more than 500 microns, are also possible.
Exemplary classes of therapeutic agents that can be released include antiproliferatives, anti-thrombotic agents, immunosuppressants, anti-restenosis agents, antilipid agents, anti-inflammatory agents, antineoplastics including antimetabolites, antiplatelets, angiogenic agents, anti-angiogenic agents, vitamins, Antibiotics, antimicrobials, metalloproteinase inhibitors, NO donors, nitric oxide release stimulators, anti-sclerosing agents, vasoactive agents, endothelial growth factors, beta blockers, AZ blockers, hormones, statins, insulin growth factors, antioxidants, membrane stabilizing agents, calcium antagonists (i.e. calcium channel antagonists), retinoids, anti-macrophage substances, antilymphocytes, cyclooxygenase inhibitors, immunomodulatory agents, angiotensin converting enzyme (ACE) inhibitors, anti-leukocytes, high-density lipoproteins (HDL) and derivatives, cell sensitizers to insulin, prostaglandins and derivatives, anti-TNF compounds, hypertension drugs, protein kinases, antisense oligonucleotides, cardio protectants, petidose inhibitors (increase blycotic metabolism), endothelin receptor agonists, interleukin-6 antagonists, anti-restenotics, vasodilators, fibrinolytic agents, PPAR gamma agonists, cardiac glycosides, Antiarrrhythmics, cardiac stimulants, bisphosphonates, Bone morphogenic proteins, imaging agents, radiotherapeutic agents, nervous system stimulants, and other miscellaneous compounds.

Some specific non-limiting examples of beneficial therapeutic agents within different therapeutic classes now follow.

Immunosuppressants include, without limitation, cyclosporine, rapamycin, tacrolimus (FK-506), everolimus, zotarolimus, pimecrolimus, etoposide, mycophenolic acid, leflunomide. Anti-thrombotic agents include, without limitation, heparin, ticlopidine, eptifibatide, coumarines, plasminogen, .alpha..sub.2-antiplasmin, streptokinase, urokinase, bivalirudin, tissue plasminogen activator (t-PA), hirudins, hirulogs, argatroban, hydroxychloroquin, pyridinolcarbamate, Angiomax, PMask (dextrophenylalanine proline arginine chloromethylketone) and dipridamole. Anti-proliferative agents include, without limitation, immunosuppressants (see above), anti-neoplastic agents (see below), enoxaparin, angiopeptin, amlodipine and doxazosin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation. Anti-inflammatory agents include, without limitation, adrenocortical steroids (such as Beclometasone, Betamethasone, Budesonide, Ciclesonide, Cloprednol, Cortisone, Desonide, Desoximetasone, Desoxycortone, Dexamethasone, Diflorasone, Flumetasone, Flunisolide, Fluorometholone, Formocortial, Hydrocortisone butyrate, Meprednisode, Methylprednisolone, 60 delta.alpha.-methylprednisolone, Prednicarbate, Prednisone, Prednisolone, Prednylidene) or non-steroidal agents (such as salicylic acid derivatives (e.g. Aspirin, Salicylic salicylate, sulfasalazine), para-aminophenol derivatives (acetaminophen, indole), heteroaroyl acetic acids (e.g. Diclofenac, Aceclofenac, Nabumetone), arypropionics acids (e.g. Ibuprofen), anthranilic acids (e.g. meclofenamic acid), enolic acids (e.g. piroxicam, tenoxicam).

