Abstract: The present invention discloses a drug delivery system for water triggered administration of medicament. It comprises a drug delivery element (100) which comprises an essentially water insoluble hydrophilic carrier matrix, being a porous or fibrous polysaccharide, and a set of components including the medicament. The drug delivery element (100) has a passive essentially dry state, wherein essentially no pharmaceutically effective amount of the medicament is released, and an active moist state, wherein at least one neutral or zwitterionic form of the medicament is released.
TUBULAR OR SHEET-SHAPED DRUG DELIVERY SYSTEM

TECHNICAL FIELD

The present invention relates to a novel tubular or sheet-shaped drug delivery system for water triggered administration of medicament, in particular within a body cavity or to the skin or mucous membranes.

BACKGROUND

All drugs and pharmaceutically active compounds are associated with a concentration range, at their site of action, within which the most desirable effect is achieved. This range has a lower limit equivalent with the lowest concentration at which the desired pharmacological effect is achieved, and an upper limit defined by the concentration at which unacceptable adverse effects become noticeable. In addition, this range may vary over time as dependant on the particular disease or condition which is treated or in any other way affected by the drug or active compound. For example, a relative high concentration of a drug which initiates sleep is desirable in the CNS when the patient is awake and desires to fall asleep. When the patient has fallen asleep, the drug has completed its task and, in the ideal case, it is desirable that the concentration is zero in order to avoid any potential side effect, i.e. the upper ideal limit has decreases to zero at the time when the patient falls asleep. With an objective to administer medicament in a practical way and simultaneously achieve an optimal concentration of the active component at the site of action at all time points, much effort has been devoted to the development of so called controlled release formulations.

A medicament in the form of a controlled release formulation may be administered by several different routes, e.g. orally or via the skin or mucous membranes. The latter two routes may be preferred, for example, in applications where a local high concentration of the medicament is desired or in order to e.g. circumvent a high first pass metabolism of a metabolically sensitive drug.

Various controlled release formulations, adapted for administration via the skin or mucous membranes and which are triggered or dependant on the presence of water or other condition related components, have been developed. WO2005035012 describes a wound dressing in the form of e.g. a foam, matrix, paste or hydrogel, comprising an absorbent material that may absorb wound exudate and one or several therapeutic ingredients contained in liposomes. The liposomes may be such adapted that they interact with wound constituents, e.g. phospholipases expressed by bacteria in the wound or proteases, to release a therein contained therapeutic ingredient to the wound. Disadvantages of this controlled release system include its limited use to applications in which specific triggers with an ability to interact and initiate release from liposomes are present.
WO0981 1877 describes a dry powder composition comprising liposome encapsulated active ingredient, e.g. an anti-inflammatory agent, and a water absorptive carrier or matrix, e.g. modified starch and maltodextrin. Release of the active ingredient is triggered by e.g. moisture by water absorption assisted release of the liposomes. Disadvantages of this controlled release system include the cumbersome or limited possibility to remove the powder from e.g. the skin, should an interruption of the exposure to the active ingredient be desired.

WO2005055964 describes a free floating powder composed of water sensitive micro-spheres with encapsulated fragrance for incorporation in e.g. cosmetic products such as deodorants, sticks, soaps, powders and sprays. The water sensitive material comprise of water soluble and water dispersible synthetic and natural polymers and co-polymers, e.g. polyvinyl alcohol. Disadvantages of this controlled release system include the cumbersome or limited possibility to remove the powder from e.g. the skin, should an interruption of the release of fragrance be desired.

WO0195888 describes a bioadhesive tablet that is activated by moisture and which may stay attached in e.g. the buccal or vaginal cavity for an extended period of time during which active ingredient, e.g. testosterone or progesterone, is delivered. The tablet comprises a water insoluble polycarboxylic polymer, e.g. polycarbophil, and a water soluble polymer, e.g. carborner 974P. Disadvantages of this controlled release system include the limited possibility of adaption to accomplish a rapid wetting of the entire system, should a high release of active ingredient be desired.

Hence, there is a great need for improved controlled release formulations and systems for administration of medicament via the skin or mucous membranes.

SUMMARY

The present invention seeks to mitigate, alleviate, circumvent or eliminate at least one, such as one or more, of the above-identified deficiencies.

It is an object of the present invention, to provide an improved controlled drug release system from which the release of medicament to mucous membranes or to e.g. the skin is dependant on user input or condition related factors.

It is another object, to provide a controlled drug release system which is generally applicable to a large variety of pharmaceutically active compounds, for administration via mucous membranes or via the skin.

It is another object, to provide an improved controlled drug release system for basic or acidic pharmaceutically active compounds, for administration via mucous membranes or via the skin.

It is another object, to provide a controlled drug release system with improved long term storage capabilities.
Accordingly, there is provided, according to one aspect, a drug delivery system for water triggered administration of medicament, having an elongated tubular form adapted for placement in a body cavity or being shaped as a sheet adapted for placement on a surface of the body, comprising a drug delivery element, wherein the drug delivery element is having a passive essentially dry state and an active moist state; the drug delivery element is comprising an essentially water insoluble hydrophilic carrier matrix being a porous or fibrous polysaccharide and a set of additional components being (i), (ii), (iii) and (iv), or (iv) and (v), wherein (i) being at least one protonated positively or deprotonated negatively charged form of the medicament, (ii) being at least one negatively or positively charged counterion accompanying the protonated positively or deprotonated negatively charged form of the medicament, respectively, to maintain electric neutrality, (iii) being a base or acid capable of reacting with and generating the neutral or zwitterionic form of the protonated positively or deprotonated negatively charged form of the medicament, respectively, in the active moist state, (iv) being a suitable pharmaceutically acceptable carrier, and (v) being at least one neutral or zwitterionic medicament; essentially all of each existing component of (i), (ii), (iii), (iv) and (v) being arranged and immobilized within the carrier matrix in the passive essentially dry state, whereby essentially no pharmaceutically effective amount of the medicament is released from the outer surface of the drug delivery element; at least one neutral or zwitterionic form of the medicament being released from the outer surface of the drug delivery element in the active moist state, by existing in a liquid form or by being dissolved, dispersed, emulsified or suspended in a liquid form of the pharmaceutically acceptable carrier; and the active moist state being a state in which the total water content of the drug delivery element exceeds e.g. 10%, by weight.

According to another aspect, the carrier matrix may comprise cellulose or modified cellulose. Advantages of cellulose or modified cellulose in this application includes the readily availability, the low cost, and the well known medical properties.

According to yet another aspect, each existing component of (i), (ii), (iii), (iv) and (v) may be immobilized at a temperature below a first temperature, said first temperature being a temperature being equal to or exceeding about 25°C, when the drug delivery element is existing in the passive essentially dry state by: each existing component of (i), (ii), (iii), (iv) and (v) may exist in a solid form or a semisolid form, by being entrapped in another solid or semisolid form of another component selected from (i), (ii), (iii), (iv) and (v) by being dissolved, dispersed, emulsified or suspended therein, or by strong molecular interaction or covalent binding thereto, or by being attached to the carrier matrix by strong molecular interaction or covalent bonding. Advantages of a pharmaceutically acceptable carrier with such properties include the ability of controlled immobilization of components by enclosure therein, e.g. as a solid solution or dispersion, which components, e.g. medicaments, would otherwise have a possibility of
unwanted leakage from the drug delivery element due to their e.g. inherent volatile or liquid properties. In addition, air sensitive components, e.g. air sensitive medicaments, may be protected from degradation during e.g. long term storage, e.g. at room temperature, when immobilized in such a pharmaceutically acceptable carrier.

