pharmaceutically acceptable salts thereof and at least one non-ionic cellulose ether, such as hydroxypropylmethylcellulose (HPMC).

This stabilizing effect of the non-ionic cellulose ether is further supported by said pharmaceutical composition having a low pH, such as within the range of between about 3 and 4, such as within the range of between about 3 and 3.5. This will make it possible to store oxytocin in room temperature for longer periods of time than previously possible, when present in such a pharmaceutical composition. A favourable environment for the oxytocin peptide in such a pharmaceutical composition should also positively affect its biological activity thereby improving its therapeutic effect as more biologically active substance is present therein throughout time.

Hence, the present invention relates to pharmaceutical compositions comprising oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7), and at least one non-ionic cellulose ether, such as hydroxypropylmethylcellulose (HPMC), said pharmaceutical composition having a pH within the range of between about 3 and 4, such as about 3 and 3.5, or as otherwise exemplified herein, wherein the stability of oxytocin and/or one or more fragment(s) and/or variant(s) thereof has been improved. The ability of a non-ionic cellulose ether, such as HPMC, to stabilize oxytocin is not previously known and is highly desirable, as it has been a long felt need in the art to provide pharmaceutical compositions comprising oxytocin that do not always need to be stored in a cold environment, and which are thereby easier to handle.

The present invention also relates to medical uses of a pharmaceutical composition as disclosed herein, such as in the treatment of vaginal atrophy. Hence, in other aspects the present invention also relates to the use of oxytocin, and/or one or more fragment(s) and/or variant(s) thereof and at least one non-ionic cellulose ether as disclosed herein in the manufacture of a medicament, said medicament having a pH within the range of between about 3 and 4 for the treatment of a climacteric disorder, such as vaginal atrophy. In addition, the invention relates to a method for preparing said pharmaceutical composition, as well as methods of treating a patient with a pharmaceutical composition according to the invention.

Detailed description

Definitions

Whenever “oxytocin”,“oxytocin peptide” and/or “oxytocin molecule” is referred to herein, this encompasses oxytocin (SEQ ID NO:1) and/or one or more fragment(s) and/or variant(s) thereof as defined herein according to the general formula SEQ ID NO:2, or any other variant and/or fragment as mentioned herein, as well as analogues and/or homologues thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7) . Whenever a fragment, variant or homologue of an oxytocin molecule/peptide is envisaged it is to be understood that such a variant, fragment or homologue encompasses a biological activity comparable to the oxytocin molecule itself (SEQ ID NO:1). As an example, it can be shown that a substance has oxytocin activity by performing tests showing the activity of the actual substance, e.g. by performing a double blind cross-over randomised protocol as described in WO0178758 (Example 1).

Accordingly, a “variant” of oxytocin as referred to herein, refers to a peptide which has been varied in its amino acid structure as compared to the oxytocin molecule in that some amino acid positions may have been altered by introducing other amino acids in such positions, such as natural or unnatural amino acids as exemplified herein, or it may have been extended by adding one or more natural or unnatural amino acid(s) to either ends of the peptide. In addition, other structural variations may also have been performed to the present peptides as referred to herein, such as synthetic modifications. Said “variant” still maintains a biological activity similar to oxytocin and said oxytocin variant is also stabilized by being present in a pharmaceutical composition according to the present invention.

Furthermore, a “fragment” of oxytocin, as referred to herein is a peptide which comprises a part of the amino acid sequence of oxytocin, but wherein one or more amino acids may have been removed from one or both of the amino acid terminal end(s). This term also refers to a fragment of a oxytocin variant as defined in SEQ ID NO:2, hence meaning that also encompassed by the present invention is any fragment of a peptide as presented by SEQ ID NO:2.