Antilipid agents include, without limitation, HMG CoA reductase inhibitors, nicotinic acid, probucol, and fibric acid derivatives (e.g. clofibrate, gemfibrozil,
gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate). Antineoplastics include, without limitation, nitrogen mustards (e.g. mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil), methyl nitrosoureas (e.g. streptozocin), 2-chloroethyl nitrosoureas (e.g. carmustine, lomustine, and chlorozotocin), alkanesulfonic acids (e.g. busulfan), ethylenimines and methylmelamines (e.g. triethylenemelamine, thiopeta and altretamine), triazines (e.g. dacarbazine), folic acid analogs (e.g. methotrexate), pyrimidine analogs (e.g. 5-fluorouracil, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, cytosine arabinoside, 5-azacytidine), purine analogs (e.g. mercaptopurine, thioguanine, azathioprine, adenosine, pentostatin, cladribine, and erythrohydroxynonyladenine), antimitotic drugs (e.g. vinblastine, vincristine, vindesine, vinorelbine, paclitaxel, docetaxel, epipodophyllotoxins, dactinomycin, daunorubicin, doxorubicin, idarubicin, epirubicin, mitoxantrone, bleomycins, plicamycin and mitomycin), phenoxodiol, etoposide, and platinum coordination complexes (e.g. cisplatin and carboplatin). Antiplatelet agents include, without limitation, insulin, dipyridamole, tirofiban, abciximab, and ticlopidine. Angiogenic agents include, without limitation, phospholipids, ceramides, cerebrosides, neutral lipids, triglycerides, diglycerides, monoglycerides, lecithin, sphingosides, angiotensin fragments, nicotine, pyruvate thiolesters, glycerolpyruvate esters, dihdyroacetone-pyruvate esters and monobutyrin. Anti-angiogenic agents include, without limitation, endostatin, angiostatin, fumagillin and ovalicin. Metalloprotease inhibitors include, without limitation, TIMP-1, TIMP-2, TIMP-3, batimastat and marimastat. NO donors include, without limitation, L-arginine, amyl nitrite, glyceryl trinitrate, sodium nitroprusside, molsidomine, diazeniumdiolates, S-nitrosothiols, and mesoionic oxatriazole derivatives. Anti-sclerosing agents include, without limitation, collagenases and halofuginone. Vasoactive agents include, without limitation, nitric oxide, adenosine, nitroglycerine, sodium nitroprusside, hydralazine, phenolamine, methoxamine, metaraminol, ephedrine, trapadil, dipyridamole, vasoactive intestinal polypeptides (VIP), arginine, and vasopressin. Endothelial growth factors include, without limitation, VEGF (Vascular Endothelial Growth Factor) including VEGF-121 and VEG-165, FGF (Fibroblast Growth Factor) including FGF-1 and FGF-2, HGF (Hepatocyte Growth Factor), and Ang1 (Angiopoietin 1). Prostaglandins include, without limitation, Alprostadil, Dinoprostone, Prostacyclin (I2) or Prostaglandin analogues (e.g. Beraprost, Bimatoprost, Illoprost, Latanoprost, Misoprostol, Trasoprost, Treprostinil). Bisphosphonates include, without limitation, zoledronate, pamidronate, risedronate, ibandronate, minodronate, alendronate, tiludronate, incadronate, olpadronate, neridronate, clodronate, etidronate, tiludronate). Bone morphogenic proteins include, without limitation, Dibotermim alfa, Eptotermim alfa and other drugs affecting bone structure and mineralization (e.g. Ipriflavone, Aluminium chlorohydrate, Strontium ranelate). Hormones include, without limitation, progester, insulin, the estrogens and estradiols (e.g. estradiol, estradiol valerate, estradiol cypionate, ethinyl estradiol, mestranol, quinestrol, estrone, estrone sulfate, and equilin). Statins include, without limitation, mevastatin, lovastatin, simvastatin, pravastatin, atorvastatin, and fluvastatin. Insulin growth factors include, without limitation,
IGF-1 and IGF-2. Antioxidants include, without limitation, vitamin A, carotenoids and vitamin E. Membrane stabilizing agents include, without limitation, certain beta blockers such as propranolol, acebutolol, labetalol, oxprenolol, pindolol and alpenolol. Calcium antagonists include, without limitation, amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine and verapamil. Retinoids include, without limitation, all-trans-retinol, all-trans-14-hydroxyretroretinol, all-trans-retinaldehyde, all-trans-retinoic acid, all-trans-3,4-didehydroretinoic acid, 9-cis-retinoic acid, 11-cis-retinal, 13-cis-retinal, and 13-cis-retinoic acid. Anti-macrophage substances include, without limitation, NO donors. Anti-leukocytes include, without limitation, 2-CdA, IL-1 inhibitors, anti-CD 116/CD18 monoclonal antibodies, monoclonal antibodies to VCAM, monoclonal antibodies to ICAM, and zinc protoporphyrin. Cyclooxygenase inhibitors include, without limitation, Cox-1 inhibitors and Cox-2 inhibitors. Immumomodulatory agents include, without limitation, immunosuppressants (see above) and immunostimulants (e.g. levamisole, isoprinosine, Interferon alpha, and Interleukin-2). ACE inhibitors include, without limitation, benazepril, captopril, cilazapril, enalapril, fosinopril sodium, lisinopril, quinapril, ramipril, spirapril, and 2B3 ACE inhibitors. Cell sensitizers to insulin include, without limitation, glitazones, PPAR agonists and metformin. Cardio protectants include, without limitation, VIP, pituitary adenylate cyclase-activating peptide (PACAP), apoA-I Milano, amlodipine, nicorandil, cilostaxone, and thienopyridine. Anti-restenotics include, without limitation, vincristine, vinblastine, actinomycin, epothilone, paclitaxel, paclitaxel derivatives (e.g. docetaxel), rapamycin, rapamycin derivatives, everolimus, tacrolimus, ZoMaxx, and Pimecrolimus. PPAR gamma agonists include, without limitation, farglitazar, rosiglitazone, muraglitazone, pioglitazone, troglitazone, and balaglitazone. Antiobiotics include, without limitation, cromolyn, Aminoglycosides (e.g. Gentamicin, Streptomycin), ansamycines (e.g. Geldanamycin, Herbinycin), Carbacephem (e.g. Loracarbef), Carbapenems (e.g. Ertaopenem, Meropenem), Cephalosporins (e.g. Cefadroxil, Ceftibuten, Cefepim), Glycopeptides (e.g. Teicoplanin, Vancomycin), Macrolides (e.g. Azithromycin, Erythromycin, Roxithromycin, Troleandomycin), Aztreonam Penicillins (e.g. Amoxicillin, Ampicillin, Flucloxacillin, Piperacillin, Ticarcillin), Polypeptides (e.g. Bacitracin, Colistin, Polymyxin B), Quinolones (e.g. ciprofloxacin, Levofloxacin, Norfloxacin), Sulfonamides (e.g. Mafenide.Sulfamethizole, Sulfanamide, Sulfasalazine, Sulfisoxazole, Tetracyclines (e.g. Demeclocycline, Doxycycline, Tetracycline). Neuromodulators or stimulant, include without limitation, neurotransmitters, such as dopamine, D-aspartic acid, Tryptophane, GABA, Acetylcholine, norepinephrine. Vasodilators, include without limitation, Papaverine, Adrenaline, Prostacycline, Theobromine, Forskoline.