According to yet another aspect, the pharmaceutically acceptable carrier or the corresponding may have a phase transition temperature associated with the transition from a solid or semisolid form to a liquid form at a temperature which is equal to a second temperature, the second temperature being a temperature which is lower than or equal to e.g. 37°C, when the drug delivery element is existing in the active moist state. Advantages of a carrier with such properties include the necessity of fulfilment of one additional requirement associated with the temperature of the surrounding, beside the requirement of existing in the active moist state, for release of medicament from the drug delivery system. For example, when the second temperature is a temperature which is slightly lower than normal body temperature but higher than ambient or room temperature, e.g. 30°C to 35°C, no release or only minimal release of medicament will occur even if the drug delivery system has been user activated, i.e. set in the active moist state, unless the drug delivery system is placed in a body cavity or on the intended site of administration. Hence, the risk of undesired release of medicament outside a bodily cavity or the intended site of administration is thereby minimized.

According to yet another aspect, the set of additional components may comprise (i), (ii), (iii) and (iv).

According to yet another aspect, the base or acid may be attached to the carrier matrix by strong molecular interaction or covalent bonding. Advantages of such attachment to the carrier matrix include, for example, the possibility of immobilization of basic or acidic medicaments, respectively, in the carrier matrix as their corresponding solid salts, with a minimized release of the corresponding counterion when the drug delivery element is brought to its activated moist state. The counterion might e.g. be preferred with respect to a relatively high long term stability of the corresponding salt form of the medicament, but disfavored by e.g. having a relatively high inherent toxicity. Hence, attachment of the base or acid to the carrier matrix by strong molecular interaction or covalent bonding, which base or acid undergoes a proton exchange reaction with the salt form of the corresponding basic or acidic medicaments in the active moist state, increases the scope of counterions that may be used in relevant medical applications. In addition, a protonated base, e.g. protonated chitosan, polylysine or other types of polymeric amines, attached to the carrier matrix by strong molecular interaction or covalent bonding, is well known to have antimicrobial and mucoadhesive properties. Hence, when in its activated moist state, the carrier matrix of the corresponding drug delivery element decreases advantageously the antimicrobial activity at the site of application, as well as being more intimately attached thereto,
whereby a more effective transport of medicament to the target tissue may advantageously be achieved.

According to yet another aspect, the additional component (i) may be at least one protonated positively charged medicament; the additional component (ii) may be at least one negatively charged counterion; the additional component (iii) may be a base; and the additional component (iv) may be selected from one or several of the group consisting of

![Chemical structures](image)

, such as compounds of formula (VII) or (VIII) which are solids or semi-solids at a temperature below 30 to 60 °C.

According to yet another aspect, the drug delivery system may be used for administration of the medicament to mucous membranes, or for transdermal or local administration of the medicament to the skin.

According to yet another aspect, the medicament may have a pharmaceutical effect at a location of the body, e.g. skin or mucous membrane, which is different or the same as the location of the body onto which the drug delivery system is placed when in use.

According to yet another aspect, the medicament may be selected from the group consisting of medicaments with at least one basic functional group, medicaments with at least one acidic functional group, medicaments with no essentially basic or acidic functional groups, i.e. neutral medicaments, and zwitterionic medicaments.
According to yet another aspect, the drug delivery system may be used for administration of the medicament to the female reproductive organs.

According to yet another aspect, the medicament of the drug delivery system may be at least one local anaesthetic.

According to yet another aspect, the medicament of the drug delivery system may be an eutectic mixture comprising at least one pharmaceutically active ingredient, which mixture is having an eutectic point in the moist state at a temperature being less than the second temperature.

According to yet another aspect, the medicament of the drug delivery system may be an eutectic mixture comprising at least one pharmaceutically active ingredient, such as an eutectic mixture of two pharmaceutically active ingredients, e.g. prilocaine and lidocaine or other well known eutectic mixtures, which mixture is having an eutectic point, e.g. in the moist state, at a temperature being equal to or lower than the second temperature. Advantages of the combination of ingredients to generate such eutectic mixtures include the potential release of medicament in a concentrated liquid form, e.g. when the melting point of one or both of the pure components of the eutectic mixture exceeds e.g. normal body temperature or the second temperature.

According to yet another aspect, the drug delivery system may comprise an integrated container adapted to contain water or an aqueous solution for enabling provision of water to the drug delivery element, e.g. upon a voluntarily active action taken by the user or patient, to accomplish transition from the passive essentially dry state to the active moist state. The user or patient may thus, in a highly practical way, initiate administration of medicament at will. Other user controlled ways of initiating administration of the prior-art include the swallowing of a tablet, the smearing of a paste or ointment on the skin or the preparation and application of an adhesive plaster. The solution according to the invention involves a simple momentarily application of pressure to the system, which represents an optimal or alternative way in the sense of user friendliness.

According to yet another aspect, the drug delivery system may comprise a or at least one pressure sensitive conduit or valve having an inlet connected to the container and an outlet connected to the drug delivery element, the conduit or valve may be adapted to be closed at a pressure being less than a first internal pressure of the container to prevent liquid transfer from the container to the drug delivery element, and the conduit or valve may be adapted to be open at a pressure exceeding a second internal pressure of the container to permit liquid transfer from the container to the drug delivery element, for user initiated transition from the passive essentially dry state to the active moist state by application of external pressure to the container to increase the internal pressure thereof.
According to yet another aspect, the drug delivery system may comprise a conduit or valve having an inlet connected to the container and an outlet connected to the drug delivery element, wherein the conduit or valve may be provided with a temperature sensitive and essentially water insoluble plug having a melting point within the range of e.g. 30°C to 40°C, the plug being solid at a temperature below its melting point to prevent liquid transfer from the container to the drug delivery element, and the plug being liquid at a temperature above its melting point to permit liquid transfer from the container to the drug delivery element. A drug delivery system comprising such a temperature sensitive valve represents a condition initiated drug release system, the condition being exceeding a temperature threshold being equal to or less than the temperature within the bodily cavity, or of the area of the body, e.g. the skin, onto/into which the drug delivery system is to be placed. Typically, the drug delivery system will remain in a passive essentially dry state, wherein no or minimal medicament is released, until it is placed in a bodily cavity, or onto the area, whereby the drug delivery system attains an active moist state leading to release of medicament. Advantageously, the user needs to undertake no other action but placing the drug delivery system at the site of action, i.e. within a body cavity or on the skin or mucous membrane, to achieve the desired exposure to the medicament. Until that event, the content of the drug delivery system, including the medicament, remains in a dormant state associated with advantages described elsewhere herein.

Further, advantageous features of various embodiments of the invention are defined in the dependent claims and within the detailed description below.