A “pH regulating agent” is any agent, such as a liquid agent, such as an aqueous liquid, which is able to regulate and/or maintain the pH of said pharmaceutical composition, wherein said pH is kept approximately in a selected range, which selected range is exemplified herein. Such a pH regulating agent can for example be a buffer, such as a

In combination, this provides an excellent composition for pharmaceutical use, wherein the biological and/or therapeutic activity of oxytocin and/or a variant and/or a fragment thereof as exemplified herein should be increased and prolonged. This pharmaceutical composition is also easier to handle for the user, as due to its improved stability it need not always be stored in a cool environment, but can instead more conveniently be kept in room temperature, e.g. during use or storage, still retaining its biological activity.

The stabilizing effect of a non-ionic cellulose ether on the oxytocin molecule in a pharmaceutical composition of the present invention is in contrast to other used pharmaceutical carriers, such as for example sodium carboxymethylcellulose (CMC), in which formulation oxytocin has been shown to more rapidly degrade and/or aggregate (see for example the comparative examples in the experimental section). Without being bound by a specific theory, this could be due to the fact that the CMC polymer is negatively charged and may be regarded as a polyanion which could interact unfavourably with the oxytocin peptide.

Accordingly, the present invention relates to a pharmaceutical composition comprising

a. oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof; and
b. at least one non-ionic cellulose ether;

wherein SEQ ID NO:2 is

X_1-X_2-X_3-X_4-Asn-Cys-X_5-X_6-X_7-X_8-NH_2

wherein

X_1 is selected from the group consisting of Cys and nothing;

X_2 is selected from the group consisting of Tyr, Phe, and nothing;

X_3 is selected from the group consisting of Ile, Val, Hoph, Phe, Cha, and nothing;

X_4 is selected from the group consisting of Gln, Ser, Thr, Cit, Arg, and Daba;

X_5 is selected from the group consisting of Pro and nothing;

X_6 is selected from the group consisting of Ile, Leu, nothing, Val, Hos, Daba, Thr, Arg, and Cit;

X_7 is selected from the group consisting of Gly, nothing, and Ala;

X_8 is selected from the group consisting of Gly and nothing;

wherein said pharmaceutical composition has a pH within the range of between about 3 and about 4, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7).

In one aspect on the present invention, when X_1 is Cys then a disulfide is formed between X_1 and Cys.

Accordingly, it is to be understood that when X_1 in formula (I) is cysteine (Cys) then the thiol group of X_1 may form a disulfide with the thiol group of the cystein that is located between the asparagine (Asn) and X_5 thereby forming a cyclic structure of formula (Ia):



In a further aspect, there is provided a pharmaceutical composition comprising oxytocin (SEQ ID NO:1) and hydroxypropylmethylcellulose, and wherein the pH of said pharmaceutical composition is within the range of between about 3 and 4, such as between about 3 and 3.5, or as otherwise exemplified herein.

In a further aspect, the present invention also relates to a pharmaceutical composition consisting of a non-ionic cellulose ether and oxytocin (SEQ ID NO:1), and/or a variant and/or a fragment thereof as presented herein (SEQ ID NO:2), as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7), and a pH regulating agent, wherein said pharmaceutical composition has a pH within the range of between about 3 and 4, such as within the range of about 3 and about 3.5. In one aspect, said pharmaceutical composition consists of oxytocin (SEQ ID NO:1), hydroxypropylmethylcellulose (HPMC), and a pH regulating agent, wherein said pharmaceutical composition has a pH within the range of between about 3 and 4, such as between about 3 and about 3.5, or as otherwise exemplified herein. In one aspect, said pH regulating agent is a buffer, such as a citrate or a lactate buffer.

In one aspect of the present invention, said pharmaceutical composition comprises oxytocin, i.e. when X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is nothing in SEQ ID NO:2, (Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2) (SEQ ID NO:1).