In a preferred embodiment, the therapeutic agent is an antineoplastic such as paclitaxel or its analogs or derivatives. In another preferred embodiment, the therapeutic agent is an anti-inflammatory compound including a dexamethasone or prednisolone compound. In yet another preferred embodiment, the therapeutic agent is an immunosuppressive
compound including sirolimus, tacrolimus, pimecrolimus and everolimus or its analogs or derivatives.

The devices and systems described herein functioning as substrates for CP may be medical devices and systems. Examples include one or more of (or portion thereof) catheters (urinary catheters, in-dwelling catheters, aspiration catheters, injection catheters, infusion catheters, drainage catheters, venous catheters, arterial catheters, central line and peripheral line catheters, balloon catheters), guide wires, electrodes, coated or uncoated stents (including coronary vascular stents, peripheral vascular stents, cerebral, urethral, ureteral, biliary, tracheal, gastrointestinal and esophageal stents), vascular grafts, stent grafts, aneurysm fillers (including Guglielmi detachable coils), devices for rotational atherectomy or thrombectomy, temporary occlusion devices, embolic protection devices, filters (for example, vena cava filters), baskets and snares e.g. for retrieval, cardiac pacemaker leads or lead tips, leads or parts of implanted devices (for example in spinal stimulation, peripheral nerve stimulation, deep brain stimulation or neuromonitoring), vascular patches, electroporation devices, iontophoresis devices, in-dwelling access ports, devices for cardiac mapping or ablation, introducers, sheaths, intraluminal paving systems, heart valves, annuloplasty rings and bands, sewing rings and cuffs, cannulas, trocars, endoscopes, probes, laparoscopes, sutures, staples, myringotomy tubes, wound or nasal packings, dressings, gauze, bone screws, halo screws, total joints, hernia meshes, needles, wound drains, contact lenses, peristaltic pump chambers, arteriovenous shunts, gastroenteric feed tubes, endotracheal tubes, anastomosis devices, vertebral disks, bone pins, suture anchors, hemostatic barriers, clamps, screws, plates, clips, shunts, tissue adhesives and sealants, tissue scaffolds, various types of dressings, extravascular wraps and bone substitutes, joint prosthesis or part thereof, such as a hip prosthesis, a knee prosthesis, a vertebral or spinal disc prosthesis, a spinal cage as well as many other devices that are implanted or inserted into the body and from which therapeutic agent is released.