**BRIEF DESCRIPTION OF THE DRAWINGS**

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

Fig. 1 is an overview of schematic illustrations used in the drawings, in which "A", "A⁺", "B", "B⁺", "C", "I⁻", "I⁺", "M⁻", "M⁺" and "M⁺" represents an acid in a neutral form, an acid in a negatively charged form, a base, a base in a positively charged form, a pharmaceutically acceptable carrier, a negatively charged counterion, a positively charged counterion, a medicament in a neutral or zwitterionic form, a medicament in a negatively charged form and a medicament in a positively charged form, respectively, a cluster of multiple irregular threads (A) represents a carrier matrix in a passive dry state, a cluster of multiple irregular threads with a plurality of accompanying water ("H₂O") molecules (B) represents the carrier matrix in an active moist state, a square represents a solid or semisolid state of matter, e.g. a solid or
semisolid acid (C), a circle represents a liquid state of matter, e.g. a liquid pharmaceutically acceptable carrier (D), an irregular continuous shape represent a dissolved state of matter, e.g. a negatively charged counterion in solution (E), an "R" with an indicative arrow ("R->") is used to indicate a singularity or plurality of elements which may be released from the drug delivery element of the invention, e.g. a liquid pharmaceutically acceptable carrier being released (F), a shape encompassed by another shape indicate the matter of the former shape to be e.g. dissolved, dispersed, emulsified or suspended in the matter of the latter shape, e.g. a dispersion of a solid or semisolid medicament (G) or a dissolved medicament (H) in a liquid pharmaceutically acceptable carrier, a dashed line ending with a dot is used to indicate matter attached by strong molecular interaction or covalent bonding, e.g. an attached solid or semisolid base (I) or an attached positively charged base being pseudo-dissolved in the surrounding environment (J);

Fig. 2A is a cross section view from the side of a drug delivery element 100 in a dry state, comprising a pharmaceutically acceptable carrier in a solid state with an immobilized solid medicament dispersed therein, according to one embodiment;

Fig 2B is the drug delivery element 100 of Fig. 2A during the transition from its dry to its moist state by absorption of water in the form of e.g. sweat or any other aqueous secretion from the lower side, showing the release of liquid medicament and in a liquid pharmaceutically acceptable carrier dissolved medicament, according to one embodiment;

Fig. 3A and 3C is a view of a drug delivery element 100 in its dry state comprising a positively charged medicament, a negatively charged counterion and a base in an immobilized solid form (A), and a negatively charged medicament, a positively charged counterion and an acid in an immobilized solid form (C), according to two embodiments;

Fig. 3B and 3D is a view of the drug delivery element 100 of Fig 3A and 3C in the corresponding moist state, respectively, comprising a neutral or zwitterionic medicament in a liquid form which is being released, a negatively charged counterion in a dissolved form and a positively charged base in a dissolved form (B), and a neutral or zwitterionic medicament in a liquid form which is being released, a positively charged counterion in a dissolved form and a negatively charged acid in a dissolved form (D), according to two embodiments;

Fig. 4A is a view of a drug delivery element 100 in its dry state comprising a positively charged medicament, a negatively charged counterion and a base in an immobilized solid form, all dispersed in an immobilized pharmaceutically acceptable carrier in a solid form, according to one embodiment;

Fig. 4B is a view of the drug delivery element 100 of Fig. 4A in a moist state, showing a positively charged base and negatively charged counterion, both being
dissolved partly is the aqueous environment of the carrier matrix and partly in a liquid form of the pharmaceutically acceptable carrier, and a liquid form of medicament and a in a liquid form of the pharmaceutically acceptable carrier dissolved form of medicament simultaneously being released from the drug delivery element 100, according to one embodiment;

Fig. 4C is a view of the drug delivery element 100 of Fig. 4A in a moist state, showing positively charged base and negatively charged counterion, both being dissolved partly is the aqueous environment of the carrier matrix and partly in a liquid form of the pharmaceutically acceptable carrier, and a in a liquid form of the pharmaceutically acceptable carrier dispersed solid form of medicament being released from the drug delivery element 100, according to one embodiment;

Fig. 4D is a view of the drug delivery element 100 of Fig. 4A in a moist state, showing positively charged base and negatively charged counterion, both being dissolved partly is the aqueous environment of the carrier matrix and partly in a liquid form of the pharmaceutically acceptable carrier, and a liquid form of medicament being released from the drug delivery element 100, according to one embodiment;

Fig. 5A is a view of a drug delivery element 100 in its dry state comprising a positively charged medicament in an immobilized solid form, a negatively charged counterion in an immobilized solid form and a base bound to the carrier matrix, according to one embodiment;

Fig. 5B is a view of the drug delivery element 100 of Fig. 5A in a moist state, showing the medicament in a liquid form being released, a negatively charged counterion in dissolved form, and a positively charged base bound to the carrier matrix and being pseudo-dissolved in the aqueous environment of the carrier matrix, according to one embodiment;

Fig. 5C is a view of a drug delivery element 100 in its dry state comprising a positively charged medicament in an immobilized solid form dispersed in an immobilized solid form of a pharmaceutically acceptable carrier, a negatively charged counterion in an immobilized solid form dispersed in an immobilized solid form of the pharmaceutically acceptable carrier, and a base bound to the carrier matrix and being partly dispersed in an immobilized solid form of the pharmaceutically acceptable carrier and partly existing in a solid form outside of the pharmaceutically acceptable carrier, according to one embodiment;

Fig. 5D is a view of a the drug delivery element 100 of Fig. 5C in a moist state, showing a neutral or zwitterionic form of the medicament being released partly as a liquid form and partly as a in a liquid form of the pharmaceutically acceptable carrier dissolved form, a negatively charged counterion partly dissolved in the aqueous environment of the carrier matrix and partly in a liquid form of the pharmaceutically acceptable carrier, and the positively charged base partly pseudo-dissolved in the
aqueous environment of the carrier matrix and partly in a liquid form of the pharmaceutically acceptable carrier, according to one embodiment;  

Fig. 6A is a view of a drug delivery element 100 in its dry state comprising a neutral or zwitterionic medicament in an immobilized solid form dispersed in an immobilized solid form of a pharmaceutically acceptable carrier, according to one embodiment;  

Fig. 6B is a view of a drug delivery element 100 of Fig. 6A in a moist state, showing a neutral or zwitterionic form of the medicament being released partly as a liquid form and partly as a in a liquid form of the pharmaceutically acceptable carrier dissolved form, and an additional amount of medicament being dissolved in a liquid form of the pharmaceutically acceptable carrier, according to one embodiment;  

Fig. 6C is a view of a drug delivery element 100 of Fig. 6A in a moist state, showing a neutral or zwitterionic form of the medicament being released as a liquid form, and a liquid form of the pharmaceutically acceptable carrier remaining within the carrier matrix, according to one embodiment;  

Fig. 6D is a view of a drug delivery element 100 of Fig. 6A in a moist state, showing a neutral or zwitterionic form of the medicament being released as a solid dispersed in liquid form of the pharmaceutically acceptable carrier, and a part of the medicament remaining as a solid dispersed in a liquid form of the pharmaceutically acceptable carrier which is remaining within the carrier matrix, according to one embodiment;  

Fig. 7A and 7B are cross sectional views from the side of a drug delivery system having an elongated tubular form comprising a drug delivery element 100 in a dry state (A), wherein a pressure sensitive conduit or valve 102 is closed by being pressed together 105 so that water in container 103 is prevented from flowing to and reaching drug element 100, and in a moist state (B), wherein an applied external pressure 104 is causing the pressure sensitive conduit or valve 102 to open by not being pressed together whereby a flow 106 of water is reaching the drug delivery element 100 causing a transition to a moist state, whereby medicament is released in various forms as described herein from the drug delivery element 100 via a drug permeable outer element 101, which is enclosing the drug delivery element 100, the container 103 and the pressure sensitive conduit or valve 102, according to one or two embodiments;  

Fig. 8A and 8B are cross sectional views from the side of a drug delivery system having an elongated tubular form comprising a drug delivery element 100 in a dry state (A), wherein a conduit or valve 102 is closed by being plugged with a solid temperature sensitive and essentially water insoluble plug 107 so that water in container 103 is prevented from flowing to and reaching drug element 100, and in a moist state (B), wherein a relatively high temperature is causing the conduit or valve 102 to open by melting of the temperature sensitive and essentially water insoluble plug 107, which
thereby becomes a liquid 107, whereby a flow 106 of water is reaching the drug delivery element 100 causing a transition to a moist state, whereby medicament is released in various forms from the drug delivery element 100 via a drug permeable outer element 101, which is enclosing the drug delivery element 100, the container 103 and the pressure sensitive conduit or valve 102, according to one or two embodiments.