The one or more variant(s) and/or fragment(s) of oxytocin of said pharmaceutical composition (SEQ ID NO:2) can also be selected from the group consisting of the following compounds, as well as pharmaceutically acceptable salts thereof:

Mesotocin: Cys-Tyr-Ile-Gln -Asn-Cys-Pro-Ile-Gly-NH_2 (SEQ ID NO:3)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Ile, X_7 is Gly, and X_8 is nothing;

Isotocin: Cys-Tyr-Ile-Ser-Asn-Cys-Pro-Ile-Gly-NH_2 (SEQ ID NO:4)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Ser, X_5 is Pro, X_6 is Ile, X_7 is Gly, and X_8 is nothing;

Annetocin: Cys-Phe-Val-Arg- Asn-Cys-Pro-Thr-Gly-NH_2 (SEQ ID NO:5)
X_1 is Cys, X_2 is Phe, X_3 is Val, X_4 is Arg, X_5 is Pro, X_6 is Thr, X_7 is Gly, and X_8 is nothing;

Vasotocin: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Arg-Gly-NH_2 (SEQ ID NO:6)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Arg, X_7 is Gly, and X_8 is nothing;

~~Vasopressin: Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2 (SEQ ID NO:7)~~
~~X_1 is Cys, X_2 is Tyr, X_3 is Phe, X_4 is Gln, X_5 is Pro, X_6 is Arg, X_7 is Gly, and X_8 is nothing;~~

Cys-Tyr-Ile-Gln-Asn-Cys-NH_2 (SEQ ID NO:8)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, and X_5-X_8 is nothing;

Cys-Tyr-Ile-Gln-Asn-Cys-Pro-NH_2 (SEQ ID NO:9)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, and X_6-X_8 is nothing;

Cys-Tyr-Ile-Gln- Asn-Cys-Pro-Leu-NH_2 (SEQ ID NO:10)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Leu, and $X_{7\text{-}8}$ is nothing;

Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 (SEQ ID NO:11)
X_1 is nothing, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is nothing;

Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2 (SEQ ID NO:12)
X_1-X_2 is nothing, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is nothing;

Gln-Asn-Cys-Pro-Leu-Gly-NH_2 (SEQ ID NO:13)
X_1-X_3 is nothing, X_4 is Gln, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is nothing;

Ile-Gln-Asn-Cys-Pro-NH_2 (SEQ ID NO:14)
X_1-X_2 is nothing, X_3 is Ile, X_4 is Gln, X_5 is Pro, and X_6-X_8 is nothing;

Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-Gly-NH_2 (SEQ ID NO:15)
X_1 is Cys, X_2 is Tyr, X_3 is Ile, X_4 is Gln, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is Gly;

Gln-Asn-Cys-Pro-Leu-Leu-NH_2 (SEQ ID NO:16)
X_1-X_3 is nothing, X_4 is Gln, X_5 is Pro, X_6 is Leu, X_7 is Leu, and X_8 is nothing;

Cys-Tyr-Val-Thr-Asn-Cys-Pro-Leu-Gly-NH_2 (SEQ ID NO:17)
X_1 is Cys, X_2 is Tyr, X_3 is Val, X_4 is Thr, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is nothing;

Cys-Tyr-Hoph-Thr-Asn-Cys-Pro-Val-Gly-NH_2 (SEQ ID NO:18)
X_1 is Cys, X_2 is Tyr, X_3 is Hoph, X_4 is Thr, X_5 is Pro, X_6 is Val, X_7 is Gly, X_8 is nothing;

Cys-Tyr-Phe-Cit-Asn-Cys-Pro-Leu-Gly-NH_2 (SEQ ID NO:19)
X_1 is Cys, X_2 is Tyr, X_3 is Phe, X_4 is Cit, X_5 is Pro, X_6 is Leu, X_7 is Gly, and X_8 is nothing;

Cys-Tyr-Cha-Arg-Asn-Cys-Pro-Hos-Ala-NH_2 (SEQ ID NO:20)
X_1 is Cys, X_2 is Tyr, X_3 is Cha, X_4 is Arg, X_5 is Pro, X_6 is Hos, X_7 is Ala, and X_8 is nothing;