Medical devices where the invention may be applied can be implanted or not implanted (e.g. utilized during surgical procedures and subsequently removed). Medical devices of the present invention can be used for treatment in body lumina and any tissue or organ, for example, the following: tumors; organs including the heart, coronary and peripheral vascular system, esophagus, trachea, the urogenital system, including kidneys, bladder, urethra, ureters, prostate, vagina, uterus and ovaries, eyes, lungs, trachea, esophagus, intestines, stomach, brain, liver and pancreas, skeletal muscle, smooth muscle, breast, dermal tissue, and cartilage, gastrointestinal tract such as the esophagus, gut, duodenum, small intestine, large intestine, colon, biliary and pancreatic duct systems, lumens of the lymphatic system, the major body cavities (peritoneal, pleural, pericardial), and so forth.
It generally understood that a power supply for the invention can take a wide variety of forms including electrochemical cells, mains power, switching power supplies, linear power supplies, and that it may be either stationary or mobile depending on the particular application needs of the delivery device. In the case that the power supply is provided with a mobile power source, such a power source may include chemical battery cells, super- or ultra-capacitors, fuel cells, a button cell, a coin cell, an alkaline cell, a lithium cell, a lithium ion cell, a zinc air cell, a nickel metal hydride cell, a printed battery, energy cell laminate, thin-film battery, power paper, and the like, or combinations thereof. Moreover, the power required to actuate the CP in the medical device can be provided, consistent with Faraday's law, by a current induced in a coil associated with the device by a change in magnetic flux in the area of the device. Hence activation of a CP drug delivery device may be achieved using an external control.

The optional control unit may provide a means of controlling the applied electric potential, current or charge to at least one CP element of the delivery device. It is also understood that such a control unit may provide means of precisely measuring current, charge, and/or electric potential applied to at least one CP element, or may provide further sensory means so as to measure the concentration of ionic species, drug species, the thickness or volume change of an CP element, etc. in order to provide feedback based control of the delivery process. Additional sensory functionality such as sensing of local temperature, pH, or pressure may also be provided by the control unit to further enhance the delivery process.

It is also understood that the power supply and optional control unit provides suitable electrical connections to a counter electrode, thereby completing the electrical circuit needed to operate at least one CP element in the delivery device. It is also understood that more than one CP element can be controlled from a single control unit by means of switch networks, multiplexed networks or by switched pulse width modulation approaches known in the art.

The skilled person will appreciate which of the embodiments mentioned above fall within the following embodiments.

According to one embodiment, many of the above mentioned drug delivery devices may consist of or consist essentially of one or more conducting polymer elements, one or more substance incorporating elements and a substrate.

In another embodiment, many of the previously described drug delivery devices may comprise a layer that consists essentially of at least one conducting polymer element and at least one substance incorporating element. The elements may be adjacent arranged in the plane of the film, perhaps patterned so that adjacent segments may be adjoinedly linked to each other.
In one embodiment, in many of the previously mentioned drug delivery devices, the conducting polymer element may be contained within a cavity of the substance incorporating element.

In another embodiment, in many of the previously mentioned drug delivery devices, the substance incorporating element may be contained within a cavity of the conducting polymer element.

In another embodiment, many of the drug delivery devices as previously mentioned, may consist or consist essentially of one or more conducting polymer elements and one or more substance incorporating elements.

In another embodiment, many of the drug delivery devices mentioned above may comprise a substance incorporating element that may be a shell, capsule or miscelle, containing the substance. A plurality of such substance incorporating elements may be mixed into a conducting polymer element and applied to a substrate to form a film consisting or consisting essentially of the conducting polymer element and the substance incorporating elements.

According to another embodiment, in many of the above mentioned drug delivery devices the substrate may be a angioplasty balloon.

According to one embodiment, any of the above mentioned drug delivery devices may be used in the fabrication of a device for use in a vascular surgical procedure such as a percutaneous transluminal angioplasty procedure, a percutaneous transluminal coronary angioplasty procedure, treatment of emboli or thrombi, treatment of aneurysms or an implantation procedure.
CLAIMS

1. A drug delivery device (20;120;160;200;220) comprising, a conducting polymer element (22;62;142;204;222) and a substance incorporating element (24;148;164;208) containing a substance (30;152;170;236), wherein, when the device is placed within a surrounding fluid (28;50;203), upon changing of an electric potential to the conducting polymer element, the conducting polymer element provides an electrically controllable flux of a fluid, an ion and/or the like (F1,F2,F7,F8,F9;F12;F18) between the surrounding environment and the device, wherein the elements are adjacently arranged to enhance transfer of the flux provided there between, wherein the flux is directed into and/or out of the conducting polymer element and into and/or out of the substance incorporating element, thereby providing an initiation and/or control of a release of the substance from the delivery device by mobilizing, convective, and/or diffusive processes.

2. The drug delivery device according to claim 1, wherein the conducting polymer element (22;42;62;82;102a-c) has an electrically controllable swelling coefficient for providing the flux (F1,F2;F3,F4,F5,F6).

3. The drug delivery device according to claim 2, wherein the device has a storage state in which the swelling coefficient is approximately zero; and wherein the device has an electrically activated state, in which the swelling coefficient is significantly higher than zero, wherein the electrically activated state is provided upon the application of an electric potential to the conducting polymer element.

