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(54) Title: AQUEOUS GELLING COMPOSITIONS OF SOLUBLE ACTIVE PHARMACEUTICAL PEPTIDES PROVIDING MODIFIED RELEASE

(57) Abstract: The present invention relates to an aqueous pharmaceutical composition comprising a peptide as the active ingredient, and one or more water-soluble or water-dispersible gelling agents.

AQUEOUS GELLING COMPOSITIONS OF SOLUBLE ACTIVE PHARMACEUTICAL PEPTIDES PROVIDING MODIFIED RELEASE

The present invention relates to an aqueous pharmaceutical composition comprising one or more water-soluble or water-dispersible gelling agents and a peptide as the active substance, in particular a peptide as melanocortin receptor ligand.

Melanocortins are a family of regulatory peptides which are formed by post-translational processing of pro-hormone pro-opiomelanocortin. Melanocortins have been found in a wide variety of normal human tissues including the brain, adrenal, skin, testis, spleen, kidney, ovary, lung, thyroid, liver, colon, small intestine and pancreas. Melanocortin peptides have been shown to exhibit a wide variety of physiological activities including the control of behavior and memory, affecting neurotrophic and antipyretic properties, as well as affecting the modulation of the immune system, the control of the cardiovascular system, analgesia, thermoregulation and the release of other neurohumoral agents including prolactin, luteinizing hormone and biogenic amines. Five melanocortin receptors (MC-R) have been characterized to date: melanocyte-specific receptor (MC1-R), corticoadrenal-specific ACTH receptor (MC2-R), melacortin-3 (MC3-R), melanocortin-4 (MC4-R) and melanocortin-5 receptor (MC5-R). There has been great interest in melanocortin (MC-R) receptors as targets for the design of novel therapeutics to treat disorders of body weight such as obesity and cachexia. Both genetic and pharmacological evidence points toward central MC4-R receptors as the principal target. The current progress with receptor-selective agonists and antagonists evidences the therapeutic potential of melanocortin receptor activation, particularly MC4-R. Due to this therapeutic potential, there is a need of new formulations for this type of compounds, in particular a need of injection formulations.

Parenteral injection of a soluble active pharmaceutical ingredient in saline classically leads to a high value of the drug plasma peak concentration (C_{max}) and an initial high variation rate of the plasmatic drug concentration that results in a short time (T_{max}) to reach the maximal concentration C_{max}, i.e. the burst effect. These two features of the pharmacokinetic (PK) profile can induce side effects, which may jeopardize the development and use of the drug.

There is thus a real need to develop a pharmaceutical composition that modifies the PK profile reducing C_{max} and increasing T_{max}, aiming to give a smooth immediate release, to reduce side effects and to increase the tolerance of the treatment.

The Applicant has now discovered that the introduction of certain gelling agents into a particular pharmaceutical composition can satisfy the abovementioned objectives.

In particular, it has discovered that by introducing at least one water-soluble or water-dispersible gelling agent into a pharmaceutical composition that comprises a particular peptide, a pharmaceutical composition with a reduced C_{max} can be obtained.

The injection of such a composition is quick and simple, does not cause any pain and does not require any particular know-how.

Furthermore, the injection of this composition makes it possible to obtain satisfactory physical properties, in particular in terms of solubility and filterability.

In a particularly advantageous manner, the Applicant has also found that the composition according to the invention ensures a peptide chemical stability.

In addition, the treatment using such a composition permits to modify the *in vitro* peptide release.

Finally, the composition according to the present invention allows a sustained-release of the active ingredient over at least 2 hours.

One subject of the present invention is thus an aqueous pharmaceutical composition comprising a peptide as the active substance and one or more water-soluble or water-dispersible gelling agents.

Other features, aspects, subjects and advantages of the present invention will emerge more clearly on reading the description and the examples which follow.

In the text herein below, unless otherwise indicated, the limits of a range of values are included in that range, especially in the expression "ranging from".

In the text herein below, the term "at least one" is equivalent to "one or more".

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "peptide" is understood to mean a peptide containing up to 50 amino acids and/or with a molecular weight up to about 6,000 Da (6,000 ± 200 Da).

The term "water-soluble" gelling agent is understood to mean that the gelling agent used in the composition according to the present invention is soluble in water. Preferably, the gelling agent has solubility in water measured at 25° C higher than 10 mg/mL, and preferably higher than 30 mg/mL.

The term "water-dispersible" gelling agent is understood to mean that the gelling agent used in the composition according to the present invention is miscible or can be dispersed

in water at a concentration measured at 25° C higher than 10 mg/mL, and preferably higher than 30 mg/mL.

The term "gelling agent" defines a compound that can be solubilized, dispersed or mixed with the pharmaceutical composition to modify its rheological behaviour, more particularly its viscosity, and can lead to a higher viscosity composition or the formation of a hydrogel. The term "gelling agent" means a gelling agent or a mixture of gelling agents.

The active ingredient of the pharmaceutical composition of the present invention is a peptide.

Preferably, the peptide is selected from a ligand of one or more of the melanocortin receptors (MC-R). The melanocortin receptor may be selected from melanocyte-specific receptor (MC1-R), corticoadrenal-specific ACTH receptor (MC2-R), melacortin-3 (MC3-R), melanocortin-4 (MC4-R) and melanocortin-5 receptor (MC5-R).

The active ingredient of the drug of the composition of the present invention may be selected from those described in the PCT applications WO 2007/008704 or WO 2008/147556.

In a preferred embodiment, the peptide is a ligand of melanocortin MC4 receptor.

In a preferred embodiment, the peptide is a compound of formula (I):

$$(R^2R^3)\text{-}A^1\text{-c}\ (A^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}A^7\text{-}A^8\text{-}A^9)\text{-}A^{10}\text{-}R^1\ (I)$$

wherein:

A^1 is Acc, HN-$(CH_2)_m$-C(O), L- or D-amino acid or deleted;

A^2 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Asp or Glu;

A^3 is Gly, Ala, β-Ala, Gaba, Aib, D-amino acid or deleted;

A^4 is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi or (X^1,X^2,X^3,X^4,X^5)Phe;

A^5 is D-Phe, D-1-Nal, D-2-Nal, D-Trp, D-Bal, D-(X^1,X^2,X^3,X^4,X^5)Phe, L-Phe or D-(Et)Tyr;

A^6 is Arg, hArg, Dab, Dap, Lys, Orn or HN-CH($(CH_2)_n$-N(R^4R^5))-C(O);

A^7 is Trp, 1-Nal, 2-Nal, Bal, Bip, D-Trp, D-1-Nal, D-2-Nal, D-Bal or D-Bip;

A^8 is Gly, D-Ala, Acc, Ala, β-Ala, Gaba, Apn, Ahx, Aha, HN-$(CH_2)_s$-C(O) or deleted;

A^9 is Cys, D-Cys, hCys, D-hCys, Pen, D-Pen, Dab, Dap, Orn or Lys;

A^{10} is Acc, HN-$(CH_2)_t$-C(O), L- or D-amino acid or deleted;

R^1 is -OH or -NH_2;

R^2 and R^3 is, independently for each occurrence, H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_1-C_{30})acyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_1-C_{30})acyl, substituted (C_2-C_{30})alkenyl, substituted (C_2-C_{30})alkynyl, substituted aryl(C_1-C_{30})alkyl or substituted aryl(C_1-C_{30})acyl;

R^4 and R^5 is, independently for each occurrence, H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_1-C_{40})acyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_1-C_{40})acyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl, substituted aryl(C_1-C_{40})alkyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl or -C(NH)-NH_2;

m is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

n is, independently for each occurrence, 1, 2, 3, 4 or 5;

s is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7;

t is, independently for each occurrence, 1, 2, 3, 4, 5, 6 or 7; and

X^1, X^2, X^3, X^4, and X^5 each is, independently for each occurrence, H, F, Cl, Br, I, (C_1-C_{10})alkyl, substituted (C_1-C_{10})alkyl, (C_2-C_{10})alkenyl, substituted (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, substituted (C_2-C_{10})alkynyl, aryl, substituted aryl, OH, NH_2, NO_2, or CN;

provided that:

(I) when R^4 is (C_1-C_{40})acyl, aryl(C_1-C_{40})acyl, substituted (C_1-C_{40})acyl, substituted aryl(C_1-C_{40})acyl, (C_1-C_{40})alkylsulfonyl or -C(NH)-NH_2, then R^5 is H, (C_1-C_{40})alkyl, (C_1-C_{40})heteroalkyl, (C_2-C_{40})alkenyl, (C_2-C_{40})alkynyl, aryl(C_1-C_{40})alkyl, substituted (C_1-C_{40})alkyl, substituted (C_1-C_{40})heteroalkyl, substituted (C_2-C_{40})alkenyl, substituted (C_2-C_{40})alkynyl or substituted aryl(C_1-C_{40})alkyl;

(II) when R^2 is (C_1-C_{30})acyl, aryl(C_1-C_{30})acyl, substituted (C_1-C_{30})acyl or substituted aryl(C_1-C_{30})acyl, then R^3 is H, (C_1-C_{30})alkyl, (C_1-C_{30})heteroalkyl, (C_2-C_{30})alkenyl, (C_2-C_{30})alkynyl, aryl(C_1-C_{30})alkyl, substituted (C_1-C_{30})alkyl, substituted (C_1-C_{30})heteroalkyl, substituted (C_2-C_{30})alkenyl, substituted (C_2- C_{30})alkynyl or substituted aryl(C_1-C_{30})alkyl;

(III) either A^3 or A^8 or both must be present in said compound;

(IV) when A^2 is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen, then A^9 is Cys, D-Cys, hCys, D-hCys, Pen or D-Pen;

(V) when A^2 is Asp or Glu, then A^9 is Dab, Dap, Orn or Lys;

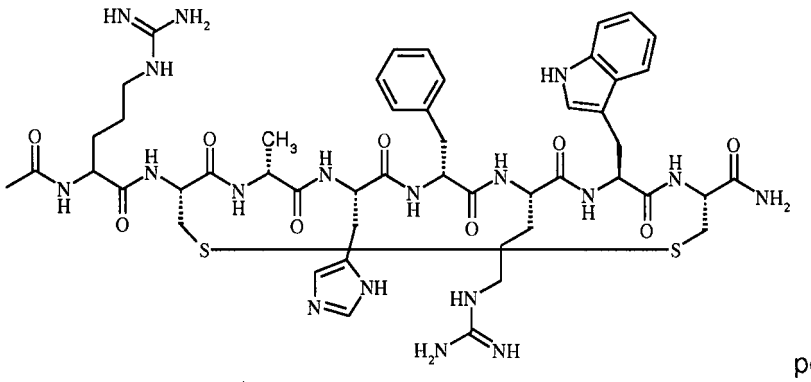
(VI) when A^8 is Ala or Gly, then A^1 is not Nle; and

(VII) when A^1 is deleted, then R^2 and R^3 cannot both be H;

or a pharmaceutically acceptable salt thereof. In a preferred embodiment, the peptide is a compound of formula (I) wherein A^1 is Arg, D-Arg, hArg or D-hArg; or a pharmaceutically acceptable salt thereof.

Preferably, the active substance of the drug composition of the present invention is the peptide of formula:

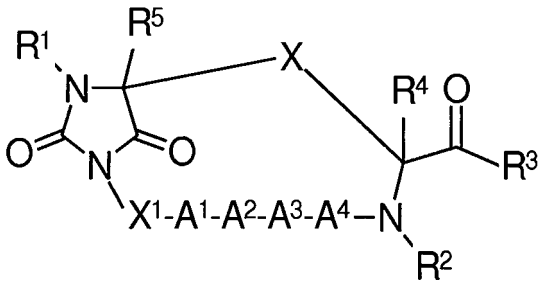
Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 (peptide 1)



peptide 1

or a pharmaceutically acceptable salt thereof.