Cys-Tyr-Val-Daba-Asn-Cys-Pro-Daba-Ala-NH_2 (SEQ ID NO:21)
X_1 is Cys, X_2 is Tyr, X_3 is Val, X_4 is Daba, X_5 is Pro, X_6 is Cit, X_7 is Ala, and X_8 is nothing;

Cys-Tyr-Hoph-Daba-Asn-Cys-Pro-Cit-Ala-NH_2 (SEQ ID NO:22)
X_1 is Cys, X_2 is Tyr, X_3 is Hoph, X_4 is Daba, X_5 is Pro, X_6 is Cit, X_7 is Ala, and X_8 is nothing;

Cys-Tyr-Phe-Arg-Asn-Cys-Pro-Val-Ala-NH_2 (SEQ ID NO:23)
X_1 is Cys, X_2 is Tyr, X_3 is Phe, X_4 is Arg, X_5 is Pro, X_6 is Val, X_7 is Ala, and X_8 is nothing; and

Cys-Tyr-Cha-Cit-Asn-Cys-Pro-Arg-Gly-NH_2 (SEQ ID NO:24)
X_1 is Cys, X_2 is Tyr, X_3 is Cha, X_4 is Cit, X_5 is Pro, X_6 is Arg, X_7 is Gly, X_8 is nothing;

Accordingly, in one aspect, the present invention relates to a pharmaceutical composition, wherein said one or more fragment(s) and/or variant(s) of oxytocin is/are selected from the group consisting of the peptides corresponding to SEQ ID NO:3-6 and SEQ ID NO:8-24.

The unnatural amino acids in said substances have the following structures:

least 50, 60, 70, 80, 90, 95, 96, 97, 98, or 99 % sequence identity to oxytocin, said variants showing an oxytocin activity, as defined herein, with the proviso that said variant is not vasopressin (SEQ ID NO:7).

Annetocin has been isolated from the earthworm, as described in Oumi T. Ukena K, Matsushima O, Ikeda T, Fujita T, Minakata H, Nomoto K, Annetocin: an oxytocin-related peptide isolated from the earthworm, Eisenia foetida, Biochem Biophys Res Commun 1994, January 14; 198(1); 393-399.

There is also a possibility to create new compounds with oxytocin activity by means of computer simulation. Methods for computer simulation are known by a person skilled in the art, e.g. as described in EP 0660 210 A2.

The invention also relates to a pharmaceutical composition comprising oxytocin or a variant thereof in both D- and L-form, as well as racemates thereof. In certain aspects the invention relates to the L-form. By inversion of the peptide sequence thereof, the D-form could be converted to the L-form. These and the peptides above can be produced by methods known to a person skilled in the art, e.g. according to Merrifield, P. B., "Solid Phase Synthesis", Angew. Chemie, 1985, No. 97, p. 801.

The pharmaceutical compositions according to the invention may in certain circumstances contain substances that extend or strengthen the effects of oxytocin. Such substances could increase the release of oxytocin and/or the member or affinity of oxytocin receptors, such as oestrogen, or drugs having an [alpha]$_2$-agonistic effect, such as clonidine.

It should be noted that pharmaceutically acceptable salts of the compounds according to the invention are included within the scope of the invention. Examples of salts of the compounds are pharmaceutically acceptable acid and base addition salts.

The expression "pharmaceutically acceptable acid addition salts" are intended to be any non-toxic organic or inorganic acid addition salt of the compounds of SEQ ID NO: 1 or SEQ ID NO: 2, and/or any other variants and/or fragments of oxytocin as described herein. Examples of illustrative inorganic acids that form suitable salts are hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and acid metal salts such as sodium monohydrogen ortophosphate and potassium hydrogensulphate. Examples of illustrative organic acids that form suitable salts are mono-, di-and tricarboxylic acids. Examples of such acids are acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic

The pH of the pharmaceutical compositions described in the above are within the range of between about 3 and 4, such as about 3 to about 3.5 or about 3.1 to about 3.6 or about 3.2 to about 3.5, or as further exemplified herein.