4. The drug delivery device according to claim 1, wherein the conducting polymer element (42;62;122;142;182;204;222) is arranged substantially between the substance incorporating element (44;64;148;184;224;226) and the surrounding environment (50;68;188).

5. The drug delivery device according to claim 4, wherein the conducting polymer element (122;182;204;222) has an electrically controllable morphology for providing the flux (F12;F15;F16;F18,F19).

6. The drug delivery device according to claim 5, wherein the conducting polymer element (122;222) comprises an electrically formable pore (130).

7. The drug delivery device according to claim 1 further comprising, a support layer (202), arranged so as to separate the substance incorporating element (208) from the surrounding environment (212); the drug delivery device (200) further comprising a channel (214), arranged through the support layer, wherein the conducting polymer element (204) is arranged within and/or around the channel and the conducting polymer element has a surface that is electrically controllable between a hydrophobic and a less hydrophobic or a hydrophilic state for providing the flux (F16).
8. The drug delivery device according to any one of the preceding claims, wherein the conducting polymer element (22;42;122;162;182;222) is a conducting polymer, optionally containing a dopant.

9. The drug delivery device according to claim 8, wherein the conducting polymer is selected from a group consisting of polypyrroles, polyanilines, polythiophenes, poly(phenylenes), poly(ethylenedioxythiophenes), poly(phenylenes), poly(para-phenylenes), polyvinylenes, and copolymers thereof, including substituted forms of the different monomers.

10. The drug delivery device according to claim 9, wherein the conducting polymer is polypyrrole.

11. The drug delivery device according to claim 8, wherein the conducting polymer is polypyrrole, doped with dodecylbenzene sulfonate, octylbenzene sulfonate and/or polystyrenesulfonate.

12. The drug delivery device according to claim 1, wherein the conducting polymer element (182) is electrically controllably degradable.

13. The drug delivery device according to claim 12, wherein the device further comprises a second conducting polymer element arranged to separate the conducting polymer element (182) and the surrounding fluid (188) and provide at least a portion of the flux (F15).

14. The device according to any one of the preceding claims, wherein at least one substance incorporating element (24;148;164;208,224) further comprises a carrier.

15. The drug delivery device (60;160;200) according to claim 14, wherein the carrier is a fluid disintegratable carrier.

16. The drug delivery device (160;200) according to claim 15, wherein the carrier is a hydroactivated carrier.

17. The drug delivery device according to any one of claims 14 to 16, wherein the carrier is a polymer material.

18. The drug delivery device according to any one of claims 14 to 16, wherein the carrier is a non-polymer material.

19. The drug delivery device (160) according to any one of the preceding claims, wherein the substance is a solid drug substance.

20. The drug delivery device according to any one of the preceding claims, wherein the drug delivery device (20;60;80;100;140) comprises a film, wherein the film comprises the conducting polymer element and the substance incorporating element.
21. The drug delivery device according to claim 20, wherein the film comprises at least one more conducting polymer element according to any one of claims 1 to 19 and/or at least one more substance incorporating element according to any one of claims 1 to 19.

22. The drug delivery device (100) according to claim 20 or 21, wherein the film is a multilayered film.

23. The drug delivery device according to any one of the preceding claims, further comprising a semipermeable membrane (86) to provide a selective passage of the flux (F9) and/or the substance (90) between the surrounding environment (88) and the device (80).

24. The drug delivery device according to any one of the preceding claims, further comprising an impermeable membrane or element, wherein said impermeable membrane or element is substantially impermeable to fluids, gas and substances.

25. The drug delivery device according to any one of the preceding claims, wherein the drug delivery device (20;40;140;200) further comprises a substrate (26;46;210;230).

26. The drug delivery device according to claim 25, wherein at least one through opening is arranged in the substrate (46).

27. The drug delivery device according to claim 25 or 26, wherein at least a portion of the substrate is an electrode (228a-c).

28. The drug delivery device according to any one of claims 25 to 27, wherein the substrate (230) is a medical device, or part of a medical device (1000), for providing an additional medical action other than the drug delivery action, the medical device preferably being a catheter, a guidewire, a stent, a balloon, a lead or an aneurysm coil.

29. The drug delivery device according to claim 28, wherein a conducting polymer element (222) and/or a substance incorporating element (226) is arranged on at least a portion of the medical device as a film.

30. The drug delivery device according to claim 28 or 29, wherein the drug delivery device (220) comprises a controllable electroporation device.