In a preferred embodiment, the peptide is a compound of formula (II):



(II)

wherein the hydantoin moiety is formed from fusing the amino group of X^1, i.e.,

wherein:

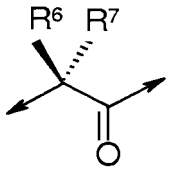
X is selected from the group consisting of $-CH_2-S-S-CH_2-$, $-C(CH_3)_2-S-S-CH_2-$, $-CH_2-$

S-S-$C(CH_3)_2$-, -$C(CH_3)_2$-S-S-$C(CH_3)_2$-, –$(CH_2)_2$-S-S-CH_2-, -CH_2-S-S-$(CH_2)_2$-, -$(CH_2)_2$-S-S-$(CH_2)_2$-, -$C(CH_3)_2$-S-S-$(CH_2)_2$-, -$(CH_2)_2$-S-S-$C(CH_3)_2$, -$(CH_2)_t$-C(O)-NR^8-$(CH_2)_r$- and -$(CH_2)_r$-NR^8-C(O)-$(CH_2)_t$-;

R^1 and R^2 each is, independently for each occurrence thereof, H, (C_1-C_{10})alkyl or substituted (C_1-C_{10})alkyl;

R^3 is -OH or -NH_2;

R^4 and R^5 each is, independently for each occurrence thereof, H, (C_1-C_{10})alkyl or substituted (C_1-C_{10})alkyl;

X^1 is 

A^1 is His, 2-Pal, 3-Pal, 4-Pal, Taz, 2-Thi, 3-Thi, (X^1, X^2, X^3, X^4, X^5)Phe or deleted;

A^2 is D-Bal, D-1-Nal, D-2-Nal, D-Phe or D-(X^1, X^2, X^3, X^4, X^5)Phe;

A^3 is Arg, hArg, Dab, Dap, Lys or Orn;

A^4 is Bal, 1-Nal, 2-Nal, (X^1, X^2, X^3, X^4, X^5)Phe or Trp;

R^6 and R^7 each is, independently for each occurrence thereof, H, (C_1-C_{10})alkyl, (C_1-C_{10})heteroalkyl, aryl(C_1-C_5)alkyl, substituted (C_1-C_{10})alkyl, substituted (C_1-C_{10})heteroalkyl or substituted aryl(C_1-C_5)alkyl or R^6 and R^7 may be joined together form a cyclic moiety;

R^8 is H, (C_1-C_{10})alkyl or substituted (C_1-C_{10})alkyl;

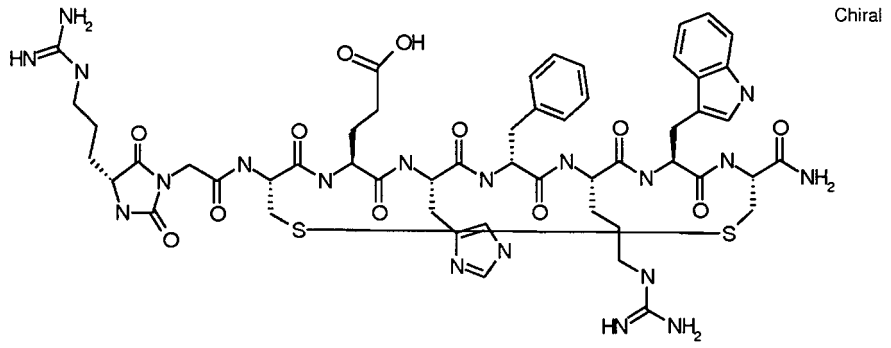
r is, independently for each occurrence thereof, 1, 2, 3, 4 or 5; and

t is, independently for each occurrence thereof, 1 or 2; or

a pharmaceutically acceptable salt thereof.

Preferably, the active substance of the drug composition of the present invention is the peptide of formula:

Hydantoin(Arg-Gly))-cyclo(Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2 (peptide 2)

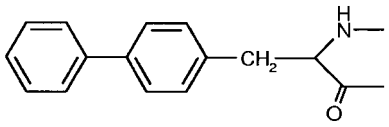


peptide 2

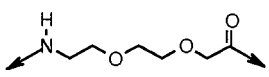
or a pharmaceutically acceptable salt thereof.

The nomenclature used to define the peptides is that typically used in the art wherein the amino group at the N-terminus appears to the left and the carboxyl group at the C-terminus appears to the right. Where the amino acid has isomeric forms, it is the L form of the amino acid that is represented unless otherwise explicitly indicated. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference. The meaning of the different symbol used above is as follows:

Abu: α-aminobutyric acid; Ac: acyl group; Acc: 1-amino-1-cyclo(C_3-C_9)alkyl carboxylic acid; A3c: 1-amino-1-cyclopropanecarboxylic acid; A4c: 1-amino-1-cyclobutanecarboxylic acid; A5c: 1-amino-1-cyclopentanecarboxylic acid; A6c: 1-amino-1-cyclohexanecarboxylic acid; Aha: 7-aminoheptanoic acid; Ahx: 6-aminohexanoic acid; Aib: α-aminoisobutyric acid; Ala or A: alanine; β-Ala: β-alanine; Apn: 5-aminopentanoic acid (HN-$(CH2)_4$-C(O); Arg or R: arginine; hArg: homoarginine; Asn or N: asparagine; Asp or D: aspartic acid; Bal: 3-benzothienylalanine; Bip: 4,4'-biphenylalanine, represented by the structure:



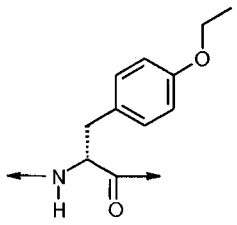
Bpa: 4-benzoylphenylalanine; 4-Br-Phe: 4-bromo-phenylalanine; Cha: β-cyclohexylalanine; hCha: homo-cyclohexylalanine; Chg: cyclohexylglycine; Cys or C: cysteine; hCys: homocysteine; Dab: 2,4-diaminobutyric acid; Dap: 2,3-diaminopropionic acid; Dip: β,β-diphenylalanine; Doc: 8-amino-3,6-dioxaoctanoic acid with the structure of:



2-Fua: β-(2-furyl)-alanine; Gaba: 4-aminobutyric acid; Gln or Q: glutamine; Glu or E:

glutamic acid; Gly or G: glycine; His or H: histidine; 3-Hyp: trans-3-hydroxy-L-proline, i.e., (2S, 3S)-3-hydroxypyrrolidine-2-carboxylic acid; 4-Hyp: 4-hydroxyproline, i.e., (2S, 4R)-4-hydroxypyrrolidine-2-carboxylic acid; Ile or I: isoleucine; Leu or L: leucine; hLeu: homoleucine; Lys or K: lysine; Met or M: methionine; β-hMet: β-homomethionine; 1-Nal: β-(1-naphthyl)alanine; 2-Nal: β-(2-naphthyl)alanine; Nip: nipecotic acid; Nle: norleucine; Oic: octahydroindole-2-carboxylic acid; Orn: ornithine; 2-Pal: β-(2-pyridiyl)alanine; 3-Pal: β-(3-pyridiyl)alanine; 4-Pal: β-(4-pyridiyl)alanine; Pen: penicillamine; Phe or F: phenylalanine; hPhe: homophenylalanine; Pro or P: proline; hPro: homoproline.

Ser or S: serine; Tle: tert-Leucine; Taz: β-(4-thiazolyl)alanine; 2-Thi: β-(2-thienyl)alanine; 3-Thi: β-(3-thienyl)alanine; Thr or T: threonine; Trp or W: tryptophan; Tyr or Y: tyrosine; D-(Et)Tyr has a structure of:



; Val or V: valine.

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain. The term "substituted alkyl" refers to an alkyl group as defined above having one, two or three substituents selected from the group consisting of halo, amino, cyano, keto (=O), $-OR_a$, $-SR_a$, $-NR_aR_b$, $-(C=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-OC(=O)R_a$, $-OC(=O)NR_aR_b$, $-NR_cC(=O)NR_aR_b$, $NR_aSO_2R_d$, SO_2R_d, SO_3R_d, cycloalkyl, aryl, heteroaryl, or heterocycle, wherein the groups R_a, R_b, and R_c are selected from hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, heterocycle, cycloalkyl, or $(C_1\text{-}C_6)$alkyl substituted with halogen, hydroxy, methoxy, nitro, amino, cyano, -(C=O)H, $-CO_2H$, -(C=O)alkyl, $-CO_2$alkyl, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxy, acyl, -C(=O)H, -C(=O)phenyl, $-CO_2$-alkyl, cycloalkyl, $-(C=O)NH_2$, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), $-(C=O)N(alkyl)_2$, $-C(=O)-(CH_2)_{1\text{-}2}NH_2$, $-C(=O)-(CH_2)_{1\text{-}2}$NH(alkyl), $-C(=O)-(CH_2)_{1\text{-}2}N(alkyl)_2$, $-NH-CH_2$-carboxy, $-NH-CH_2-CO_2$-alkyl, phenyl, benzyl, phenylethyl, or phenyloxy. The group R_d may be selected from the same groups as R_a, R_b and R_c but is not hydrogen.

Alternatively, the groups R_a and R_b may together form a heterocyclo or heteroaryl ring. It should be understood that when a substituted alkyl group is substituted with an aryl, cycloalkyl, heteroaryl, or heterocyclo, such rings are as defined below and thus may have one to three substituents as set forth below in the definitions for these terms. When the term "alkyl" is used as a suffix following another specifically named group, e.g., arylalkyl or heteroarylalkyl, the term defines, with more specificity, at least one of the substituents that the substituted alkyl will contain. For example, arylalkyl refers to an aryl bonded through an alkyl, or in other words, a substituted alkyl group having from 1 to 12 carbon atoms and at least one substituent that is aryl (e.g., benzyl or biphenyl). "Lower arylalkyl" refers to substituted alkyl groups having 1 to 4 carbon atoms and at least one aryl substituent.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6 carbon atoms and having one double bond are most preferred.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred. A substituted alkenyl or alkynyl will contain one, two, or three substituents as defined above for alkyl groups.

The term "alkylene" refers to bivalent straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, e.g., $\{-CH_2-\}_n$, wherein n is 1 to 12, preferably 1 to 8. Lower alkylene groups, that is, alkylene groups of 1 to 4 carbon atoms, are most preferred. The terms "alkenylene" and "alkynylene" refer to bivalent radicals of alkenyl and alkynyl groups, respectively, as defined above. Substituted alkylene, alkenylene, and alkynylene groups may have substituents as defined above for substituted alkyl groups.

The term "alkoxy" refers to the group OR_e wherein R_e is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocycle, or cycloalkyl. Thus, an alkoxy includes such groups as methoxy, ethoxy, cyclopropyloxy, pyrrolidinyloxy, and so forth. The term "aryloxy" refers to the groups O(aryl) or O(heteroaryl), wherein aryl and heteroaryl are as defined below.

The term "alkylthio" refers to an alkyl or substituted alkyl group as defined above bonded through one or more sulfur (-S-) atoms, e.g., -S (alkyl) or -S (alkyl-R_a).

The term "alkylamino" refers to an alkyl or substituted alkyl group as defined above bonded through one or more nitrogen (-NR_f-) groups, wherein R_f is hydrogen, alkyl, substituted alkyl, or cycloalkyl. The term "acyl" refers to an alkyl or substituted alkyl group as defined above bonded through one or more carbonyl {-C(=O)-} groups. When the term acyl is used in conjunction with another group, as in acylamino, this refers to the carbonyl

group {-C(=O)} linked to the second named group. Thus, acylamino refers to $-C(=O)NH_2$, substituted acylamino refers to the group -C(=O)NRR, and acylaryl refers to -C(=O)(aryl).

The term "aminoacyl" refers to the group $-NR_fC(=O)R_g$, wherein R_g is hydrogen, alkyl, or substituted alkyl, and R_f is as defined above for alkylamino groups.

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo. Unless otherwise indicated, any haloalkyl, haloalkoxy or haloalkylthio group contains one or more halo atoms which halo atoms may be the same or different.

The term "carboxy" when used alone refers to the group CO_2H. Carboxyalkyl refers to the group CO_2R, wherein R is alkyl or substituted alkyl.

The term "sulphonyl" refers to a sulphoxide group (i.e., $-S(O)_{1-2}-$) linked to an organic radical including an alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, or substituted alkynyl group, as defined above. The organic radical to which the sulphoxide group is attached may be monovalent (e.g., $-SO_2$-alkyl), or bivalent (e.g., $-SO_2$-alkylene, etc.).