The concentration of the at least one non-ionic cellulose ether, such as hydroxypropylmethylcellulose (HPMC) is provided in relation to the pH regulating agent of the pharmaceutical composition, such as a buffer, as presented herein, e.g. 2 wt% or 3 wt% non-ionic cellulose ether in 25 mM buffer provides a certain viscosity due to the amount of the at least one non-ionic cellulose ether present in said buffer. Accordingly, the concentration of the non-ionic cellulose ether is presented in weight % (wt%) in said buffer, or other pH regulating agent. In the total pharmaceutical composition, the amount of non-ionic cellulose ether is somewhat less due to the addition of the therapeutic substance (oxytocin and/or one or more fragment(s) and/or variant(s) thereof as disclosed herein) to said composition.

The concentration of oxytocin and/or one or more fragment(s) and/or variant(s) thereof as defined herein is provided in relation to the total pharmaceutical composition, i.e. the buffer and the non-ionic cellulose ether, and optionally other additives such as a preservative. Hence, 1 mg/g oxytocin means that 1 mg oxytocin is present in 1g of total pharmaceutical composition. In addition, as previously mentioned herein, 1mg/ml means that 1 mg of oxytocin is present in 1ml of total pharmaceutical composition

In the context of the present invention, a dosage form of oxytocin, and/or one or more fragment(s) and/or variant(s) thereof administered to a subject in need thereof may comprise between about 50 and 600 IU of oxytocin and/or one or more fragment(s) and/or variant(s) thereof as defined herein, such as about 100, 200, 250, 300, 350 or 400 IU. One international unit (IU) of oxytocin is the equivalent of about 1,67 micrograms of pure peptide. Accordingly, a composition of 1 g of oxytocin gel, 400 IU, is equivalent to about 0.67 mg/g (*Ph Eur*).

The present invention also relates to the pharmaceutical compositions as disclosed herein for use as medicaments. In one aspect of the present invention, the invention relates to a pharmaceutical composition comprising oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7), and hydroxypropylmethylcellulose (HPMC),

The pharmaceutical compositions as defined herein are all encompassed for topical use, such as for vaginal use. When for vaginal use, this could be for the treatment of a climacteric disorder, such as vaginal atrophy or any other disorders mentioned in WO0178758. Hence, in one aspect the present invention relates to a pharmaceutical composition comprising oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof and hydroxypropylmethylcellulose (HPMC), optionally in combination with buffers, other pH regulating agents or additional components as exemplified herein, such as benzoic acid for vaginal use, such as for the treatment of a climacteric disorder, e.g. vaginal atrophy. The pH of such a pharmaceutical composition can be within the range of about 3 to about 4, such as about 3 to about 3.5, about 3.1 to about 3.6 or about 3.1 to about 3.8, or as otherwise exemplified herein.

In all aspects of the present invention, it is to be understood that whenever it is referred to a certain medical use of said pharmaceutical composition, such as in the use in treating vaginal atrophy, this also refers to the use of oxytocin and/or one or more fragment(s) and/or variant(s) thereof, as defined herein, and at least one non-ionic cellulose ether in the manufacture of a medicament for the treatment of the certain disease, such as exemplified herein, wherein said medicament has a pH within the range of between about 3 and 4, such as about 3 and 3.5, or as further exemplified herein.