31. The drug delivery device according to any one of claims 25 to 30, wherein a conducting polymer element (22;42;102a;142) is arranged between the substrate (26;46;106;144) and a substance incorporating element (24;44;104a-b;148).
32. The drug delivery device according to any one of claims 25 to 30, wherein a substance incorporating element (64;104a;164;208;226) is arranged between the substrate (66;106;166;210;230) and a conducting polymer element (62;102b-c;162;204;222).

33. The drug delivery device according to any one of claims 25 to 30, wherein a substance incorporating element (64;124;164) is enclosed in a cavity defined by a conducting polymer element (62;122;162) and the substrate (66;126;166).

34. The drug delivery device according to any one of claims 1 to 30, wherein one or more cavities are comprised within a conducting polymer element (142;182) or between two or more conducting polymer elements (102a-c), wherein a substance incorporating element (104a-b;148;184) is substantially arranged within such a cavity.

35. The drug delivery device according to any one of claims 1 to 30, wherein one or more cavities are comprised within a conducting polymer element or between two or more conducting polymer elements (104a-b), wherein a conducting polymer element (102b) is substantially arranged within such a cavity.

36. The drug delivery device according to any one of claims 28 to 30, wherein the medical device (1000) comprises a chamber (205) and a housing (207), the chamber being defined by the housing, wherein a substance incorporating element (224) is arranged within the chamber, wherein the housing comprises a conducting polymer element (222).

37. The drug delivery device according to any one of claims 28 to 30, wherein the medical device comprises a chamber (205) and a housing (207), the chamber being defined by the housing, wherein a fluid is contained within the chamber, wherein the housing comprises a substance incorporating element (226), and a conducting polymer element (222) arranged to separate the substance incorporating element from the surroundings (203).

38. The drug delivery device according to claim 37, wherein the fluid is an aqueous infusate liquid comprising at least one of saline, a sugar solution, a contrast agent, whole blood, or blood plasma.

39. The drug delivery device according to claim 37 or 38, wherein the housing further comprises an inner layer (230) facing the chamber, the layer being a fluid permeable membrane.

40. The drug delivery device according to any one of the preceding claims, wherein a plurality of outwardly protruding elements (232a-b) are arranged on an outer facing surface of the drug delivery device (220).
41. The drug delivery device according to claim 40, wherein a bonding layer (234a-b) connects at least one of the outwardly protruding elements (232a-b) to the delivery device (220).

42. The drug delivery device according to claim 40 or 41, wherein the device (220) comprises a cup-like cavity, the cup-like cavity being defined by the surface of the delivery device (220) and two or more of the outwardly protruding elements (232a-b) and having an opening for accessing at least a portion of the surrounding environment (203).

43. The drug delivery device according to any one of claims 40 to 42, wherein the device is provided with an electrical isolation between at least one of the outwardly protruding elements (232a-b) and the conducting polymer element (222) and the outwardly protruding element provides a counter electrode or a reference electrode for the drug delivery device.

44. A drug delivery device (500;600;620;700;760;840) comprising, a conducting polymer element (502;602;622;662;682;702;882), a substance incorporating element (504;604;624;704;844;864) containing a substance, and a film, wherein the conducting polymer element and the substance incorporating element are adjacently arranged within the film, and wherein when the device is placed in a surrounding environment (508;688;828;868), upon changing of an electric potential to the conducting polymer element, the conducting polymer element provides a mechanical work on the substance incorporating element, thereby providing a release (M1 ;M5;M8;M16;M18) of the substance (592;710;754;796;850;870) from the delivery device by fracturing, pressurizing, and/or tensioning processes.

45. The drug delivery device according to claim 44, wherein the conducting polymer element (522;542;602;622;702;842) is a conducting polymer, optionally containing a dopant.

46. The drug delivery device according claim 45, wherein the conducting polymer is selected from a group consisting of polypyrroles, polyanilines, polythiophenes, polyethylenedioxythiophenes, poly(phenylenes), poly(para-phenylenes), polyvinylenes, and copolymers thereof, including substituted forms of the different monomers.

47. The drug delivery device according to claim 46, wherein the conducting polymer is polypyrrole.

48. The drug delivery device according to claim 45, wherein the conducting polymer is polypyrrole, doped with dodecylbenzene sulfonate and/or octylbenzene sulfonate.

49. The drug delivery device according to any one of claims 44 to 48, wherein the thickness of the film is 500 um or thinner, 100 um or thinner, 50 um or thinner, 10 um or thinner, or 1 um or thinner.
50. The drug delivery device (720) according to any one of claims 44 to 49, wherein the film comprises at least two layers.