The term "cycloalkyl" refers to substituted and unsubstituted monocyclic or bicyclic hydrocarbon groups of 3 to 9 carbon atoms which are, respectively, fully saturated or partially unsaturated, including a fused aryl ring, for example, an indan. A cycloalkyl group may be substituted by one or more (such as one to three) substituents selected from alkyl, substituted alkyl, aminoalkyl, halogen, cyano, nitro, trifluoromethyl, hydroxy, alkoxy, alkylamino, sulphonyl, $-SO_2$(aryl), $-CO_2H$, $-CO_2$-alkyl, -C(=O)H, keto, $-C(=O)-(CH_2)_{1-2}NH_2$, $-C(=O)-(CH_2)_{1-2}NH$(alkyl), $-C(=O)-(CH_2)_{1-2}N(alkyl)_2$, acyl, aryl, heterocycle, heteroaryl, or another cycloalkyl ring of 3 to 7 carbon atoms. The term "cycloalkylene" refers to a cycloalkyl forming a link or spacer between two other groups, i.e., a cycloalkylene is a cycloalkyl that is bonded to at least two other groups. The term cycloalkyl includes saturated or partially unsaturated carbocyclic rings having a carbon-carbon bridge of three to four carbon atoms or having a benzene ring joined thereto. When the cycloalkyl group is substituted with a further ring, said further ring may have one to two substituents selected from R_k, wherein R_k is lower alkyl, hydroxy, lower alkoxy, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, nitro, and lower alkyl substituted with one to two hydroxy, lower alkoxy, amino, halogen, cyano, trifluoromethyl, trifluoromethoxy, and/or nitro.

The term "aryl" refers to substituted and unsubstituted phenyl, 1-naphthyl and 2-naphthyl, with phenyl being preferred. The aryl may have zero, one, two or three substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, alkylthio, halo, hydroxy, nitro, cyano, amino, trifluoromethyl, trifluoromethoxy, sulphonyl, $-SO_2$(aryl), -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxy, acyl, -C(=O)H, -C(=O)phenyl, $-CO_2$-alkyl, cycloalkyl, $-(C=O)NH_2$, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), $-(C=O)N(alkyl)_2$, $-NH-CH_2-$

carboxy, -NH-CH_2-CO_2-alkyl, -C(=O)-$(CH_2)_{1-2}NH_2$, -C(=O)-$(CH_2)_{1-2}$NH(alkyl), -C(=O)-$(CH_2)_{1-2}N(alkyl)_2$, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, heterocyclo, heteroaryl, or a (C_3-C_7)cycloalkyl ring. The term "arylene" refers to an aryl as defined above forming a link or spacer between two other groups, i.e., an arylene is an aryl that is bonded to at least two other groups. When the aryl group is substituted with a further ring, said further ring may have one to two substituents selected from R_k, wherein R_k is defined as above.

The term "heterocyclo" or "heterocycle" refers to substituted and unsubstituted non-aromatic 3- to 7-membered monocyclic groups, 7- to 11-membered bicyclic groups, and 10- to 15-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quatemized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain one, two or three substituents selected from the group consisting of halo, amino, cyano, alkyl, substituted alkyl, trifluoromethyl, trifluoromethoxy, sulphonyl, -SO_2(aryl), -NH(alkyl), -NH(cycloalkyl), -N$(alkyl)_2$, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, carboxy, -CO_2-alkyl, cycloalkyl, -C(=O)H, acyl, -(C=O)NH_2, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl),-(C=O)N$(alkyl)_2$, -NH-CH_2-carboxy, -NH-CH_2-CO_2-alkyl, -C(=O)-$(CH_2)_{1-2}NH_2$, -C(=O)-$(CH_2)_{1-2}$NH(alkyl), -C(=O)-$(CH_2)_{1-2}N(alkyl)_2$, heterocyclo, heteroaryl, a (C_3-C_7)cycloalkyl ring, keto, =N-OH, =N-O-lower alkyl, or a five or six-membered ketal, i.e., 1,3-dioxolane or 1,3-dioxane. When the heterocyclo group is substituted with a further ring, said further ring may have one to two substituents selected from R_k, wherein R_k is defined as above. Exemplary monocyclic groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The

fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain one, two or three substituents selected from the group consisting of halo, amino, cyano, alkyl, substituted alkyl, trifluoromethyl, trifluoromethoxy, sulphonyl, $-SO_2$(aryl), -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, alkoxy, alkylthio, hydroxy, nitro, phenyl, benzyl, phenylethyl, phenyloxy, phenylthio, carboxy, $-CO_2$-alkyl, cycloalkyl, -C(=O)H, acyl, $-(C=O)NH_2$, -(C=O)NH(alkyl), -(C=O)NH(cycloalkyl), $-(C=O)N(alkyl)_2$, $-NH-CH_2$-carboxy, $-NH-CH_2-CO_2$-alkyl, $-C(=O)-(CH_2)_{1-2}NH_2$, $-C(=O)-(CH_2)_{1-2}NH(alkyl)$, $-C(=O)-(CH_2)_{1-2}N(alkyl)_2$, heterocylco, heteroaryl, or a (C_3-C_7)cycloalkyl ring. The heterocyclo ring may have a sulfur heteroatom that is substituted with one or more oxygen (=O) atoms. Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like. Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The peptide of the drug composition of the present invention may be in the form of a salt or as a free base.

According to one preferred embodiment, the peptide is in a salt form.

Preferably, the pharmaceutically acceptable salt of the peptide is acetate or heptanoate.

More preferably, the pharmaceutically acceptable salt of the peptide is acetate.

In a preferred embodiment, the active substance of the composition of the present invention is the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 in a salt form, preferably in an acetate or heptanoate salt. In a more preferred embodiment, the peptide Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 is in an acetate salt.

Advantageously, the peptide or the salt thereof is present in a concentration ranging from 0.1 to 25 % by weight relative to the total weight of the composition. More preferably, the peptide or the salt thereof is present in a concentration ranging from 0.1 to 10 % by weight,

even more preferentially from 0.2 to 6 % by weight and even more preferentially still from 0.3 to 2 % by weight relative to the total weight of the composition.

According to the invention, the pharmaceutical composition comprises a water-soluble or water-dispersible gelling agent.

For the purposes of the present invention, the term "gelling agent" means an agent which, when introduced at a concentration between 0.5 and 40 % by weight in an aqueous solution makes it possible to achieve a dynamic viscosity of at least 100 cPs and preferably of at least 500 cPs, at 25° C and at a shear rate between 1 and 10 s^{-1}. This viscosity may be measured using a viscometer, for example a controlled-stress viscometer in cone-plate geometry, for instance a Haake RS1 viscometer from Thermo Electron.

Mention may be made, as gelling agents, for example, of polyols such as glycerol and propylene glycol, polyethers such as polyethylene glycols, cellulose derivatives such as microcrystalline cellulose, sodium caboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose, mono- or polysaccharides such as sodium hyalunorate, chitosan, starch and starch derivatives, polyvinylpyrrolidone, gelatin, zinc acetate, and mixtures thereof.

The gelling agent contains one or more polyethers, one or more polyols and a mixture thereof.

According to the present invention, the gelling agent is chosen from polyethers, polyols and mixtures thereof.

More preferably, the gelling agent is chosen from polyethers and polyols.

Preferably, the gelling agent is present in a concentration ranging from 0.5 to 70 % by weight relative to the total weight of the composition. More preferably, the gelling agent is present in a concentration ranging from 10 to 50 % by weight, even more preferentially from 15 to 40 % by weight and even more preferentially still from 20 to 40 % by weight relative to the total weight of the composition.

In a preferred embodiment, the present invention relates to an aqueous pharmaceutical composition comprising:

- a peptide as the active ingredient, and
- one or more water-soluble or water-dispersible gelling agents,

the peptide being selected from a ligand of one or more of melanocortin receptors (MC-R) or a pharmaceutically acceptable salt thereof, and
the gelling agent being present in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition.

In another preferred embodiment, the present invention relates to an aqueous pharmaceutical composition comprising:

- a peptide as the active ingredient, and
- one or more water-soluble or water-dispersible gelling agents,

the peptide being selected from a ligand of one or more of melanocortin receptors (MC4-R) or a pharmaceutically acceptable salt thereof, and
the gelling agent being present in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition.

In another preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, and a gelling agent in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition.

In another preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, an acetate or a heptanoate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, and a gelling agent in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition. In a most preferred embodiment, the active ingredient is the acetate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2,

In a preferred embodiment, the gelling agent is a polyether or a mixture of polyethers.

Preferably, the gelling agent is a polyether present in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition. More preferably, the gelling agent is a polyether and present in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition. Even more preferentially, the gelling agent is a polyether and present in a concentration ranging from 20 to 35 % by weight relative to the total weight of the composition.

In a more preferred embodiment, the gelling agent is a polyether chosen from polyethylene glycols. In another preferred embodiment, the gelling agent is the polyether PEG 400.

In a particular embodiment, the gelling agent is the polyether PEG 400 and is present in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition. More preferably, the gelling agent is the polyether PEG 400 and is present in a concentration ranging from 20 to 35 % by weight relative to the total weight of the composition.

In another preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, and a polyethylene glycol as gelling agent in a concentration ranging from 15 to 40 % by weight, and more preferably from 20 to 35 % by weight relative to the total weight of the composition.

In another preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, an acetate or a heptanoate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 in a concentration of 0.1 to 10 % by weight relative to the total weight of the composition, and a polyethylene glycol as gelling agent in a concentration ranging from 15 to 40 % by weight, and more preferably from 20 to 35 % by weight relative to the total weight of the composition. In a most preferred embodiment, the active ingredient is the acetate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2,

In another preferred embodiment, the gelling agent is a polyol or a mixture of polyols.

Preferably, the gelling agent is a polyol present in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition. More preferably, the gelling agent is a polyol present in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition. Even more preferentially, the gelling agent is a polyol and present in a concentration ranging from 25 to 40 % by weight relative to the total weight of the composition.

More particularly, the gelling agent is glycerol as polyol.

In a particular embodiment, the gelling agent is glycerol as polyol and is present in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition. More preferably, the gelling agent is glycerol as polyol and is present in a concentration ranging from 25 to 40 % by weight relative to the total weight of the composition.

In a more preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, and glycerol as gelling agent in a concentration ranging from 15 to 40 % by weight, and more preferably from 25 to 40 % by weight relative to the total weight of the composition.

In a more preferred embodiment, the composition according to the present invention comprises, as active ingredient, an acetate or a heptanoate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, and glycerol as gelling agent in a

concentration ranging from 15 to 40 % by weight, and more preferably from 25 to 40 % by weight relative to the total weight of the composition. In a most preferred embodiment, the active ingredient is the acetate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2,

The composition according to the invention may also comprise one or more additives such as surfactants. These additives include fatty acids and salts thereof, polyols, polyoxyethers, poloxamers, polysorbates and polyoxyethylene fatty acid esters.

In a preferred embodiment, the composition according to the invention comprises only the peptide as active substance and the water-soluble or water-dispersible gelling agent.

Preferably, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof and one or more polyols as gelling agent.

More preferably, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof and glycerol as gelling agent.

Even more preferably, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition and glycerol as gelling agent in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition. Of course, water (water of injectable grade) is present to complete the formulation to 100 % (w/w) (q.s. 100 %).

In a more preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, glycerol as gelling agent in a concentration ranging from 25 to 40 % by weight relative to the total weight of the composition, and water (WFI q.s. 100 %).

In a more preferred embodiment, the aqueous composition according to the present invention comprises, as active ingredient, an acetate or a heptanoate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, glycerol as gelling agent in a concentration ranging from 25 to 40 % by weight relative to the total weight of the composition, and water (WFI q.s. 100 %). In a most preferred embodiment, the active ingredient is the acetate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2.

More preferably still, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.3 to 2 % by weight relative to the total weight of the composition and glycerol as gelling agent in a concentration ranging from 25 to 40 % by weight relative to the total weight of the composition. Of course, water (water of injectable grade) is present to complete the formulation to 100 % (w/w) (q.s. 100 %).

In another preferred embodiment, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof and one or more polyethers as gelling agent.

Preferably, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof and one or more polyethylene glycols as gelling agent.

In another preferred embodiment, the composition according to the present invention comprises, as active ingredient, Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, a polyethylene glycol as gelling agent in a concentration ranging from 15 to 40 % by weight, and more preferably from 20 to 35 % by weight relative to the total weight of the composition, and water (WFI q.s. 100 %).