As shown herein, the presence of at least one non-ionic cellulose ether in the pharmaceutical composition effectively improves the stability of the oxytocin molecule therein. Hence, the present invention also relates to the use of at least one non-ionic cellulose ether for stabilizing, alternatively improving the stability of a pharmaceutical composition comprising oxytocin (SEQ ID NO:1) and/or one or more fragment(s) and/or variant(s) of oxytocin, as defined in SEQ ID NO:2 or as otherwise defined herein, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7). In one aspect, the invention relates to the use of the at least one non-ionic cellulose ether hydroxypropylmethylcellulose (HPMC) for stabilizing, alternatively improving the stability a pharmaceutical composition comprising oxytocin (SEQ ID NO:1) and/or a fragment and/or a variant of oxytocin, as well as pharmaceutically acceptable salts thereof as defined in SEQ ID NO:2, or as otherwise defined herein, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7), said pharmaceutical composition optionally in addition comprising a buffer, other pH regulating agents or additional components as exemplified herein, such as a preservative. As previously mentioned herein, the combination of using a low pH in the pharmaceutical composition further improves the

stabilizing effect of the at least one non-ionic cellulose ether. Without being bound by a specific theory, the at least one non-ionic cellulose ether appears to stabilize the oxytocin molecule and/or one or more fragment(s) and/or variant(s) thereof as defined herein by making it less prone to degradation and/or aggregation or other structural changes, potentially by not interfering with the oxytocin molecule.

Whenever it is referred to an improved stability/stabilizing effect herein, this may mean the reduction of aggregation and/or degradation or other structural changes of the oxytocin molecule in the pharmaceutical composition defined herein, but is not bound to this specific theory. In accordance with such a theory, a reduction in aggregation and/or degradation or other structural changes is accompanied by an improved stability of the oxytocin molecule. The improvement in stability by a pharmaceutical composition comprising at least one non-ionic cellulose ether is further illustrated in the experimental section comprising comparative examples with the gel CMC.

In another aspect, the present invention relates to a method for preparing a pharmaceutical composition with improved stability comprising the steps of:
a) preparing a buffer solution and adjusting the pH thereof,
b) adding oxytocin (SEQ ID NO: 1) and/or one or more fragment(s) and/or variant(s) thereof in accordance with SEQ ID NO:2 or as otherwise defined herein, as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7), to said buffer, and
c) adding at least one non-ionic cellulose ether to the solution obtained in step b);
wherein optionally a preservative, such as benzoic acid, is added to the buffer solution of step a) before said oxytocin (SEQ ID NO:1) and/or one or more fragment(s) and/or variant(s) thereof in accordance with SEQ ID NO:2 or as otherwise defined herein is/are added to said buffer solution and wherein the pH of said pharmaceutical composition is regulated to fall within the range of between about 3 and about 4, such as within the range of about 3 and about 3.5, or as otherwise exemplified herein. After step c) the solution is left for a while to obtain a viscous solution or a gel. Typically, said viscous solution or gel is obtained after about 1-2 days. Said method also in some aspects encompasses the use of other pH regulating agents than buffers, such as organic and inorganic acids and bases, such as acetic acid, citric acid, phosphoric acid and hydrochloric acid and sodium hydroxide, which would hence be used in step a) of said method.

In the present method, what is intended is that it is the stability of oxytocin, and/or one or more fragment(s) and/or variant(s) thereof as disclosed herein that is improved by

wherein oxytocin, and/or said one or more fragment(s) and/or variant(s) thereof is/are present in an amount of about 0.1 to 1.5 mg/g, such as 0.5 to about 1.5 mg/g, about 0.5 to about 1mg/g, about 0.5 to about 1.2 mg/g, about 0.2 to about 0.5 mg/g, about 0.1 to about 0.8 mg/g, or about 0.2 to about 1.2 mg/g of the total composition, and wherein said at least one non-ionic cellulose ether is present in an amount of about 1-3 wt%, such as about 2 wt% or 3 wt% in a pH regulating agent, such as a buffer, said buffer having a concentration of about 25 mM to about 100 mM. In one aspect, said at least one non-ionic cellulose ether is hydroxypropyl methylcellulose, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7).

In some aspects, the pharmaceutical compositions according to the present invention can optionally comprise other components, such as inert components or components having a physical or biological function. In some aspects, an antibiotic or an analgesic is additionally present in a pharmaceutical composition according to the invention.