Fig. 9A and 9B are cross sectional views from the side of a drug delivery system having an elongated tubular form comprising a drug delivery element 100 with an exposed distal end and a proximal end enclosed by an outer element 101 in a dry state at a temperature below the melting point of the material of plug 107, wherein a conduit or valve 102 is closed by being plugged with a solid temperature sensitive and essentially water insoluble plug 107 so that water in container 103 is prevented from flowing to and reaching drug element 100 (A), and in a dry state, wherein a pressure sensitive conduit or valve 102 is closed by being pressed together 105 so that water in container 103 is prevented from flowing to and reaching drug element 100 (B), according to two embodiments;

Fig. 10 depicts the generic formula of examples of various suitable pharmaceutically acceptable carriers and additives, wherein formula (I) represents triglycerides of glycerol and independently selected short (R is comprising 1 to 5 carbon atoms), medium (R is comprising 6 to 11 carbon atoms) or long (R is comprising 12 to 33 carbon atoms) carboxylic acid residues, in which each residue independently may be saturated or unsaturated with 1 to 4 double bonds, formula (II) represents the corresponding monoglycerides, formula (III) represents the corresponding diglycerides, formula (IV) represents the corresponding free fatty acids, formula (V) and (VI) represents ethers comprising independently selected polyethylene glycol moieties, in which m and n are integer numbers independently selected from the ranges of 0 to 30 and 1 to 30, respectively, formula (VII) and (VIII) represent mixed polyethylene/polypropylene and polyethylene glycol derivatives of an average molecular weight of 300 to about 10,000,000 g/mol, Formula (IX) and (X) represent exemplary small molecular additives, according to various embodiments of the invention;

Fig. 11A and 11B are cross sectional views from the side of a sheet formed drug delivery system comprising a sheet formed drug delivery element 100 with an exposed distal end and a proximal end adjacent to an outer element 101 in a dry state at a temperature below the melting point of the material of plug 107, wherein a plurality of conduits or valves 102 are closed by being plugged with a solid temperature sensitive and essentially water insoluble plug 107 so that water in container 103 is prevented from flowing to and reaching drug element 100 (A), and in a dry state, wherein a plurality of pressure sensitive conduits or valves 102 are closed by being pressed
together 105 so that water in container 103 is prevented from flowing to and reaching drug element 100 (B), according to two embodiments;

Fig. 12A is the drug delivery element of Fig. 11A in an active moist state wherein a relatively high temperature has caused the conduit or valve 102 to open by melting of the temperature sensitive and essentially water insoluble plug 107, which thereby becomes a liquid 107, whereby a flow 106 of water is reaching the drug delivery element 100 causing a transition to a moist state, whereby medicament is released in various forms from the exposed distal end of the drug delivery element 100, e.g. to a contacting area of the skin of a patient, according to one embodiment; and

Fig. 12B is the drug delivery element of Fig. 11B in an active moist state wherein an applied external pressure 104 to the outer element 101 has caused the pressure sensitive conduit or valve 102 to open by not being pressed together whereby a flow 106 of water is reaching the drug delivery element 100 causing a transition to a moist state, whereby medicament is released in various forms from the exposed distal end of the drug delivery element 100, e.g. to a contacting area of the skin of a patient, according to one embodiment.

**DETAILED DESCRIPTION**

In the detailed description below, references to the herewith attached drawings and figures are made.

The drug delivery system of the invention essentially comprises a drug delivery element 100, being adapted to withhold or release the medicament, i.e. drug, as dependent on the amount of water present therein, and an outer element 101, adapted to fully or partly enclose the drug delivery element 100 and optionally other elements of the drug delivery system. The medicament resides in a dormant non-releasable storable form when the drug delivery element 100 is essentially dry, i.e. when existing in a passive essentially dry state. For example, the medicament may be immobilized in the passive state by existing in a solid salt-form or by being dissolved, dispersed, emulsified or suspended in another element, e.g. a solid or semisolid pharmaceutical acceptable carrier, which resides in the drug delivery element 100. Additional examples of ways by which the medicament may be immobilized in the passive state include e.g. strong molecular interactions, such as e.g. ionic bonds between a positively or negatively charged form of the medicament and an oppositely charged group or component associated with the drug delivery element 100. Independent of the mechanism for mobilization of the medicament in the passive state, it is preferred that all such related components are selected, as readily understood in the art, such that effective mobilization is achieved at all temperatures below a first temperature, such as e.g. below 35, 30 or below 25°C, in order to enable practical and long-term storage of the drug delivery system at ambient temperature, without leakage of medicament therefrom.
The medicament is released in a bio-available form, unless hindered to do so due to other factors, e.g. a too low a temperature, as disclosed herein, when becoming wet or moist, i.e. when turned into an active moist state. Hence, the release of medicament from the drug delivery system is water triggered. When the medicament is immobilized in the passive dry state by being e.g. dissolved, dispersed, emulsified or suspended in a solid or semisolid pharmaceutical acceptable carrier residing in the drug delivery element 100, the release of medicament in the corresponding active state is dependent on the lowering of the melting or transition point of the solid or semisolid carrier to a liquid form thereof when additional water is present. The lowered melting or transition point, i.e. a second temperature, is preferably lower than normal body temperature at the site of administration, e.g. lower than about 37°C or preferably lower than 35°C, to enable release of medicament at the intended site of administration. The drug delivery system may be further adapted for placement within a bodily cavity and for administration of medicament therein and thereto, upon user or condition triggered activation. The drug delivery system may also be further adapted for placement on typically the skin, e.g. in the form of an adhesive plaster or patch, and for administration of medicament thereto, i.e. typically dermally, upon user or condition triggered activation. The drug delivery element 100 essentially comprises a carrier matrix, adapted to provide mechanical stability to and withhold the medicament and other constituents or components, such as e.g. suitable chemicals, essential for the intended function of the drug delivery element 100. In the dormant passive essentially dry state, the medicament may exist in the form of a solid salt, in a neutral form immobilized in a solid or semisolid suitable pharmaceutically acceptable carrier, in a zwitterionic form immobilized in a solid or semisolid suitable pharmaceutically acceptable carrier or in the form of a salt immobilized in a solid or semisolid suitable pharmaceutically acceptable carrier, whereby no or minimal release of medicament from the drug delivery element 100 occurs. In the active moist state, the medicament may exist in a bio-available neutral or zwitterionic form, for example as a neutral free base or as a protonated neutral acid. The transition of the dormant into the bio-available form of the medicament is dependent on the presence of water, without which the necessary process cannot occur effectively. Examples of such processes or principles, which form basis for the transition of a dormant form of the medicament into a bio-available or releasable form of the medicament, include: (A) the reaction of the salt form of a medicament comprising a basic functionality, e.g. an amine or amidine group, with a stronger or at least comparably strong base present within the drug delivery element 100, (B) the reaction of the salt form of a medicament comprising an acidic functionality, e.g. a carboxylic acid or tetrazole group, with a stronger or at least comparably strong acid present within the drug delivery element 100 and (C) the absorption of water into a suitable pharmaceutically acceptable carrier present within the drug delivery element.
100, whereby the carrier undergoes a phase transition from solid or semisolid into liquid, at the present temperature. In the latter case (C), the liquid carrier may comprise dissolved or dispersed medicament and leak out from the drug delivery element 100, optionally through channels or pores of the outer element 101, such as e.g. channels or pores of a suitable film or sheet mounted in contact with and between the drug delivery element 100 and e.g. the skin of a patient, to reach the site of intended administration. The user or condition controlled administration of medicament depends on and is related to user or condition controlled provision of water to the drug delivery element 100. The provided water may originate from an external source, e.g. from a mucous membrane of the user or in form or sweat or any other aqueous secretion, or from an internal source, e.g. from one or several internal containers 103, residing in e.g. the outer element 101, which may controllably be brought in connection with the drug delivery element 100. Various mechanically based valves and systems for such user or condition, e.g. temperature, controlled connections of the internal container 103 with the drug delivery element 100 is known in the art and the skilled person will easily identify which ones of these may be applied to the present drug delivery system. Exemplary novel and advantageous pressure and temperature sensitive control systems are disclosed herein and illustrated in Figs. 7 to 9 and 11 to 12.