In another preferred embodiment, the composition according to the present invention comprises, as active ingredient, an acetate or a heptanoate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition, a polyethylene glycol as gelling agent in a concentration ranging from 20 to 35 % by weight relative to the total weight of the composition, and water (WFI q.s. 100 %). In a most preferred embodiment, the active ingredient is the acetate salt of Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2.

More preferably, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof and PEG 400 as gelling agent.

Even more preferably, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof in a concentration ranging from 0.1 to 10 % by weight relative to the total weight of the composition and PEG 400 as gelling agent in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition. More preferably still, the composition according to the invention comprises only the peptide of formula Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically

acceptable salt thereof in a concentration ranging from 0.3 to 2 % by weight relative to the total weight of the composition and PEG 400 as gelling agent in a concentration ranging from 20 to 35 % by weight relative to the total weight of the composition. Of course, water (water of injectable grade) is present to complete the formulation to 100 % (w/w) (q.s. 100 %).

The composition of the present invention may be prepared by mixing the peptide, the water-soluble or water-dispersible gelling agent(s) and the optional additives (if any) in water.

The pharmaceutical composition according to the invention is administered by parenteral route. In a preferred embodiment, the composition of the present invention is administered by subcutaneous route, and preferably by a subcutaneous infusion.

The pharmaceutical composition according to the invention is easily administered by the parenteral route through 27 Gauge (G) needle and more preferably through 29 G needle.

In a preferred embodiment, the composition according to the invention is formulated such that the peptide is released within a subject in need thereof for an extended period of time.

The composition according to the invention may be useful for a parenteral administration with a sustained-release of the peptide for at least 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours or 24 hours.

In a preferred embodiment, the composition according to the invention allows a sustained release for at least 2 hours. In another preferred embodiment, the composition according to the invention allows a sustained release for at least 3 hours. In another preferred embodiment, the composition according to the invention allows a sustained release for at least 6 hours. In a more preferred embodiment, the composition according to the invention allows a sustained release for at least 8 hours. In another more preferred embodiment, the composition of the present invention allows a sustained release for at least 10 hours and more preferably 12 hours.

The pharmaceutical composition according to the invention is particularly useful to treat disorders of body weight such as obesity and cachexia.

The following examples are presented to illustrate the above procedures and should not be considered as limiting the scope of the invention.

Experimental part

Example 1: Preparation process

Various compositions according to the present invention are prepared with peptide 1 as active ingredient according to the following process:

The gelling agent is blended (when miscible) or dissolved (when soluble) in water for injection under magnetic stirring at room temperature for 15 min at least. The peptide salt is precisely weighed and dissolved in the previously prepared composition under magnetic stirring until obtaining a clear solution. Examples of formulation compositions are reported in Table 1:

Table 1

Composition #	Peptide 1 salt	Content of peptide 1 salt	Gelling agent	Content of gelling agent	WFI [(1)] content
1	acetate	0.4 %	PEG 400	32 %	q.s. 100 %
2	acetate	0.4 %	PEG 400	22 %	q.s. 100 %
3	acetate	0.4 %	glycerol	38 %	q.s. 100 %
4	heptanoate	0.4 %	PEG 400	32 %	q.s. 100 %

[(1)] means Water For Injection.

The content of peptide salt is expressed in weight percentage of product relative to the total weight of the composition. The content of gelling agent is expressed in weight percentage of agent relative to the total weight of the composition.

The four formulations of Table 1 are used in the different tests described in examples 2, 4 and 5 below.

Example 2: Filterability testing

The filterability of compositions 1-4 was evaluated manually using a Millex GV PVDF (low protein binding Durapore® PolyVinylidene DiFluoride) 0.22µm filter equipped with a 1 mL Terumo syringe.

All the formulations were shown to be filterable.

Example 3: Solubility testing

The solubility of the peptide 1 salts in the gelling compositions of Table 1 was evaluated using HPLC analysis after filtration. Specifications of Methods 1 and 2 used for this evaluation are given in Table 2.

Table 2

	HPLC Method 1	HPLC Method 2
Column	YMC-ODS-AM 250x4.6mm 5µm	YMC-ODS-AM 150x4.6mm 3µm
Temperature	30° C	40° C
Mobile phase	A: NaH_2PO_4 (50 mM, pH 2.5) B: Acetonitrile	A: H_2O + TFA (0.05 %) B: Acetonitrile + TFA (0.05 %) C: Methanol + TFA (0.05 %)
Flow	1.0 mL/min	1.0 mL/min
UV detection	220 nm	220 nm
Retention time	~ 31.5 min	~ 24.6 min
Analysis duration	60 min	60 min
Standard (100 %)	0.6 mg/mL	0.6 mg/mL
Injected volume	10 µL	10 µL
Dilution solvent	Acetic acid 0.1 N	Acetic acid 0.1 N
Gradient	Time % A % B Curve 0 90 10 / 35 83 17 6 50 70 30 6 51 90 10 6 60 90 10 6	Time % A % B % C Curve 0 85 5 10 / 45 70 15 15 6 47 85 5 10 6 60 85 5 10 6

In all formulations, the peptide salts presented a solubility of at least 4 mg/mL. More precisely, the peptide 1 acetate salt showed a solubility of 100 mg/mL at least, in 32 % PEG 400 and in 38 % glycerol. The peptide 1 heptanoate salt showed a solubility of 28.1 mg/mL in 32 % PEG 400. This means that in all formulations of Table 1, the peptide salt is entirely solubilized.

Example 4: Injectability testing

The injectability of compositions 1-4 was evaluated using a traction/compression machine which measures the injection strength during the simulated injection of the formulation from a 1 mL syringe fitted with a needle.

The maximal tolerated strength is 15 N and the most suitable needle diameter for a daily subcutaneous injection is not less than 27 Gauge.

All formulations have shown to be injectable through a 27 G needle.

Example 5: *In vitro* testing

An *in vitro* testing test was developed and used to evaluate the impact of the aqueous formulations 1-4 on the peptide release profile. This test is based on the peptide diffusion from the formulation through an agarose layer into phosphate buffer saline pH 7.4 kept at 37° C.

100 mg of agarose was dissolved at 80° C in 5 mL of water under magnetic stirring. After the total agarose dissolution, the solution was cooled at 60° C.

200 µL of the formulation, which corresponds to 800 µg of peptide, were introduced in a vial. The formulation was suspended with 300 µL of the warm agarose solution heated at 60° C. The blend was then mixed and cooled at room temperature for 10 min, resulting in the first gel layer.

300 µL of 60° C warm agarose formulation-free was added on top of the first gel layer to form a second layer. The second gel layer was then cooled at room temperature for 10 min.

The second agarose layer was topped with 3.4 mL of PBS buffer kept at 37° C, as a release medium.

The vial was stoppered with a stirring rod and put in a horizontally rotating shaker in 200 rpm at 37° C.

500 µL of release medium was withdrawn for UV analysis in the upper part of the vial at the following times after the start of the test: 15 min, 30 min, 1 h, 3 h, 5 h, 9 h, 16 h, 24 h and 30 h.

Aliquots withdrawn for analysis were replaced with equal volumes of fresh PBS buffer. Each sampling was diluted at ½ in fresh PBS buffer before UV analysis.

The peptide content was measured using the UV spectrophotometer (Perkin Elmer®) at 280 nm. The peptide concentration was calculated at each time point, taking into account each peptide quantity previously withdrawn.

The concentration of the peptide released in the medium was reported as a function of the time.

The time when 50 % of the peptide is released from the formulation to the release medium ($T_{50\%}$) was evaluated graphically, and used to compare various formulations.

In vitro release profile of gelling formulations that significantly modify peptide release is given in Figure 1.

In comparison to the reference in saline, formulations 1 and 3 demonstrate a very significant peptide release slowing down. The $T_{50\%}$ values are respectively equal to 17.7 h and 19.9 h for formulations 1 and 3, versus the value for the reference in saline which is 7.8 h.

The release slowing down is also confirmed for formulations 2 and 4 with a $T_{50\%}$ being equal to 20.7 h for formulation 4 and equal to 16.2 h for formulation 2.

Example 6: Chemical stability

Formulations manufactured with PEG 400 or glycerol as gelling agent, were stored for 3 months at 40° C and 6 months at 5° C and 25° C.

A HPLC analysis was performed at various time points to evaluate the chemical stability of these compounds, using HPLC Methods 1 and 2 described in Table 2.

The selected formulations were manufactured at the maximal tolerated excipient content and

- either at the maximal estimated dose for human as follows:

  • 100 mg acetate salt of peptide 1 / mL of 30 % PEG 400 (formulation A),
  • 100 mg acetate salt of peptide 1 / mL of 32.5 % glycerol (formulation B),

- or at the maximal heptanoate solubility in 30 % PEG 400 as follows:

  • 28 mg heptanoate salt of peptide 1 / mL of 30 % PEG 400 (formulation C).

Supportive stability data of the above-mentioned formulations are respectively shown in Tables 3, 4 and 5.

Table 3 (formulation A)

	T0	Temp.	T1M	Δ (%)	T2M	Δ (%)	T3M	Δ (%)	T6M	Δ (%)
Estimated Content (mg/mL)	88.1	40° C			73.3	-16.8	67.6	-23.3		
		25° C	89.7	1.9	89.2	1.3	87.6	-0.5	87.5	-0.6
		5° C					89.9	2.0	92.7	5.2
Sum of Total impurities (%)	4.3	40° C			16.0	11.7	21.1	16.8		
		25° C	4.9	0.6	5.6	1.3	6.1	1.8	7.9	3.6
		5° C					5.1	0.8	4.8	0.5

Table 4 (formulation B)

	T0	Temp.	T1M	Δ (%)	T2M	Δ (%)	T3M	Δ (%)	T6M	Δ (%)
Estimated Content (mg/mL)	88.5	40° C			70.7	-20.1	65.6	-25.9		
		25° C	89.7	1.4	88.9	0.4	87.0	-1.7	88.6	0.1
		5° C					88.3	-0.2	93.0	5.1
Sum of Total impurities (%)	4.2	40° C			18.7	14.7	23.6	19.4		
		25° C	4.7	0.5	5.4	1.2	6.2	2.0	8.0	3.8
		5° C					4.7	0.5	4.7	0.5

The increase of the total impurities is moderate after 6 months at 25° C and does not exceed 5 %. After 6 months at 5° C, these formulations do not present any significant increase of the total impurities level.

Table 5 (formulation C)

	T0	Temp.	T1M	Δ (%)	T2M	Δ (%)	T3M	Δ (%)	T6M	Δ (%)
Estimated Content (mg/mL)	27.5	40° C			23.6	-14.1	21.7	-21.2		
		25° C	26.3	-4.3	28.7	4.5	28.6	4.2		
		5° C					23.1	-16.0		
Sum of Total impurities (%)	5.6	40° C			14.4	8.8	23.8	18.2		
		25° C	6.9	1.3	7.3	1.7	9.0	3.4	12.9	7.3
		5° C					7.0	1.4	8.5	2.9

Formulation C also presents a moderate increase of the total impurities after 3 months at 25° C which does not exceed 5 %.

After 6 months at 5° C, this formulation presents a moderate increase of the total impurities level; this increase of total impurities tends to be quite higher than the one obtained for the previous formulations with acetate salt, but still remains lower than 5 %.

The selected formulations were then manufactured to evaluate the possibility to inject at lower doses:

- 10 mg acetate salt of peptide 1 / mL of 30 % PEG 400 (formulation D),
- 7.5 mg heptanoate salt of peptide 1 / mL of 22.5 % PEG 400 (formulation E).

Supportive stability data of the above-mentioned formulations are respectively shown in Tables 6 and 7:

Table 6 (formulation D)

	T0	Temp.	T1M	Δ (%)	T3M	Δ (%)
Estimated Content (mg/mL)	10.0	40° C	9.9	-0.5	9.1	-9.1
		25° C			10.1	1.3
Sum of Total impurities (%)	2.4	40° C	4.7	2.3	6.9	4.5
		25° C			3.0	0.6

Table 7 (formulation E)

	T0	Temp.	T3M	Δ (%)
Estimated Content (mg/mL)	6.3	40° C	5.5	-12.8
		25° C	6.3	0.5
Sum of total impurities (%)	7.7	40° C	10.6	2.9
		25° C	7.1	0.6

After 3 months at 40° C, these formulations present a moderate increase of the total impurities tending to 5 % and do not present any significant increase of the total impurities level after 3 months at 25° C.