51. The drug delivery device according to claim 50, wherein the film comprises at least one more conducting polymer element and/or at least one more substance incorporating element.

52. The drug delivery device according to any one of claims 44 to 51, wherein the film comprises a layer comprising a conducting polymer element (502;602;622;682;822) and a substance incorporating element (504;604;624;684;824).

53. The drug delivery device according to claim 52, wherein one or more cavities (703;830) are comprised within a conducting polymer element (622;702;822) or between two or more conducting polymer elements (502), wherein a substance incorporating element (504;624;704;824) is substantially arranged within such a cavity.

54. The drug delivery device according to claim 52, wherein one or more cavities (685) are comprised within a substance incorporating element (604;684) or between two or more substance incorporating elements (504;584), wherein a conducting polymer element (502;582;602) is substantially arranged within such a cavity.

55. The drug delivery device according to claim 53 or 54, wherein the conducting polymer element (502;582;682;722;862;882) is electrically controllably expandable and/or contractable in a direction (-s) that is substantially in plane with the film to provide the mechanical work.

56. The drug delivery device according to any one of claims 44 to 55, wherein the conducting polymer element (502;642;762) is electrically controllably expandable in a direction substantially towards the substance incorporating element (504;644;764) to provide the mechanical work.

57. The drug delivery device according to any one of claims 44 to 55, wherein the conducting polymer element (582) is electrically controllably contractable in a direction substantially away from a substance incorporating element (584) to provide the mechanical work.

58. The drug delivery device according to any one of claims 44 to 57, further comprising a semipermeable membrane, wherein the semipermeable membrane is selectively permeable to the substance or a fluid.

59. The drug delivery device according to any one of claims 44 to 58, further comprising an impermeable membrane or element, wherein said impermeable membrane or element is substantially impermeable to fluids, gas and substances.
60. The drug delivery device according to any one of claims 44 to 59, further comprising a sealing element or layer (530;890) being substantially impermeable to fluids and/or substances, wherein the sealing element is arranged to separate at least a portion of the drug delivery device (520;880) from the surrounding environment (528;888).

61. The drug delivery device according to claim 60, wherein the sealing element or layer (530;890) is an at least partially releasable element or layer that is releasable by the mechanical work.

62. The drug delivery device according to any one of claims 44 to 59, wherein the substance incorporating element (844) comprises a sealing element or layer being substantially impermeable to fluids and/or substances, wherein the sealing element or layer partly or fully encapsulates a substance.

63. The drug delivery device according to claim 60 or 62, wherein the sealing element or layer is a breakable element or layer that is breakable via the mechanical work, thereby providing a pathway to enhance the release of the substance by diffusive processes or subsequent mechanical work.

64. The drug delivery device according to any one of claims 44 to 63, wherein at least one constraint element or layer (550;570a,570b;650;670;752;770;792a,792b) is arranged in contact with the film.

65. The drug delivery device according to claim 64, wherein a constraint element (570b) is arranged so as to protrude from an outer surface of the film.

66. The drug delivery device according to claim 64 or 65, wherein a constraint layer (792a,792b) is arranged so as to fully or partially cover an outer surface of the film.

67. The drug delivery device according to any one of claims 44 to 66, wherein a substance incorporating element (864) is a breakable element that breaks or fractures via the mechanical work.

68. The drug delivery device according to any one of claims 44 to 67, wherein the substance incorporating element (504;604;684;704;884) further comprises a carrier.

69. The drug delivery device according to claim 68, wherein the carrier is a fluid disintegratable carrier.

70. The drug delivery device according to claim 69, wherein the carrier is a hydroactivated carrier.

71. The drug delivery device according to any one of claims 68 to 70 wherein the carrier is a polymer material.
72. The drug delivery device according to any one of claims 68 to 70, wherein the carrier is a non-polymeric material.

73. The drug delivery device according to any one of claims 44 to 72, wherein the substance is a solid drug substance.

74. The drug delivery device according to any one of claims 44 to 73, wherein the drug delivery device further comprises a substrate (506;606;626;666;766;826).

75. The drug delivery device according to claim 74, wherein at least one through opening (831) is arranged in the substrate (666;826).

76. The drug delivery device according to claim 74 or 75, wherein at least a portion of the substrate is an electrode.

77. The drug delivery device according to claim 74, wherein the conducting polymer element (762;782;802) and the substrate (766;786;806) are arranged in contact to form a gas sealed interface therebetween, wherein the drug delivery device further comprises an enclosed conducting element (772;790;810a,810b) arranged along the gas sealed interface, wherein the enclosed conducting element provides the formation of gas upon application of an electric potential to the device for enhancing the mechanical work.