According to one embodiment, the drug delivery system may be used for administration of the medicament to the skin or mucous membranes of a patient.

According to one embodiment, the drug delivery system may be used for administration of the medicament to the female reproductive organs or parts thereof. Examples of such organs or parts thereof include the vaginal cavity, the cervix and the cervix canal. In order to accomplish selective delivery of medicament the drug delivery system may comprise an outer sheet or film, as well known in the art, which is practically impermeable to medicaments, located adjacent to the areas within the vaginal cavity to which no or only a minimal amount of medicament is to be administered. For example, the drug delivery system may comprise an outer non-permeable film located at all areas of its outer surface with exception of the part which is adjacent to the cervix, when placed in the vaginal cavity, for selective administration of medicaments, e.g. local anesthetics, to the cervix and optionally to the cervix canal.

According to one embodiment, the drug delivery system may have an elongated tubular form. Advantages of such an elongated tubular form include optimal delivery of medicament within bodily cavities, such as e.g. the vagina or the mouth. The tubular form shaped drug delivery system may be shaped in a suitable irregular shape to maximize the contact surface within the body cavity in which it is placed. For example, the most forward part of the drug delivery system intended for administration of medicaments, e.g. local anesthetic’s, to the cervix when placed in the vaginal cavity, may have a larger diameter in comparison to the rest of the elongated drug delivery
system. In this application, the elongated drug delivery system might further be suitably bent to maximize the contact area with the cervix. The exact shape and dimensions of the drug delivery system is dependent on the bodily cavity in which it is intended for use, and is well known to the skilled person.

According to one embodiment, the drug delivery system may have a shape in the form of a sheet, plaster or patch. It may, advantageously, be provided with one or several adhesive elements to allow fastening on e.g. the skin. The drug delivery system may be shaped in a suitable irregular shape to maximize the contact surface with the body onto which it is placed. The exact shape and dimensions of the drug delivery system is dependent on the bodily surface onto which it is intended for use, and is well known to the skilled person.

According to one embodiment, the drug delivery element 100 or the outer element 101, or suitable parts of any of these elements, may be adapted to swell in the presence of water, e.g. when the drug delivery system is brought into the active state. The contact area with the inside of and positioning of the drug delivery system in the body cavity in which it is placed, is thereby advantageously maximized. In the case of placement onto other bodily parts, the contact area with the surface of and positioning of the drug delivery system on the body part onto which it is placed, is thereby also advantageously maximized. Suitable medically acceptable materials with such swelling properties are well known to the skilled person.

According to one embodiment, the outer element 101 may be a water and medicament permeable film or sheet with low friction. Examples of suitable such films or sheets include outer sheets or films of tampons women use during their menstrual period, which sheets or films are associated with a low friction for improved application.

According to one embodiment, the carrier matrix may be an essentially water insoluble hydrophilic polysaccharide, such as e.g. a porous or fibrous polysaccharide, or the like. Examples of such hydrophilic polysaccharide include e.g. cellulose, such as cotton, modified cellulose, or the like.

According to one embodiment, the drug delivery system may comprise a drug delivery element 100, an optional outer element 101, a charged form of one or several medicaments being either a positively charged form, e.g. a protonated positively charged form of a medicament with basic properties, or a negatively charged form, e.g. a de-protonated negatively charged form of a medicament with acidic properties, one or several pharmaceutically acceptable counterions with a charge which is opposite the charge of the charged form of one or several medicaments, a pharmaceutically acceptable base, capable of converting the positively charged form of one or several medicaments into a neutral or switterionic form, or a pharmaceutically acceptable acid,
capable of converting the negatively charged form of one or several medicaments into a neutral or switterionic form, and optionally a pharmaceutically acceptable carrier.

According to one embodiment, the pharmaceutically acceptable carrier may be selected from the group consisting of compounds (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), each depicted in Fig. 10, or mixtures thereof.

According to one embodiment, the pharmaceutically acceptable carrier may comprise a mixture of compounds (V), (VII) and/or (VIII) and (IX), each depicted in Fig. 10. Such a carrier is suitable for administration of medicaments, e.g. local anesthetic's, e.g. to the cervix, due to advantageous thermo gelling properties.

According to one embodiment, the pharmaceutically acceptable carrier may comprise a mixture of compounds (II) and/or (III) and (IV), each depicted in Fig. 10, in which the R-group may be represented by an unsaturated straight carbon chain comprising 15 to 23 carbon atoms and one or two Z-double bonds, such as e.g. the carbon chains of linoleic acid, or preferably oleic acid. Such a carrier is suitable for administration of medicaments, e.g. local anesthetic's, e.g. to the cervix, due to advantageous mucoadhesive properties.

According to one embodiment, the pharmaceutically acceptable carrier may be a singularity or plurality of compounds selected from the group of compounds consisting of compounds of formula (V), (VI), (VII) and (VIII), each depicted in Fig. 10. The compound or the mixture of compounds may preferably be selected such that they exist in a solid or semisolid form in the dormant state, and in a liquid form in the active state, i.e. in the presence of water.

According to one embodiment, the pharmaceutically acceptable carrier may be a hydrophilic compound or mixture of compounds, which is miscible with water in all proportions. This compound or mixture of compounds may, when being employed as carrier in the drug delivery element 100 and when being mixed with other optional components therein, exist as a solid or semisolid in the dormant dry state at a temperature below 25, 30, 35 or preferably below 40 °C. This compound or mixture of compounds may, when exposed to water in the active state at a temperature above 10, 20, 25 or 30 °C, undergo a transition to a liquid state, whereby therein dissolved or dispersed medicament may be released from the drug delivery element 100. Suitable such compounds or mixtures of compounds are well known in the art and include e.g. suitable compounds of formula (V), (VI), (VII) and (VIII) depicted in Fig. 10, or the like.