Example 7: *In vivo* testing

PK profiles of the formulations according to the invention were evaluated in rats. Eight rats divided in two groups of four were used per formulation. Each animal received a subcutaneous (SC) injection at a dose of 0.5 mg/kg, and then blood sampling was

performed via a jugular catheter at different time points alternately on each group. Plasma concentrations were determined by LC-MS analysis. PK parameters were calculated by a WinNonLin analysis.

PK values were compared to the one obtained after the injection of the peptide in a saline solution under the same conditions. PK profile is presented in Figure 2 (PK profiles in rats - 450 nmole/kg, 0.5 mg/kg, SC).

PK parameters of the formulation 2 and saline reference are shown in Table 8.

Table 8

	Reference	Formulation 2
T_{max} (min)	30	60
C_{max} (ng/ml)	346	164
$T_{1/2}$ (min)	49.4	52.4
MRT (min)	74.5	102
AUC (min.ng/ml)	29.6	20.1

C_{max}: maximum plasma concentration of the drug appearing in the PK profile; AUC: Area Under the Curve; MRT: Medium Residence Time; T_{max}: time corresponding to the C_{max} value; $T_{1/2}$: half-life.

These results confirm a significant decrease of C_{max} together with an increase of T_{max} by a factor 2, for a concentration of 22 % of PEG 400. Formulation 2 appears to be efficient enough to significantly reduce the C_{max} and increase the T_{max} in rats.

The PK profile and parameters of formulation 4 are presented in Figure 3 (PK profiles in rats -450 nmole/kg, 0.5 mg/kg, SC) and Table 9 (PK parameters of the formulation 4 and DMA/saline reference) respectively.

Table 9

	Reference	Formulation 4
T_{max} (min)	60	120
C_{max} (ng/ml)	362	163
$T_{1/2}$ (min)	186	189
MRT (min)	145	191
AUC (min.ng/ml)	71.7	35.9

Similarly to formulation 2, formulation 4 presents a C_{max} decrease by more than a factor 2 and a T_{max} increase by a factor 2.

CLAIMS

1. Aqueous pharmaceutical composition comprising:

- a peptide as the active ingredient, and
- one or more water-soluble or water-dispersible gelling agents,

the peptide being selected from a ligand of one or more of melanocortin receptors (MC-R) or a pharmaceutically acceptable salt thereof, and
the gelling agent being present in a concentration ranging from 10 to 50 % by weight relative to the total weight of the composition.

2. Composition according to claim 1, wherein the peptide is a ligand of melanocortin MC4 receptor.

3. Composition according to any one of the preceding claims, wherein the peptide is Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2 or a pharmaceutically acceptable salt thereof.

4. Composition according to any one of the preceding claims, wherein the peptide is in a salt form.

5. Composition according to any one of the preceding claims, wherein the pharmaceutically acceptable salt of the peptide is acetate or heptanoate, and preferably acetate.

6. Composition according to any one of the preceding claims, wherein the peptide or the salt thereof is present in a concentration ranging from 0.1 to 25 % by weight, preferably from 0.1 to 10 % by weight relative to the total weight of the composition.

7. Composition according to any one of the preceding claims, wherein the gelling agent is chosen from polyethers and polyols.

8. Composition according to any one of the preceding claims, wherein the gelling agent is present in a concentration ranging from 15 to 40 % by weight relative to the total weight of the composition.

9. Composition according to claim 7, wherein the polyether is chosen from polyethylene glycols and preferably is PEG 400.

10. Composition according to claim 9, wherein the polyether is PEG 400 present in a concentration ranging from 15 to 40 % by weight and preferably from 20 to 35 % by weight relative to the total weight of the composition.

11. Composition according to claim 7, wherein the polyol is glycerol.

12. Composition according to claim 11, wherein the polyol is glycerol present in a concentration ranging from 15 to 40 % by weight and preferably from 25 to 40 % by weight relative to the total weight of the composition.

13. Composition according to any one of the preceding claims, wherein the peptide is released within a subject in need thereof for an extended period of time.

14. Composition according to claim 7, wherein said release of said compound extends for at least 2 hours, preferably for at least 6 hours, more preferably for at least 8 hours, even more preferably for at least 10 hours, and better still for at least 12 hours.

Figure 1

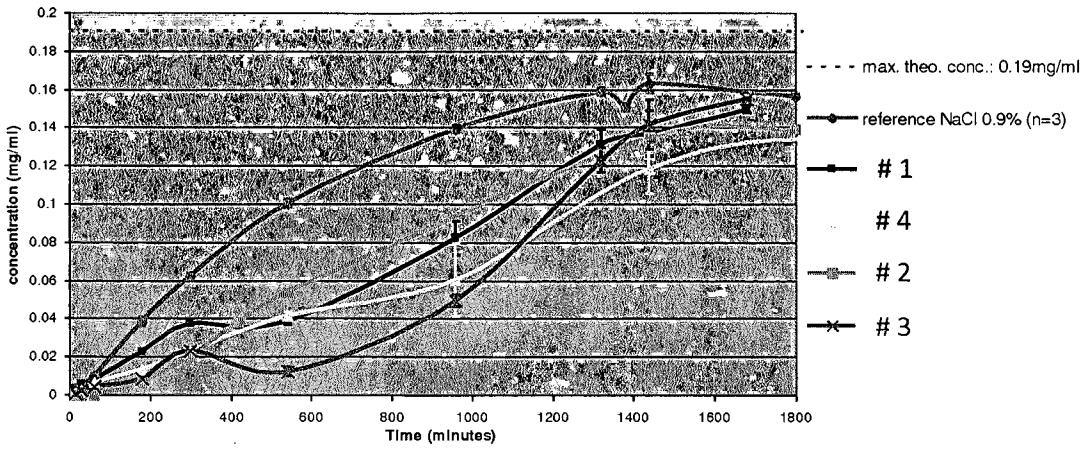


Figure 2

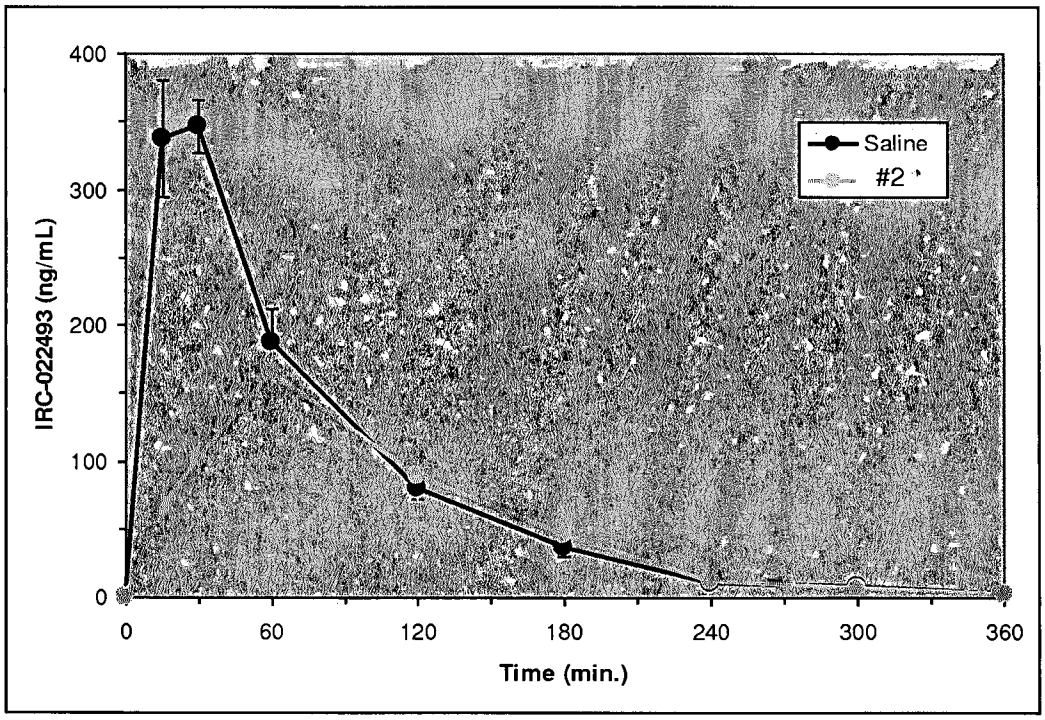
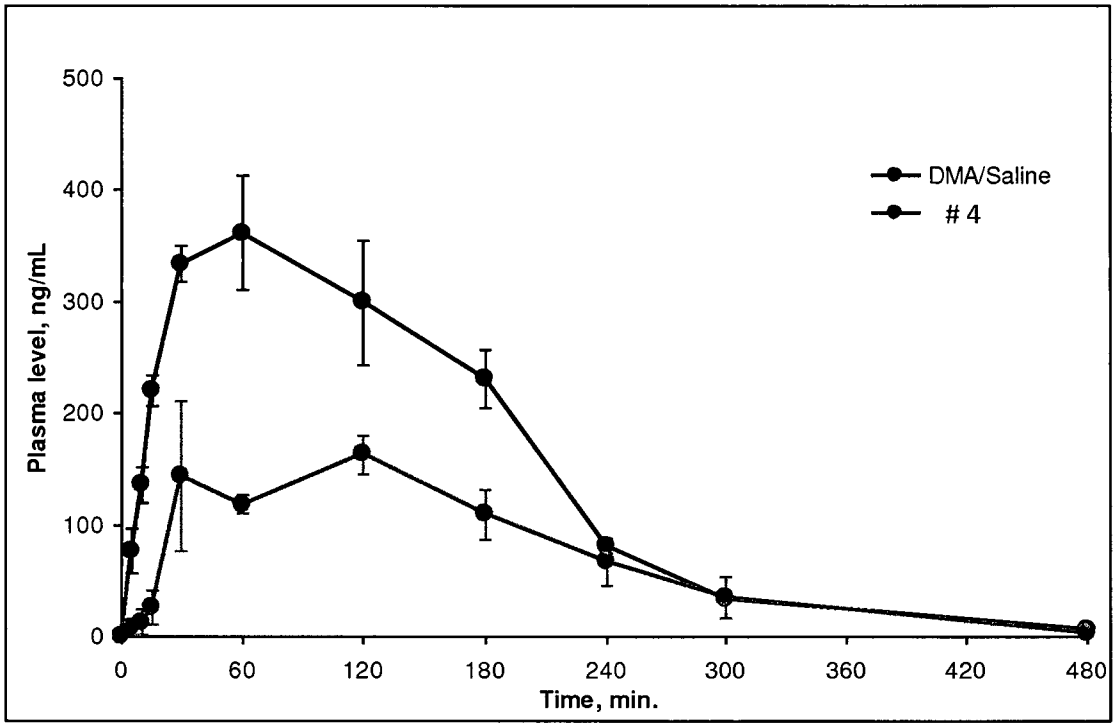


Figure 3


500
400
300
200
100
0
Plasma level, ng/mL
0
60
120
180
240
300
360
420
480
Time, min.
DMA/Saline
4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/061732

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K38/12 A61K47/10 A61K38/00
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/060352 A1 (IPSEN PHARMA SAS [FR]; DONG ZHENG XIN [US]; ZHANG JUNDONG [US]) 19 May 2011 (2011-05-19) page 18, lines 11-20 claim 15	1-14
X	WO 2009/120656 A1 (PALATIN TECHNOLOGIES INC [US]; DODD JOHN H [US]; PITT STEPHEN [US]) 1 October 2009 (2009-10-01) page 13, lines 1-2 page 14, lines 7-15 page 15, lines 19-26 page 19 - page 20	1,2,4-14
A,P	WO 2012/172433 A2 (IPSEN PHARMA SAS [FR]; RICHARD JOEL [FR]; LAREDJ FAIZA [FR]; BARONNET) 20 December 2012 (2012-12-20) the whole document	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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2

INTERNATIONAL SEARCH REPORT

Information on patent family members

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		EP 2501225 A1	26-09-2012
		JP 2013510879 A	28-03-2013
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		WO 2011060352 A1	19-05-2011
WO 2009120656 A1	01-10-2009	WO 2009120656 A1	01-10-2009
		WO 2009151714 A2	17-12-2009
WO 2012172433 A2	20-12-2012	NONE	

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A61K 38/12(2006.01)
A61K 47/10(2006.01)
A61K 38/00(2006.01)