78. The drug delivery device according to any one of claims 74 to 77, wherein the substrate (506;606;706;766;846) is a medical device, or part of a medical device (1000), for providing an additional medical action other than the drug delivery action, the medical device preferably being a catheter, a guidewire, a stent, a balloon, a lead, or an aneurysm coil.

79. The drug delivery device according to claim 78, wherein the drug delivery device (230) comprises a controllable electroporation device.

80. The drug delivery device according to any one of claims 74 to 79, wherein a conducting polymer element (642;762;862;882) is arranged between the substrate (646;766;866;886) and a substance incorporating element (644;764;864;890).

81. The drug delivery device according to any one of claims 74 to 79, wherein a substance incorporating element (724a,744a,824) is enclosed in a region defined by a conducting polymer element (722;724;822) and the substrate (726;746;826).

82. The drug delivery device according to any one of claims 44 to 81, further comprising at least one outwardly protruding element that is arranged on an outer surface of the drug delivery device.
83. The drug delivery device according to claim 82, wherein at least one constraint element or layer (570b) according to claim 65 provides the at least one outwardly protruding element.

84. The drug delivery device according to claim 82 or 83, wherein the device comprises at least two outwardly protruding elements and a cup-like cavity; the cup-like cavity being defined by the surface of the delivery device and two or more of the outwardly protruding elements, the cup-like cavity having an opening for accessing at least a portion of the surrounding fluid (568).

85. The drug delivery device according to any one of claims 82 to 84, wherein the device is provided with an electrical isolation between at least one of the outwardly protruding elements and the conducting polymer element and the outwardly protruding element provides a counter electrode or a reference electrode for the drug delivery device.

86. The drug delivery device according to any one of claims 1 to 85, wherein the substance is selected from anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, antineoplastic agents, anti-mitotic agents, anti-thrombotic agents, anti-restenotics, antibiotics, vascular cell growth promoters, vascular cell growth inhibitors, vasodilating agents, neuro-transmitters, immunosuppressive agents and neuro-modulators.

87. The drug delivery device according to claim 86, wherein the substance is an antineoplastic agent, including paclitaxel or its analogs or derivatives.

88. The drug delivery device according to claim 86, wherein the substance is an immunosuppressive agent, including sirolimus, tacrolimus, pimecrolimus and everolimus or its analogs or derivatives.

89. The drug delivery device according to claim 86, wherein the substance is an anti-inflammatory agent including a dexamethasone or prednisolone compound or its analogs or derivatives.

90. A method for delivering a substance to a target location, the method comprising:
   a) bringing at least a part of a drug delivery device as claimed in any one of the claims 1-89, in contact with the target location (48;201;672), and
   b) delivering the substance by providing an electrical potential to the device.

91. The method according to claim 90 further comprising, providing a flux when the delivery device is dependent on any one of the claims 1 to 43.

92. The method according to claim 91 further comprising, repeating the step of claim 91.
93. The method according to claim 90 further comprising, providing a mechanical work when the delivery device is dependent on any one of the claims 44 to 89.

94. The method according to claim 93 further comprising, repeating the step of claim 93.

95. The method according to claim 90 further comprising, forming a cell when the delivery device is dependent on claim 42 or 84; wherein the cell is defined by the cup-like cavity and the target location.

96. A surgical method comprising a step of drug delivery by applying a drug delivery device according to any one of claims 1 to 89 to a target site and delivering the substance by providing an electrical potential to the device; wherein the surgical procedure is a percutaneous transluminal angioplasty procedure, a percutaneous transluminal coronary angioplasty procedure, treatment of emboli or thrombi, treatment of aneurysms or an implantation procedure.
Prior Art
Fig 1
Fig 2

Fig 3
### INTERNATIONAL SEARCH REPORT

**International application No**

PCT/SE2008/000084

#### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** A61K9/00

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

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61L A61M

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

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>X</td>
<td>US 5 800 421 A (LEMELSON JEROME H [US]) 1 September 1998 (1998-09-01) column 1, line 5 - line 11 column 3, line 39 - line 57 column 3, line 64 - column 5, line 38; figures 1-3 claims</td>
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<td>WO 2007/125455 A (KONINKL PHILIPS ELECTRONICS NV [NL]; VAN BRUGGEN MICHEL PAUL BARBAR [N]) 8 November 2007 (2007-11-08) page 1, line 22 - page 2, line 7 page 4, line 3 - line 5 page 8, line 4 - page 9, line 1, figures claims</td>
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<td>Further documents are listed in the continuation of Box C</td>
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Date of the actual completion of the international search

27 October 2008

Date of mailing of the international search report

04/11/2008

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