The invention also relates to a method for treating a climacteric disorder, such as vaginal atrophy, in a patient in need thereof comprising administering a suitable amount of a pharmaceutical composition comprising

a. oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7); and
b. at least one non-ionic cellulose ether;

to a patient in need thereof, wherein the pH of said pharmaceutical composition is within the range of between about 3 and 4, or as otherwise exemplified herein. Said pharmaceutical composition for use in a method for treating a climacteric disorder can be any pharmaceutical composition as disclosed herein. In one aspect said pharmaceutical composition which is administered to a patient in need thereof comprises oxytocin and hydroxypropylmethylcellulose (HPMC).

The present invention also relates to a method for treating any disorder as previously mentioned herein comprising administering a suitable amount of a pharmaceutical composition comprising

a. oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7); and
b. at least one non-ionic cellulose ether;

In another aspect, the present invention relates to a pharmaceutical composition comprising about: 0.2 mg/g oxytocin, 3 wt% hydroxypropylmethylcellulose in a 22 mM lactate buffer, and optionally 1 mg/g benzoic acid.

As previously mentioned herein, a dosage form of a pharmaceutical composition comprising oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof as defined herein, may comprise between about 50 and 600 IU of oxytocin and/or one or more fragment(s) and/or variant(s) thereof as defined herein, such as about 100, 200, 250, 300, 350 or 400 IU.

The present invention also relates to a kit comprising a pharmaceutical composition comprising

a. oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7); and
b. at least one non-ionic cellulose ether;

and a dispenser for dispensing said pharmaceutical composition optionally in combination with instructions for use of said pharmaceutical composition, wherein the pH of said pharmaceutical composition is within the range of between about 3 and 4, or as otherwise exemplified herein. In a kit as presented herein, any pharmaceutical composition as disclosed herein can be used. Said dispenser present in said kit may e.g. be in the form of a plastic tube. The kit may also comprise one or more containers each comprising one or more of a pharmaceutically acceptable carrier, adjuvant and/or excipient.

The pharmaceutical composition disclosed herein may e.g. be an aqueous composition comprising the oxytocin and the non-ionic cellulose ether.

The present invention is illustrated in the following experimental section, but is not intended to be limited thereto.

Claims

1. A pharmaceutical composition comprising
    a. oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof; and
    b. at least one non-ionic cellulose ether;

    wherein SEQ ID NO:2 is

    X_1-X_2-X_3-X_4-Asn-Cys-X_5-X_6-X_7-X_8-NH_2

    wherein

    X_1 is selected from the group consisting of Cys and nothing;

    X_2 is selected from the group consisting of Tyr, Phe, and nothing;

    X_3 is selected from the group consisting of Ile, Val, Hoph, Phe, Cha, and nothing;

    X_4 is selected from the group consisting of Gln, Ser, Thr, Cit, Arg, and Daba;

    X_5 is selected from the group consisting of Pro and nothing;

    X_6 is selected from the group consisting of Ile, Leu, nothing, Val, Hos, Daba, Thr, Arg, and Cit;

    X_7 is selected from the group consisting of Gly, nothing, and Ala;

    X_8 is selected from the group consisting of Gly and nothing;

    wherein said pharmaceutical composition has a pH within the range of between 3 and 4, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7).
2. A pharmaceutical composition according to claim 1, wherein said one or more fragment(s) and/or variant(s) of oxytocin is/are selected from the group consisting of the peptides corresponding to SEQ ID NO:3-6 and 8-24.
3. A pharmaceutical composition according to claim 1 or 2, wherein said pH is within the range of between 3 and 3.8.
4. A pharmaceutical composition according to any of claims 1-3, wherein said pH is within the range of between 3 and 3.5.
5. A pharmaceutical composition according to any of the preceding claims, wherein said pH is within the range of between 3 and 3.3.
6. A pharmaceutical composition according to any of the preceding claims, wherein the pH of said composition is regulated by adding a pH regulating agent to said composition.
7. A pharmaceutical composition according to claim 6, wherein said pH regulating agent is a buffer.