权利要求书1页 说明书18页 附图2页

(54)发明名称

提供改良释放的可溶性活性药物肽的水性胶凝组合物

(57)摘要

本发明涉及水性药物组合物，包含作为活性成分的肽，和一种或多种水溶性或水可分散性胶凝剂。

CN 104487049 A

1. 水性药物组合物，包含：

- 作为活性成分的肽，和

- 一种或多种水溶性或水可分散性胶凝剂，

所述肽选自一种或多种黑皮质素受体 (MC-R) 的配体或其药学上可接受的盐，且

所述胶凝剂以相对于组合物总重量按重量计 10 至 50％范围的浓度存在。

2. 根据权利要求 1 的组合物，其中所述肽为黑皮质素 MC4 受体的配体。

3. 根据前述权利要求中任一项的组合物，其中所述肽为 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2或其药学上可接受的盐。

4. 根据前述权利要求中任一项的组合物，其中所述肽呈盐形式。

5. 根据前述权利要求中任一项的组合物，其中所述肽的药学上可接受的盐为乙酸盐或庚酸盐，优选为乙酸盐。

6. 根据前述权利要求中任一项的组合物，其中所述肽或其盐以相对于所述组合物总重量按重量计 0.1 至 25％、优选按重量计 0.1 至 10％范围的浓度存在。

7. 根据前述权利要求中任一项的组合物，其中所述胶凝剂选自聚醚和多元醇。

8. 根据前述权利要求中任一项的组合物，其中所述胶凝剂以相对于所述组合物总重量按重量计 15 至 40％范围的浓度存在。

9. 根据权利要求 7 的组合物，其中所述聚醚选自聚乙二醇，优选 PEG400。

10. 根据权利要求 9 的组合物，其中所述聚醚为以相对于所述组合物总重量按重量计 15 至 40％、优选按重量计 20 至 35％范围的浓度存在的 PEG 400。

11. 根据权利要求 7 的组合物，其中所述多元醇为甘油。

12. 根据权利要求 11 的组合物，其中所述多元醇为以相对于所述组合物总重量按重量计 15 至 40％、优选按重量计 25 至 40％范围的浓度存在的甘油。

13. 根据前述权利要求中任一项的组合物，其中所述肽在需要其的对象体内释放延长的时间段。

14. 根据权利要求 7 的组合物，其中所述化合物的所述释放延长至少 2 小时、优选至少 6 小时、更优选至少 8 小时、甚至更优选至少 10 小时、仍更优选至少 12 小时。

提供改良释放的可溶性活性药物肽的水性胶凝组合物

[0001] 本发明涉及水性药物组合物，其包含一种或多种水溶性或水可分散性胶凝剂和作为活性物质的肽，特别地是作为黑皮质素 (melanocortin) 受体配体的肽。

[0002] 黑皮质素是调节肽的家族，其通过翻译后处理激素原阿黑皮质素原 (pro-hormone pro-opiomelanocortin) 而形成。黑皮质素已在多种正常人组织中发现，包括脑、肾上腺、皮肤、睾丸、脾、肾、卵巢、肺、甲状腺、肝、结肠、小肠和胰。已显示黑皮质素肽展现出多种生理活性，包括控制行为和记忆、影响神经营养和解热性质，以及影响免疫系统的调节、控制心血管系统、镇痛、温度调节和释放其它神经体液剂（包括催乳素、促黄体素和生物胺）。迄今为止已表征五种黑皮质素受体 (MC-R)：黑素细胞 - 特异性受体 (MC1-R)、肾上腺皮质 - 特异性 ACTH 受体 (MC2-R)、黑皮质素 -3(MC3-R)、黑皮质素 -4(MC4-R) 和黑皮质素 -5 受体 (MC5-R)。已对黑皮质素 (MC-R) 受体作为用于设计治疗体重病症如肥胖和恶病质的新型治疗剂的靶标产生极大兴趣。基因和药理学证据均指向中枢 MC4-R 受体作为首要目标。受体 - 选择性激动剂和拮抗剂的当前进展证实了黑皮质素受体活化的治疗潜力，特别是 MC4-R。由于这种治疗潜力，需要这类化合物的新制剂，特别是需要注射制剂。

[0003] 胃肠外注射于盐水中的可溶性活性药物成分经典地导致高数值的药物血浆峰浓度 (C_{max}) 和初始高变化率的血浆药物浓度，后者导致短时间 (T_{max}) 达到最大浓度 C_{max}，即突释效应。药动学 (PK) 曲线的这两种特征可诱导副作用，其可危及药物的开发和使用。

[0004] 因此确实需要开发下述药物组合物，即其改良 PK 曲线以减少 C_{max} 并增加 T_{max}，旨在得到平滑即释，从而减少副作用以及增加治疗的耐受性。

[0005] 申请人现在已发现：将某些胶凝剂引入特定药物组合物可满足上述目标。

[0006] 特别地是，已发现通过将至少一种水溶性或水可分散性胶凝剂引入包含特定肽的药物组合物，可以获得具有减少 C_{max} 的药物组合物。

[0007] 此类组合物的注射是快速且简单的，不会引起任何疼痛并且不需要任何特定技术。

[0008] 此外，该组合物的注射可能获得令人满意的物理性质，特别是在溶解度和可滤性方面。

[0009] 以特别有利的方式，申请人还发现根据本发明的组合物确保了肽的化学稳定性。

[0010] 此外，使用此类组合物的治疗允许改良体外肽释放。

[0011] 最后，根据本发明的组合物允许活性成分在至少 2 小时内持续释放。

[0012] 因此，本发明的一个主题为水性药物组合物，其包含作为活性物质的肽和一种或多种水溶性或水可分散性胶凝剂。

[0013] 本发明的其它特征、方面、主题和优势在阅读以下描述和实施例后将更为清楚。

[0014] 在下文中，除非另外指出，否则数值范围的限值包括在该范围内，尤其是在表述“在…范围”中。

[0015] 在下文中，术语“至少一种”等效于“一种或多种”。

[0016] 除非另外指出，否则列出下列定义以阐述并定义用于描述本发明的各种术语的含义和范围。

[0017] 术语“肽”被理解为意指含有至多50个氨基酸和/或分子量高达约6,000Da(6,000±200Da)的肽。

[0018] 术语“水溶性”胶凝剂被理解为意指根据本发明组合物中使用的胶凝剂可溶于水中。优选地,胶凝剂具有在25℃测量的高于10mg/mL、优选高于30mg/mL的水溶解度。

[0019] 术语“水可分散性”胶凝剂被理解为意指根据本发明组合物中使用的胶凝剂为可混溶的或可以以在25℃测量的高于10mg/mL、优选高于30mg/mL的浓度分散于水中。

[0020] 术语“胶凝剂”定义可与药物组合物溶解、分散或混合以改变其流变行为、更特别是其粘度并可产生较高粘度组合物或形成水凝胶的化合物。术语“胶凝剂”意指胶凝剂或胶凝剂混合物。

[0021] 本发明的药物组合物的活性成分为肽。

[0022] 优选地,肽选自一种或多种黑皮质素受体(MC-R)的配体。黑皮质素受体可选自黑素细胞-特异性受体(MC1-R)、肾上腺皮质-特异性ACTH受体(MC2-R)、黑皮质素-3(MC3-R)、黑皮质素-4(MC4-R)和黑皮质素-5受体(MC5-R)。

[0023] 本发明的药物组合物的活性成分可选自于PCT申请WO 2007/008704或WO 2008/147556中所述的那些。

[0024] 在一个优选实施方案中,肽为黑皮质素MC4受体的配体。

[0025] 在一个优选实施方案中,肽为式(I)化合物或其药学上可接受的盐:

[0026] $(R^2R^3)-A^1-c(A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9)-A^{10}-R^1$ (I)

[0027] 其中:

[0028] A^1为Acc、HN-$(CH_2)_m$-C(O)、L-或D-氨基酸或缺失;

[0029] A^2为Cys、D-Cys、hCys、D-hCys、Pen、D-Pen、Asp或Glu;

[0030] A^3为Gly、Ala、β-Ala、Gaba、Aib、D-氨基酸或缺失;

[0031] A^4为His、2-Pal、3-Pal、4-Pal、Taz、2-Thi、3-Thi或$(X^1、X^2、X^3、X^4、X^5)$Phe;

[0032] A^5为D-Phe、D-1-Nal、D-2-Nal、D-Trp、D-Bal、D-$(X^1、X^2、X^3、X^4、X^5)$Phe、L-Phe或D-(Et)Tyr;

[0033] A^6为Arg、hArg、Dab、Dap、Lys、Orn或HN-CH($(CH_2)_n$-N(R^4R^5))-C(O);

[0034] A^7为Trp、1-Nal、2-Nal、Bal、Bip、D-Trp、D-1-Nal、D-2-Nal、D-Bal或D-Bip;

[0035] A^8为Gly、D-Ala、Acc,Ala、β-Ala、Gaba、Apn、Ahx、Aha、HN-$(CH_2)_s$-C(O)或缺失;

[0036] A^9为Cys、D-Cys、hCys、D-hCys、Pen、D-Pen、Dab、Dap、Orn或Lys;

[0037] A^{10}为Acc、HN-$(CH_2)_t$-C(O)、L-或D-氨基酸或缺失;

[0038] R^1为-OH或$-NH_2$;

[0039] R^2和R^3在每次出现时独立地为H、(C_1-C_{30})烷基、(C_1-C_{30})杂烷基、(C_1-C_{30})酰基、(C_2-C_{30})烯基、(C_2-C_{30})炔基、芳基(C_1-C_{30})烷基、芳基(C_1-C_{30})酰基、取代的(C_1-C_{30})烷基、取代的(C_1-C_{30})杂烷基、取代的(C_1-C_{30})酰基、取代的(C_2-C_{30})烯基、取代的(C_2-C_{30})炔基、取代的芳基(C_1-C_{30})烷基或取代的芳基(C_1-C_{30})酰基;

[0040] R^4和R^5在每次出现时独立地为H、(C_1-C_{40})烷基、(C_1-C_{40})杂烷基、(C_1-C_{40})酰基、(C_2-C_{40})烯基、(C_2-C_{40})炔基、芳基(C_1-C_{40})烷基、芳基(C_1-C_{40})酰基、取代的(C_1-C_{40})烷基、取代的(C_1-C_{40})杂烷基、取代的(C_1-C_{40})酰基、取代的(C_2-C_{40})烯基、取代的(C_2-C_{40})炔基、取代的芳基(C_1-C_{40})烷基、取代的芳基(C_1-C_{40})酰基、(C_1-C_{40})烷基磺酰基或-C(NH)-NH_2;

[0041] m 在每次出现时独立地为 1、2、3、4、5、6 或 7；

[0042] n 在每次出现时独立地为 1、2、3、4 或 5；

[0043] s 在每次出现时独立地为 1、2、3、4、5、6 或 7；

[0044] t 在每次出现时独立地为 1、2、3、4、5、6 或 7；且

[0045] X^1、X^2、X^3、X^4和 X^5在每次出现时各自独立地为 H、F、Cl、Br、I、(C_1-C_{10}) 烷基、取代的 (C_1-C_{10}) 烷基、(C_2-C_{10}) 烯基、取代的 (C_2-C_{10}) 烯基、(C_2-C_{10}) 炔基、取代的 (C_2-C_{10}) 炔基、芳基、取代的芳基、OH、NH_2、NO_2、或 CN；

[0046] 前提条件是：

[0047] (I) 当 R^4为 (C_1-C_{40}) 酰基、芳基 (C_1-C_{40}) 酰基、取代的 (C_1-C_{40}) 酰基、取代的芳基 (C_1-C_{40}) 酰基、(C_1-C_{40}) 烷基磺酰基或 -C(NH)-NH_2时，那么 R^5为 H、(C_1-C_{40}) 烷基、(C_1-C_{40}) 杂烷基、(C_2-C_{40}) 烯基、(C_2-C_{40}) 炔基、芳基 (C_1-C_{40}) 烷基、取代的 (C_1-C_{40}) 烷基、取代的 (C_1-C_{40}) 杂烷基、取代的 (C_2-C_{40}) 烯基、取代的 (C_2-C_{40}) 炔基或取代的芳基 (C_1-C_{40}) 烷基；