According to one embodiment, the salt form of a medicament comprising a basic functionality may be the salt form generated upon reaction with an acid selected from the group of pharmaceutically acceptable acids consisting of 1-hydroxynaphthoic, 2,2-dichloroacetic, 2-hydroxyethanesulfonic, 2-oxoglutaric, 4-acetamidobenzoic, 4-aminosalicylic, acetic, adipic, ascorbic, aspartic, benzenesulfonic,
benzoic, camphoric, camphor-10-sulfonic, capric, caproic, caprylic, carbonic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic, glucuronic, glutamic, glutaric, glycerophosphoric, glycolic, hippuric, hydrobromic, hydrochloric, isobutyric, lactic, lactobionic, lauric, maleic, malonic, mandelic, methanesulfonic, naphthalene-1,5-disulfonic, naphthalene-2-sulfonic, nicotinic, nitric, oleic, oxalic, palmitic, pamoic, phosphoric, propionic, pyroglutamic, salicylic, sebacic, stearic, succinic, sulfuric, tartaric, thiocyanic, toluenesulfonic and undecylenic. It is readily understood by the skilled person which acids are suitable for a particular medicament comprising a basic functionality, to give a positively charged form of that medicament suitable for prolonged storage in the dormant state of the drug delivery system of the invention. Such a positively charged form of a medicament comprising a basic functionality may advantageously be combined with a pharmaceutically acceptable solid or immobilized base in the present drug delivery system. Such base is preferably a strong enough base to generate the neutral form of the medicament in the active wet state, as well known by the skilled person.

According to one embodiment, the base existing in a solid or semisolid form in the dormant state, and employed for the generation of a neutral and bioavailable form of a medicament from a positively charged form of that medicament in the active wet state, may be selected from carbonates or hydroxides of the group of elements consisting of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

According to one embodiment, the salt form of a medicament comprising an acidic functionality may comprise a cation of aluminum, calcium, lithium, magnesium, potassium, sodium, zinc or diethanolamine.

According to one embodiment, the acid existing in a solid or semisolid form in the dormant state, and employed for the generation of a neutral and bioavailable form of a medicament from a negatively charged form of that medicament in the active wet state, may be selected from pharmaceutically acceptable acids disclosed in other embodiments herein that normally exist in a solid or semisolid form.

According to one embodiment, the drug delivery system may comprise a drug delivery element 100, an optional outer element 101, a positively charged form of one or several medicaments, e.g. a protonated positively charged form of a medicament with basic properties, one or several pharmaceutically acceptable counterions with negative charge, a pharmaceutically acceptable base capable of converting the positively charged form of one or several medicaments into a neutral or zwitterionic form, and optionally a pharmaceutically acceptable carrier.

According to one embodiment, the drug delivery system may comprise a drug delivery element 100, an optional outer element 101, a positively charged form of one or several medicaments, e.g. a protonated positively charged form of a medicament with
basic properties, one or several pharmaceutically acceptable counterions with negative charge, a base attached to the drug delivery element 100 by strong molecular interaction or covalent bonding selected from the group consisting of chitosan, polylysine and other types of polymeric amines as known in the art, and optionally a pharmaceutically acceptable carrier.

According to one embodiment, the drug delivery system may comprise a drug delivery element 100, an optional outer element 101, one or several protonated positively charged forms of a basic known normally dermally administered drug, e.g. comprising an amine group or any other basic functionality, one or several pharmaceutically acceptable counterions with negative charge, a pharmaceutically acceptable base capable of converting the positively charged form of the one or several known normally dermally administered drugs into a neutral or switterionic form, e.g. a neutral free base, and optionally a pharmaceutically acceptable carrier.

According to one embodiment, the drug delivery system may comprise a drug delivery element 100, an optional outer element 101, a positively charged form of one or several local anesthetics, e.g. a protonated positively charged form of a basic local anesthetic with an amine group or any other basic functionality, one or several pharmaceutically acceptable counterions with negative charge, a pharmaceutically acceptable base capable of converting the positively charged form of the one or several local anesthetics into a neutral or switterionic form, e.g. a neutral free base, and optionally a pharmaceutically acceptable carrier. Examples of basic local anesthetics include, but is not limited to, trimecaine, ropivacaine, prilocaine, mepivacaine, lidocaine, levobupivacaine, etidocaine, cinchocaine, bupivacaine, articaine, tetracaine, proxymetacaine, procaine, propoxyxycaine, piperocaine, dimethocaine, cyclomethycaine, cocaine, chlorprocaine, benzocaine and mixtures thereof, such as e.g. mixtures of lidocaine and prilocaine.

According to one embodiment, the drug delivery system may comprise a drug delivery element 100, an optional outer element 101, one or several neutral medicaments, e.g. medicaments essentially without basic or acidic properties, and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may preferably exist as a solid or semisolid at a temperature of 30 or 40°C or less when being essentially dry and comprising the one or several neutral medicaments. The pharmaceutically acceptable carrier may preferably exist as a liquid, capable of wetting the outer surface of the drug delivery element 100, at a temperature of e.g. 35°C or more, preferably e.g. 20°C or more or 30°C or more, when comprising the one or several neutral medicaments and more than 5% by weight of water, such as more than 10%, 20%, 30%, 40%, 50%, 75% or 90% by weight of water. Suitable pharmaceutically acceptable carriers are well known in the art and include e.g. suitable compounds of formula (V), (VI), (VII) and (VII) depicted in Fig. 10, or the like.
According to one embodiment, medicaments that may be administered
dermally or to mucous membranes by employment of the present drug delivery system
may have a local pharmacological effect. Such medicaments are well known in the art.

According to one embodiment, medicaments that may be administered
dermally or to mucous membranes by employment of the present drug delivery system
may have a systemic pharmacological effect. Such medicaments are well known in the art.

According to one embodiment, the drug delivery system may comprise an
eutectic mixture comprising at least one pharmaceutically active ingredient, which
mixture is having an eutectic point in the moist state at a temperature being less than the
second temperature.

According to one embodiment, the first temperature may be a temperature
which is higher than normal storage, ambient or room temperature, such as higher than
e.g. 25°C or preferably higher than 30°C, more preferably higher than 40°C.

According to one embodiment, the second temperature may be equal to or
lower than an internal body temperature at the site of placement of the drug delivery
system, such as typically lower than e.g. 37°C, preferably lower than 35 or 30°C.

According to one embodiment, the second temperature may be equal to or
lower than an internal body temperature at the site of placement of the drug delivery
system and simultaneously higher than normal storage, ambient or room temperature.
Examples of suitable intervals of the second temperature include 25 to 37°C, more
preferred 27 to 35°C and most preferred 28 to 32°C.