19. A pharmaceutical composition according to any of the preceding claims for vaginal use.
20. A pharmaceutical composition according to any of the preceding claims for use in the treatment of a climacteric disorder, such as vaginal atrophy.
21. Use of at least one non-ionic cellulose ether for improving the stability of a pharmaceutical composition comprising oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2 as defined in claim 1 or 2.
22. Use according to claim 21, wherein said at least one non-ionic cellulose ether is hydroxypropylmethylcellulose (HPMC).
23. Use according to claim 21, wherein said pharmaceutical composition is as defined in any of claims 1-16.
24. Method for preparing a pharmaceutical composition with improved stability comprising the steps of:

    a) preparing a buffer solution and adjusting the pH thereof,

    b) adding oxytocin and/or one or more fragment(s) and/or variant(s) thereof as defined in claim 1, to said buffer solution, and thereafter

    c) adding at least one non-ionic cellulose ether to the solution obtained in step b);

    wherein optionally a preservative, such as benzoic acid, is added to the buffer solution of step a) before said oxytocin and/or one or more fragment(s) and/or variant(s) thereof is/are added to said buffer solution,

    and wherein the pH of said pharmaceutical composition is regulated to fall within the range of between 3 and 4, such as within the range of 3 and 3.5.
25. Method according to claim 24, for the preparation of a pharmaceutical composition according to any of claims 1-16 or 27-28.
26. Method according to any of claims 24-25, wherein said at least one non-ionic cellulose ether is hydroxypropylmethylcellulose (HPMC).
27. A pharmaceutical composition comprising
    a. oxytocin (SEQ ID NO:1), and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, as well as pharmaceutically acceptable salts thereof; and
    b. at least one non-ionic cellulose ether;

    wherein SEQ ID NO:2 is

    X_1-X_2-X_3-X_4-Asn-Cys-X_5-X_6-X_7-X_8-NH_2

    wherein

X_1 is selected from the group consisting of Cys and nothing,
X_2 is selected from the group consisting of Tyr, Phe, and nothing,
X_3 is selected from the group consisting of Ile, Val, Hoph, Phe, Cha, and nothing, X_4 is selected from the group consisting of Gln, Ser, Thr, Cit, Arg, and Daba,
X_5 is selected from the group consisting of Pro, and nothing,
X_6 is selected from the group consisting of Ile, Leu, nothing, Val, Hos, Daba, Thr, Arg, and Cit,
X_7 is selected from the group consisting of Gly, nothing, and Ala,
X_8 is selected from the group consisting of Gly, and nothing,
wherein said oxytocin and/or one or more fragment(s) and/or variant(s) thereof according to SEQ ID NO:2, or a pharmaceutically acceptable salt thereof is/are present in said pharmaceutical composition in a concentration of about 0.5 to about 1.5 mg/g of the total pharmaceutical composition, and said at least one non-ionic cellulose ether is present in an amount of about 1-3 wt%, such as about 2 or 3 wt%, in a pH regulating agent, such as a buffer, said pH regulating agent having a concentration of between about 25 mM to about 100 mM, with the proviso that said oxytocin variant is not vasopressin (SEQ ID NO:7).

28. A pharmaceutical composition according to claim 27, wherein said at least one non-ionic cellulose ether is hydroxypropyl methylcellulose and is present in an amount of about 2 wt% in a buffer with a concentration of about 25 mM, said buffer being a lactate buffer or a citrate buffer.
29. Use of a pharmaceutical composition according to any one of claims 1-16 or 27-28 in the manufacture of a medicament for the treatment and/or prevention of a climacteric disorder.
30. Use according to claim 29, wherein said disorder is vaginal atrophy.
31. A kit comprising a pharmaceutical composition according to any one of claims 1-16 or 27-28 and a dispenser for said pharmaceutical composition, optionally in combination with instructions for use of said pharmaceutical composition.