[0048] (II) 当 R^2为 (C_1-C_{30}) 酰基、芳基 (C_1-C_{30}) 酰基、取代的 (C_1-C_{30}) 酰基或取代的芳基 (C_1-C_{30}) 酰基时，那么 R^3为 H、(C_1-C_{30}) 烷基、(C_1-C_{30}) 杂烷基、(C_2-C_{30}) 烯基、(C_2-C_{30}) 炔基、芳基 (C_1-C_{30}) 烷基、取代的 (C_1-C_{30}) 烷基、取代的 (C_1-C_{30}) 杂烷基、取代的 (C_2-C_{30}) 烯基、取代的 (C_2-C_{30}) 炔基或取代的芳基 (C_1-C_{30}) 烷基；

[0049] (III) A^3或 A^8或两者必须存在于所述化合物中；

[0050] (IV) 当 A^2为 Cys、D-Cys、hCys、D-hCys、Pen 或 D-Pen 时，那么 A^9为 Cys、D-Cys、hCys、D-hCys、Pen 或 D-Pen；

[0051] (V) 当 A^2为 Asp 或 Glu 时，那么 A^9为 Dab、Dap、Orn 或 Lys；

[0052] (VI) 当 A^8为 Ala 或 Gly 时，那么 A^1不为 Nle；以及

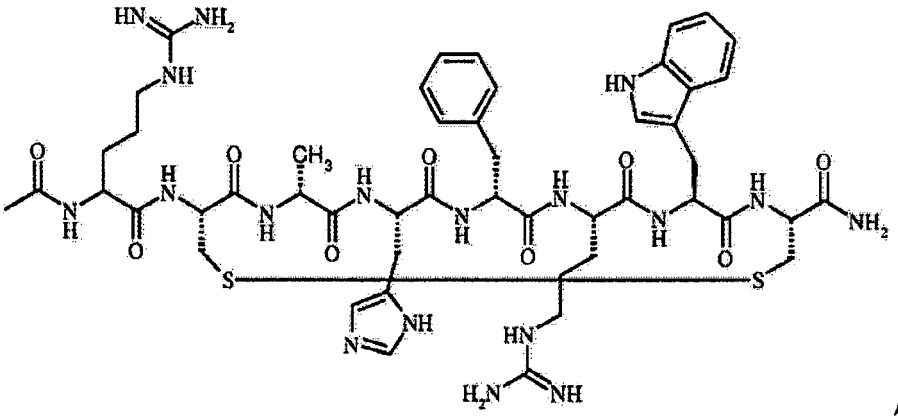
[0053] (VII) 当 A^1缺失时，那么 R^2和 R^3不可能均为 H。

[0054] 在一个优选实施方案中，肽为式 (I) 化合物或其药学上可接受的盐，其中 A^1为 Arg、D-Arg、hArg 或 D-hArg。

[0055] 优选地，本发明的药物组合物的活性物质为下式的肽：

[0056] Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2(肽 1)

[0057]

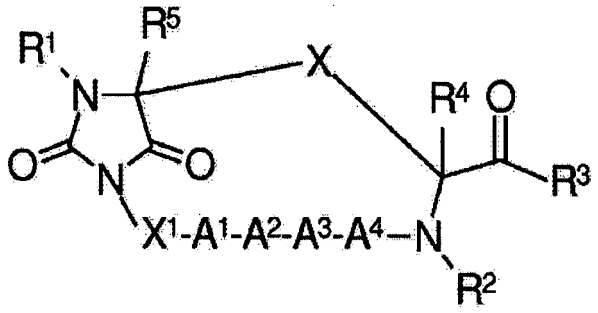


肽 1

[0058] 或其药学上可接受的盐。

[0059] 在一个优选实施方案中，肽为式 (II) 的化合物或其药学上可接受的盐：

[0060]



(II)

[0061] 其中乙内酰脲部分通过稠合 X^1 的氨基而形成，即，

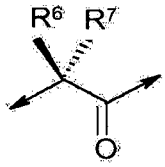
[0062] 其中：

[0063] X 选自下组：$-CH_2-S-S-CH_2-$、$-C(CH_3)_2-S-S-CH_2-$、$-CH_2-S-S-C(CH_3)_2-$、$-C(CH_3)_2-S-S-C(CH_3)_2-$、$-(CH_2)_2-S-S-CH_2-$、$-CH_2-S-S-(CH_2)_2-$、$-(CH_2)_2-S-S-(CH_2)_2-$、$-(CH_2)_2-S-S-C(CH_3)_2$、$-(CH_2)_t-C(O)-NR^8-(CH_2)_r-$ 和 $-(CH_2)_r-NR^8-C(O)-(CH_2)_t-$；

[0064] R^1 和 R^2 在其每次出现时各自独立地为 H、(C_1-C_{10}) 烷基或取代的 (C_1-C_{10}) 烷基；

[0065] R^3 为 -OH 或 $-NH_2$；

[0066] R^4 和 R^5 在其每次出现时各自独立地为 H、(C_1-C_{10}) 烷基或取代的 (C_1-C_{10}) 烷基；

[0067] X^1 为 

[0068] A^1 为 His、2-Pal、3-Pal、4-Pal、Taz、2-Thi、3-Thi、(X^1、X^2、X^3、X^4、X^5)Phe 或缺失；

[0069] A^2 为 D-Bal、D-1-Nal、D-2-Nal、D-Phe 或 D-(X^1、X^2、X^3、X^4、X^5)Phe；

[0070] A^3 为 Arg、hArg、Dab、Dap、Lys 或 Orn；

[0071] A^4 为 Bal、1-Nal、2-Nal、(X^1、X^2、X^3、X^4、X^5)Phe 或 Trp；

[0072] R^6 和 R^7 在其每次出现时各自独立地为 H、(C_1-C_{10}) 烷基、(C_1-C_{10}) 杂烷基、芳基 (C_1-C_5) 烷基、取代的 (C_1-C_{10}) 烷基、取代的 (C_1-C_{10}) 杂烷基或取代的芳基 (C_1-C_5) 烷基或 R^6 和 R^7 可以结合在一起形成环状部分；

[0073] R^8 为 H、(C_1-C_{10}) 烷基或取代的 (C_1-C_{10}) 烷基；

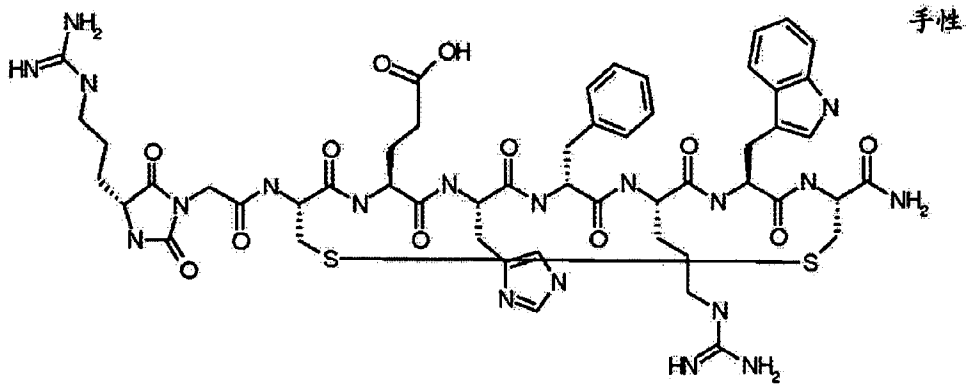
[0074] r 在其每次出现时独立地为 1、2、3、4 或 5；且

[0075] t 在其每次出现时独立地为 1 或 2。

[0076] 优选地，本发明的药物组合物的活性物质为下式的肽：

[0077] 乙内酰脲 (Arg-Gly))- 环 (Cys-Glu-His-D-Phe-Arg-Trp-Cys)-NH_2（肽 2）

[0078]



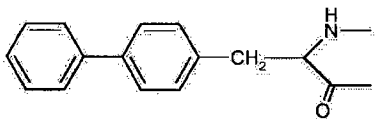
肽 2

[0079] 或其药学上可接受的盐。

[0080] 用于定义肽的命名为本领域中常用的命名，其中 N- 末端处的氨基出现在左边，C- 末端处的羧基出现在右边。当氨基酸具有异构形式时，其为所表示的氨基酸的 L 形式，除非另有明确指明。除非另有定义，否则本文所使用的所有技术和科学术语具有与本发明所属领域普通技术人员通常理解的含义相同的含义。同时，本文提及的所有公布、专利申请、专利和其它参考文献以引用方式并入。上文所用不同符号的含义如下：

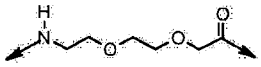
[0081] Abu：α- 氨基丁酸；Ac：酰基；Acc：1- 氨基 -1- 环 (C_3-C_9) 烷基羧酸；A3c：1- 氨基 -1- 环丙烷羧酸；A4c：1- 氨基 -1- 环丁烷羧酸；A5c：1- 氨基 -1- 环戊烷羧酸；A6c：1- 氨基 -1- 环己烷羧酸；Aha：7- 氨基庚酸；Ahx：6- 氨基己酸；Aib：α- 氨基异丁酸；Ala 或 A：丙氨酸；β-Ala：β- 丙氨酸；Apn：5- 氨基戊酸 (HN-$(CH2)_4$-C(O)；Arg 或 R：精氨酸；hArg：高精氨酸；Asn 或 N：天冬酰胺；Asp 或 D：天冬氨酸；Bal：3- 苯并噻吩基丙氨酸；Bip：4,4'- 联苯基丙氨酸，由以下结构表示：

[0082]



[0083] Bpa：4- 苯甲酰基苯基丙氨酸；4-Br-Phe：4- 溴 - 苯丙氨酸；Cha：β- 环己基丙氨酸；hCha：高 - 环己基丙氨酸；Chg：环己基甘氨酸；Cys 或 C：半胱氨酸；hCys：高半胱氨酸；Dab：2,4- 二氨基丁酸；Dap：2,3- 二氨基丙酸；Dip：β，β- 二苯基丙氨酸；Doc：8- 氨基 -3,6- 二氧杂辛酸，具有以下结构：

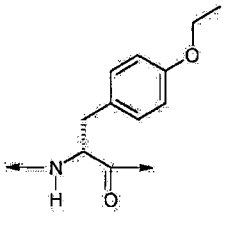
[0084]



[0085] 2-Fua：β-(2- 呋喃基)- 丙氨酸；Gaba：4- 氨基丁酸；Gln 或 Q：谷氨酰胺；Glu 或 E：谷氨酸；Gly 或 G：甘氨酸；His 或 H：组氨酸；3-Hyp：反 -3- 羟基 -L- 脯氨酸，即 (2S,3S)-3- 羟基吡咯烷 -2- 羧酸；4-Hyp：4- 羟基脯氨酸，即 (2S,4R)-4- 羟基吡咯烷 -2- 羧酸；Ile 或 I：异亮氨酸；Leu 或 L：亮氨酸；hLeu：高亮氨酸；Lys 或 K：赖氨酸；Met 或 M：蛋氨酸；β-hMet：β- 高甲硫氨酸；1-Nal：β-(1- 萘基) 丙氨酸；2-Nal：β-(2- 萘基) 丙氨酸；Nip：哌啶甲酸；Nle：正亮氨酸；Oic：八氢吲哚 -2- 羧酸；Orn：鸟氨酸；2-Pal：β-(2- 吡啶基) 丙氨酸；3-Pal：β-(3- 吡啶基) 丙氨酸；4-Pal：β-(4- 吡啶基) 丙氨酸；Pen：青霉

胺；Phe 或 F：苯丙氨酸；hPhe：高苯丙氨酸；Pro 或 P：脯氨酸；hPro：高脯氨酸。

[0086] Ser 或 S：丝氨酸；Tle：叔-亮氨酸；Taz：β-(4-噻唑基)丙氨酸；2-Thi：β-(2-噻吩基)丙氨酸；3-Thi：β-(3-噻吩基)丙氨酸；Thr 或 T：苏氨酸；Trp 或 W：色氨酸；Tyr 或 Y：酪氨酸；D-(Et)Tyr 具有以下结构：

[0087]  Val 或 V：缬氨酸。

[0088] 下列为本说明书中使用术语的定义。除非另外指出，否则本文为基团或术语提供的起始定义适用于在整篇本说明书中单独或作为另一基团的部分的该基团或术语。除非另有定义，否则本文所使用的所有技术和科学术语具有与本发明所属领域普通技术人员通常理解的含义相同的含义。