According to one embodiment, the second temperature may be equal to or
lower than the body temperature, e.g. an internal body temperature, at the site of
placement of the drug delivery system and simultaneously higher than normal storage,
ambient or room temperature and the first temperature may be a temperature which is
higher than normal storage, ambient or room temperature. Examples of suitable
combinations of the first and the second temperature include (first temperature / second
temperature): higher than 30°C / lower than 35°C; higher than 40°C / lower than 30°C;
higher than 40°C / 27 to 35°C; and higher than 40°C / 28 to 32°C. Adaption of the drug
delivery system according to any of the latter two combinations allow for optimal long
term storage of the same in a dry inactive state, and release of medicament in the active
moist state only when applied within a body cavity or on e.g. the skin or on a mucous
membrane.

According to one embodiment, the active moist state may be a state which is
entered when the drug delivery element 100 exceeds 5, 10, 20, 30, 40, 50, 60, 70 or 80
%, by weight, of water.

According to one embodiment, the drug delivery system may comprise one or
several integrated container adapted to contain water or an aqueous solution for
enabling provision of water to the drug delivery element 100. The provision of water may be user or condition, e.g. temperature, controlled by the inclusion of one or several pressure sensitive conduits or valves or one or several temperature sensitive and essentially water insoluble plugs, respectively, along the fluid connection between the one or several containers and the drug delivery element 100. When the user increases the internal pressure of the one or several containers, e.g. by applying an external pressure with the fingers, the pressure sensitive conduits or valves open(s) to allow fluid transfer from the containers to the drug delivery element 100. When the temperature of the temperature sensitive and essentially water insoluble plugs increases above a critical temperature, the plugs melt to allow fluid transfer from the containers to the drug delivery element 100. The critical temperature is preferably slightly lower than the temperature of the cavity in which, or the surface onto which, the drug delivery system is applied and higher than the storage temperature of the drug delivery system, at which it is stored before use. Examples of ranges of suitable critical temperatures include 30 to 35 °C, 28 to 33 °C or 32 to 37 °C.

According to one embodiment, the drug delivery system may comprise one or several integrated containers adapted to contain water or an aqueous solution for enabling provision of water to the drug delivery element 100. The provision of water may be temperature controlled by the inclusion of one or several temperature sensitive and essentially water insoluble plugs along the fluid connection between the container and the drug delivery element 100. When the temperature of the temperature sensitive and essentially water insoluble plugs increases above a critical temperature, the plugs melt to allow fluid transfer from the container to the drug delivery element 100. The critical temperature is preferably slightly lower than an abnormally high temperature of the cavity in which, or of the surface onto which, the drug delivery system is applied and higher than the normal temperature of the cavity or surface in/on which the drug delivery system is applied. Examples of ranges of suitable critical temperatures include 36 to 38 °C, 37 to 39 °C, 38 to 40 °C or about 38 °C. Advantages of a drug delivery system with such a temperature sensitive plug include automatic delivery of suitable medicaments triggered by an abnormally high temperature which may be a symptom, e.g. fever, of the condition the medicament is intended to be administered to treat or ameliorate.

**EXAMPLE**

Below follows a non-limiting example of a drug delivery element 100 of the drug delivery system of the invention:

A mixture consisting of room temperature solid carrier in the form of RENEX PEG-1500-FL- (CQ) from Croda Nordica AB (15.23 g), a medicament in the form of powdered licocaine hydrochloride monohydrate (1.37 g) and a base in the form of
powdered potassium carbonate (0.79 g) was rapidly stirred at 60 °C until the solid components were homogenously distributed in the liquid matrix (15 minutes). The mixture was then allowed to reach ambient temperature under continued stirring to yield a white amorphous solid.

The obtained solid (11.18 g) was then heated to 60 °C while stirring until liquefied (10 minutes) and poured onto a water insoluble hydrophilic carrier matrix in the form of medical cotton (3.14 g). The obtained hot mixture was kneaded while cooling to form an exemplary cotton based drug delivery element 100 of the invention in a passive essentially dry state.

To each of a set of empty polypropylene SPE tubes (6 ml) with preassembled bottom polypropylene frits (20 um porosity) was added 0.7 to 1.1 g of the cotton based drug delivery element 100, followed by insertion of top frits of the same kind, one per tube, and application of approximately 10 kg of pressure thereon to compress the cotton based drug delivery element 100 between the bottom- and top-frits. Water (0 to 150 uL) was then injected into the cotton based drug delivery element 100 of each of the tubes by employment of a needle stuck through the bottom-frit. Each of the tubes were then attached at the male luer-fitting to the female luer-fitting of a respective injection needle, with its needle tip stuck into a hard rubber mat, whereby liquid or gaseous transfer was prevented from the bottom of each of the tubes. Addition of ^heptane (2.8 to 3.9 ml) through the top opening of each of the tubes then immediately followed. The tubes were divided into two different groups, each group kept at a temperature of 21 to 23 °C (group I) or at a temperature of 36 to 38 °C (group II). The ^heptane phase of each of the tubes were analyzed by TLC (2 uL applied on silica gel coated 5x10 cm glass-sheets eluted with methylene chloride : methanol 92.5 : 7.5 v : v) at the following time points after water injection: 1, 3 and 6 hours. The concentration of lidocaine was estimated by visual comparison of the intensity of the spots, when visualized under UV (254 nm), with spots of reference solutions of lidocaine and assigned to one of the following categories: < 2mM (low), 2 to 5 mM (medium) and 5 to 10 mM (high).

The amounts of ingredients added to the tubes, calculated water contents and the analytical results are depicted in the tables below.
From the analytical results obtained and within the investigated ranges, it is shown that exemplary drug delivery element 100 releases no or minimal amounts of medicament at a relatively low temperature of 21 to 23 °C, i.e. a normal ambient storage temperature, independent of water content, i.e. independent of existing in an essentially dry or in a moist state. Furthermore, at a relatively high temperature of 36 to 38 °C, i.e. a temperature essentially corresponding to human body temperature, it is shown that release of medicament is positively correlated to the water content, i.e. dependent on the existence in one of an essentially dry state or a moist state.

<table>
<thead>
<tr>
<th>Ingredients charged</th>
<th>Water content of the drug delivery element 100 based on added water (weight-%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Tube #</td>
<td>Ia</td>
</tr>
<tr>
<td>Drug delivery element 100</td>
<td>0.77</td>
</tr>
<tr>
<td>Water (ul) n-heptane (ml)</td>
<td>3.08</td>
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</table>

<table>
<thead>
<tr>
<th>Analytical results [&lt;2 mM (low), 2 to 5 mM (medium) and 5 to 10 mM (high)]</th>
<th>Water content of the drug delivery element 100 based on added water (weight-%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Tube #</td>
<td>Ia</td>
</tr>
<tr>
<td>1 hour</td>
<td>low</td>
</tr>
<tr>
<td>3 hours</td>
<td>low</td>
</tr>
<tr>
<td>6 hours</td>
<td>low</td>
</tr>
</tbody>
</table>

| Tube #                                                                   | IIa | IIb | IIc | IID  | IIe  |
| 1 hour                                                                   | 0.93 | 0.73 | 1.10 | 0.96 | 0.76 |
| 3 hours                                                                   | 0.0  | 29  | 86  | 112  | 119  |
| 6 hours                                                                   | 3.72 | 2.92 | 4.40 | 3.84 | 3.04 |

From the analytical results obtained and within the investigated ranges, it is shown that exemplary drug delivery element 100 releases no or minimal amounts of medicament at a relatively low temperature of 21 to 23 °C, i.e. a normal ambient storage temperature, independent of water content, i.e. independent of existing in an essentially dry or in a moist state. Furthermore, at a relatively high temperature of 36 to 38 °C, i.e. a temperature essentially corresponding to human body temperature, it is shown that release of medicament is positively correlated to the water content, i.e. dependent on the existence in one of an essentially dry state or a moist state.
Although the present invention has been described above with reference to specific illustrative embodiments, it is not intended to be limited to the specific form set forth herein. Any combination of the above mentioned embodiments should be appreciated as being within the scope of the invention. Rather, the invention is limited only by the accompanying claims and other embodiments than the specific above are equally possible within the scope of these appended claims.

In the claims, the term "comprises/comprising" does not exclude the presence of other species or steps. Additionally, although individual features may be included in different claims, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms "a", "an", "first", "second" etc do not preclude a plurality.
1. Drug delivery system for water triggered administration of medicament, having an elongated tubular form adapted for placement in a body cavity, or being shaped as a sheet adapted for placement on a surface, of the body of a human or animal, comprising a drug delivery element (100), wherein said drug delivery element (100) is having a passive essentially dry state and an active moist state; said drug delivery element (100) is comprising an essentially water insoluble hydrophilic carrier matrix being a porous or fibrous polysaccharide and a set of additional components being (i), (ii), (iii) and (iv), or (iv) and (v), wherein (i) being at least one protonated positively or deprotonated negatively charged form of said medicament, (ii) being at least one negatively or positively charged counterion accompanying said protonated positively or deprotonated negatively charged form of said medicament, respectively, to maintain electric neutrality, (iii) being a base or acid capable of reacting with and generating the neutral or zwitterionic form of said protonated positively or deprotonated negatively charged form of said medicament, respectively, in said active moist state, (iv) being a suitable pharmaceutically acceptable carrier, and (v) being at least one neutral or zwitterionic medicament; essentially all of each existing component of (i), (ii), (iii), (iv) and (v) being arranged and immobilized within said carrier matrix in said passive essentially dry state, whereby essentially no pharmaceutically effective amount of said medicament is released from the outer surface of said drug delivery element (100); at least one neutral or zwitterionic form of said medicament being released from said outer surface of said drug delivery element (100) in said active moist state, by existing in a liquid form or by being dissolved, dispersed, emulsified or suspended in a liquid form of said pharmaceutically acceptable carrier; and said active moist state being a state in which the total water content of said drug delivery element (100) exceeds 5%, by weight.

2. Drug delivery system according to claim 1, wherein said carrier matrix comprises cellulose or modified cellulose.

3. Drug delivery system according to any one of the preceding claims, wherein each existing component of (i), (ii), (iii), (iv) and (v) are immobilized at a temperature below a first temperature, said first temperature being a temperature being equal to or exceeding 25°C, when said drug delivery element (100) is existing in said passive essentially dry state by:
   - existing in a solid form or a semisolid form,
- by being entrapped in another solid or semisolid form of another component selected from (i), (ii), (iii), (iv) and (v) by being dissolved, dispersed, emulsified or suspended therein, or by strong molecular interaction or covalent binding thereto, or
- by being attached to said carrier matrix by strong molecular interaction or covalent bonding.

4. Drug delivery system according to any one of the preceding claims, wherein said pharmaceutically acceptable carrier or the corresponding is having a phase transition temperature associated with the transition from a solid or semisolid form to a liquid form at a temperature which is equal to a second temperature, said second temperature being a temperature which is lower than or equal to 37°C, when said drug delivery element (100) is existing in said active moist state.

5. Drug delivery system according to any one of the preceding claims, wherein said set of additional components comprise (i), (ii), (iii) and (iv).

6. Drug delivery system according to claim 5, wherein said base or acid is attached to said carrier matrix by strong molecular interaction or covalent bonding.

7. Drug delivery system according to claim 5 or 6, wherein:
   (i) is at least one protonated positively charged medicament;
   (ii) is at least one negatively charged counterion;
   (iii) is a base; and
   (iv) is selected from one or several of the group consisting of
8. Drug delivery system according to any one of the preceding claims, for administration of said medicament to mucous membranes.

9. Drug delivery system according to any one of the preceding claims, for transdermal or local administration of said medicament to the skin.

10. Drug delivery system according to any one of the preceding claims, wherein said medicament is administrated to the female reproductive organs.

11. Drug delivery system according to any one of the preceding claims, wherein said medicament is having a pharmaceutical effect at a location of said body which is essentially the same as the location of said body onto which said drug delivery system is placed when in use.

12. Drug delivery system according to any one of the preceding claims, wherein said medicament is having a pharmaceutical effect at a location of said body which is different from the location of said body onto which said drug delivery system is placed when in use.
13. Drug delivery system according to any one of the preceding claims, wherein said medicament is selected from the group consisting of medicaments with at least one basic functional group, medicaments with at least one acidic functional group, medicaments with no essentially basic or acidic functional groups and zwitterionic medicaments.

14. Drug delivery system according to any one of the preceding claims, wherein said medicament is at least one local anesthetic.

15. Drug delivery system according to any one of claims 4 to 14, wherein said medicament is an eutectic mixture comprising at least one pharmaceutically active ingredient, which mixture is having an eutectic point in said moist state at a temperature being less than said second temperature.

16. Drug delivery system according to any one of the preceding claims, comprising at least one integrated container (103) adapted to contain water or an aqueous solution, for enabling provision of water to said drug delivery element (100) to accomplish transition from said passive essentially dry state to said active moist state.

17. Drug delivery system according to claim 16, further comprising at least one pressure sensitive conduit or valve (102) having an inlet connected to said container (103) and an outlet connected to said drug delivery element (100), said conduit or valve (102) being adapted to be closed at a pressure being less than a first internal pressure of said container (103) to prevent liquid transfer from said container to said drug delivery element (100), and said conduit or valve (102) being adapted to be open at a pressure exceeding a second internal pressure of said container (103) to permit liquid transfer from said container (103) to said drug delivery element (100), for user initiated transition from said passive essentially dry state to said active moist state by application of external pressure to said container (103) to increase the internal pressure thereof.

18. Drug delivery system according to claim 16 or 17, comprising at least one conduit or valve (102) having an inlet connected to said container (103) and an outlet connected to said drug delivery element (100), wherein said conduit or valve (102) is provided with at least one temperature sensitive and essentially water insoluble plug (107) having a melting point within the range of 30°C to 40°C, said plug (107) being solid at a temperature below its melting point to prevent liquid transfer from said container (103) to said drug delivery element (100), and said plug (107) being liquid at a temperature above its melting point to permit liquid transfer from said container (103) to said drug delivery element (100).
Fig. 1

Fig. 2
INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2015/050279

A. CLASSIFICATION OF SUBJECT MATTER

IPCs: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61 K, A61 L, A61 M

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

SE, DK, FI, NO classes as above

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

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 200406481 1 A1 (MAGLE AB ET AL), 5 August 2004 (2004-08-05); claims</td>
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<td>Y</td>
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<tr>
<td>X</td>
<td>US 7175853 B1 (BRACHT STEFAN), 13 February 2007 (2007-02-1 3); abstract; claims</td>
<td>1-15</td>
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Date of the actual completion of the international search
22-06-2015

Date of mailing of the international search report
23-06-2015

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International Patent Classification (IPC)

A61K9/14 (2006.01)
A61K 5/70 (2006.01)
A61L 75/44 (2006.01)
A61M37/00 (2006.01)
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