[0089] 术语“烷基”是指具有 1 至 12 个碳原子、优选 1 至 8 个碳原子的直链或支链烃基。低级烷基，即 1 至 4 个碳原子的烷基，是最优选的。当关于烷基或其它基团使用下标时，下标是指该基团可含有的碳原子数。术语“取代的烷基”是指具有一个、两个或三个取代基的如上文所定义的烷基，所述取代基选自下组：卤代、氨基、氰基、酮（=O）、$-OR_a$、$-SR_a$、$-NR_aR_b$、$-(C=O)R_a$、$-CO_2R_a$、$-C(=O)NR_aR_b$、$-NR_aC(=O)R_b$、$-NR_aCO_2R_b$、$-OC(=O)R_a$、$-OC(=O)NR_aR_b$、$-NR_cC(=O)NR_aR_b$、$NR_aSO_2R_d$、SO_2R_d、SO_3R_d、环烷基、芳基、杂芳基或杂环，其中基团 R_a、R_b 和 R_c 选自氢、(C_1-C_6) 烷基、芳基、杂芳基、杂环、环烷基、或被卤素、羟基、甲氧基、硝基、氨基、氰基、$-(C=O)H$、$-CO_2H$、$-(C=O)$ 烷基、$-CO_2$ 烷基、$-NH$（烷基）、$-NH$（环烷基）、$-N$（烷基）$_2$、羧基、酰基、$-C(=O)H$、$-C(=O)$ 苯基、$-CO_2-$ 烷基、环烷基、$-(C=O)NH_2$、$-(C=O)NH$（烷基）、$-(C=O)NH$（环烷基）、$-(C=O)N$（烷基）$_2$、$-C(=O)-(CH_2)_{1-2}NH_2$、$-C(=O)-(CH_2)_{1-2}NH$（烷基）、$-C(=O)-(CH_2)_{1-2}N$（烷基）$_2$、$-NH-CH_2-$ 羧基、$-NH-CH_2-CO_2-$ 烷基、苯基、苄基、苯乙基或苯基氧基取代的 (C_1-C_6) 烷基。基团 R_d 可选自与 R_a、R_b 和 R_c 相同的基团但不为氢。可选地，基团 R_a 和 R_b 可一起形成杂环或杂芳基环。应理解，当取代的烷基被芳基、环烷基、杂芳基或杂环取代时，此类环如下定义且由此可具有一个至三个在下面这些术语的定义中列出的取代基。当术语“烷基”在另一个特别命名的基团之后用作后缀时，例如芳基烷基或杂芳基烷基，该术语以更高特异性定义取代的烷基将含有的至少一个取代基。例如，芳基烷基是指通过烷基键合的芳基，或换句话说，取代的烷基具有 1 至 12 个碳原子和至少一个为芳基的取代基（例如苄基或联苯基）。“低级芳基烷基”是指取代的烷基，其具有 1 至 4 个碳原子和至少一个芳基取代基。

[0090] 术语“烯基”是指具有 2 至 12 个碳原子和至少一个双键的直链或支链烃基。2 至 6 个碳原子且具有一个双键的烯基是最优选的。

[0091] 术语“炔基”是指具有 2 至 12 个碳原子和至少一个三键的直链或支链烃基。2 至 6 个碳原子且具有一个三键的炔基是最优选的。取代的烯基或炔基将含有一个、两个或三个如上文对于烷基所定义的取代基。

[0092] 术语“亚烷基”是指具有 1 至 12 个碳原子、优选 1 至 8 个碳原子的二价直链或支链烃基，例如 $\{-CH_2-\}_n$，其中 n 为 1 至 12，优选 1 至 8。低级亚烷基基团，即 1 至 4 个碳原子

的亚烷基基团，是最优选的。术语“亚烯基”和“亚炔基”是指分别为烯基和炔基的二价基团，如上文所定义。取代的亚烷基、亚烯基和亚炔基可以具有如上文对于取代的烷基所定义的取代基。

[0093] 术语“烷氧基”是指基团 OR_e，其中 R_e 为烷基、取代的烷基、烯基、取代的烯基、炔基、取代的炔基、杂环或环烷基。因此，烷氧基包括如甲氧基、乙氧基、环丙基氧基、吡啶基氧基等基团。术语“芳氧基”是指基团 O（芳基）或 O（杂芳基），其中芳基和杂芳基如下定义。

[0094] 术语“烷基硫基”是指通过一个或多个硫（-S-）原子键合的如上文所定义的烷基或取代的烷基，例如 -S（烷基）或 -S（烷基 $-R_a$）。

[0095] 术语“烷氨基”是指通过一个或多个氮（$-NR_f-$）基团键合的如上文所定义的烷基或取代的烷基，其中 R_f 为氢、烷基、取代的烷基或环烷基。术语“酰基”是指通过一个或多个羰基 {-C（=O）-} 基团键合的如上文所定义的烷基或取代的烷基。当与另一基团结合使用术语酰基（如在酰基氨基中）时，这是指与第二命名的基团连接的羰基 {-C（=O）}。因此，酰基氨基是指 $-C(=O)NH_2$，取代的酰基氨基是指基团 -C（=O）NRR，且酰基芳基是指 -C（=O）（芳基）。

[0096] 术语“氨基酰基”是指基团 $-NR_fC(=O)R_g$，其中 R_g 为氢、烷基或取代的烷基，且 R_f 如上文对于烷氨基所定义。

[0097] 术语“卤代”或“卤素”是指氯、溴、氟和碘。除非另外指出，否则任何卤代烷基、卤代烷氧基或卤代烷基硫基含有一个或多个卤代原子（其卤代原子可以相同或不同）。

[0098] 术语“羧基”当单独使用时，是指基团 CO_2H。羧基烷基是指基团 CO_2R，其中 R 为烷基或取代的烷基。

[0099] 术语“磺酰基”是指与有机基团连接的亚砜基团（即 $-S(O)_{1-2}-$），所述有机基团包括如上文所定义的烷基、烯基、炔基、取代的烷基、取代的烯基、或取代的炔基。亚砜基团与其连接的有机基团可以为单价（例如 $-SO_2-$ 烷基）、或二价（例如 $-SO_2-$ 亚烷基等）。

[0100] 术语“环烷基”是指取代和未取代的 3 至 9 个碳原子的单环或双环烃基，其分别为完全饱和的或部分不饱和的，包括稠合芳基环，例如茚满。环烷基可被一个或多个（如一个至三个）选自以下的取代基取代：烷基、取代的烷基、氨基烷基、卤素、氰基、硝基、三氟甲基、羟基、烷氧基、烷氨基、磺酰基、$-SO_2$（芳基）、$-CO_2H$、$-CO_2-$ 烷基、-C（=O）H、酮、-C（=O）$-(CH_2)_{1-2}NH_2$、-C（=O）$-(CH_2)_{1-2}NH$（烷基）、-C（=O）$-(CH_2)_{1-2}N$（烷基）$_2$、酰基、芳基、杂环、杂芳基、或 3 至 7 个碳原子的另一环烷基环。术语“亚环烷基”是指在两个其它基团之间形成环状物或间隔子的环烷基，即亚环烷基为与至少两个其它基团键合的环烷基。术语环烷基包括具有三个至四个碳原子的碳 - 碳桥或具有与其联接的苯环的饱和的或部分不饱和的碳环。当环烷基被另一个环取代时，所述另一个环可具有一个至两个选自 R_k 的取代基，其中 R_k 为低级烷基、羟基、低级烷氧基、氨基、卤素、氰基、三氟甲基、三氟甲氧基、硝基，和被一个至两个羟基、低级烷氧基、氨基、卤素、氰基、三氟甲基、三氟甲氧基和 / 或硝基取代的低级烷基。

[0101] 术语“芳基”是指取代和未取代的苯基、1- 萘基和 2- 萘基，其中苯基是优选的。芳基可具有零个、一个、两个或三个选自下组的取代基：烷基、取代的烷基、烷氧基、烷基硫基、卤代、羟基、硝基、氰基、氨基、三氟甲基、三氟甲氧基、磺酰基、$-SO_2$（芳基）、-NH（烷基）、-NH（环烷基）、-N（烷基）$_2$、羧基、酰基、-C（=O）H、-C（=O）苯基、$-CO_2-$ 烷基、环烷

基、-(C = O)NH_2、-(C = O)NH(烷基)、-(C = O)NH(环烷基)、-(C = O)N(烷基)$_2$、-NH-CH_2-羧基、-NH-CH_2-CO_2-烷基、-C(=O)-$(CH_2)_{1-2}NH_2$、-C(=O)-$(CH_2)_{1-2}$NH(烷基)、-C(=O)-$(CH_2)_{1-2}$N(烷基)$_2$、苯基、苄基、苯乙基、苯基氧基、苯基硫基、杂环、杂芳基、或(C_3-C_7)环烷基环。术语"亚芳基"是指在两个其它基团之间形成环状物或间隔子的如上文所定义的芳基,即亚芳基是与至少两个其它基团键合的芳基。当芳基被另一个环取代时,所述另一个环可具有一个至两个选自R_k的取代基,其中R_k如上文所定义。

[0102] 术语"杂环"是指取代和未取代的非芳族3-至7-元单环基团、7-至11-元双环基团和10-至15-元三环基团,其在至少一个环中具有至少一个杂原子(O、S或N)。含有杂原子的杂环基团的各环可含有一个或两个氧或硫原子和/或一个至四个氮原子,前提条件是各环中杂原子的总数为四个或四个以下,且另一前提条件是该环含有至少一个碳原子。完成双环和三环基团的稠环可仅含有碳原子并且可以为饱和的、部分饱和的或不饱和的。氮和硫原子可任选地被氧化并且氮原子可任选地被季铵化。杂环基团可以在任何可用的氮或碳原子上连接。杂环可以含有一个、两个或三个选自下组的取代基:卤代、氨基、氰基、烷基、取代的烷基、三氟甲基、三氟甲氧基、磺酰基、-SO_2(芳基)、-NH(烷基)、-NH(环烷基)、-N(烷基)$_2$、烷氧基、烷基硫基、羟基、硝基、苯基、苄基、苯乙基、苯基氧基、苯基硫基、羧基、-CO_2-烷基、环烷基、-C(=O)H、酰基、-(C = O)NH_2、-(C = O)NH(烷基)、-(C = O)NH(环烷基)、-(C = O)N(烷基)$_2$、-NH-CH_2-羧基、-NH-CH_2-CO_2-烷基、-C(=O)-$(CH_2)_{1-2}NH_2$、-C(=O)-$(CH_2)_{1-2}$NH(烷基)、-C(=O)-$(CH_2)_{1-2}$N(烷基)$_2$、杂环、杂芳基、(C_3-C_7)环烷基环、酮、=N-OH、=N-O-低级烷基、或五元或六元缩酮,即,1,3-二氧戊环或1,3-二噁烷。当杂环基团被另一个环取代时,所述另一个环可具有一个至两个选自R_k的取代基,其中R_k如上文所定义。示例性的单环基团包括氮杂环丁基、吡咯烷基、氧杂环丁基、咪唑啉基、噁唑烷基、异噁唑啉基、噻唑烷基、异噻唑烷基、四氢呋喃基、哌啶基、哌嗪基、2-氧代哌嗪基、2-氧代哌啶基、2-氧代吡咯烷基、2-氧代氮杂䓬基、氮杂䓬基、4-哌啶酮基、四氢吡喃基、吗啉基、硫吗啉基、硫吗啉基亚砜、硫吗啉基砜、1,3-二氧戊环和四氢-1,1-二氧代噻吩基等。示例性的双环杂环基团包括奎宁环基。

[0103] 术语"杂芳基"是指取代和未取代的芳族5-或6-元单环集团、9-或10-元双环基团和11-至14-元三环集团,其在至少一个环中具有至少一个杂原子(O、S或N)。含有杂原子的杂芳基的各环可含有一个或两个氧或硫原子和/或一个至四个氮原子,前提条件是各环中杂原子的总数为四个或四个以下,且各环含有至少一个碳原子。完成双环和三环基团的稠环可仅含有碳原子并且可以为饱和的、部分饱和的或不饱和的。氮和硫原子可任选地被氧化并且氮原子可任选地被季铵化。为双环或三环的杂芳基必须包括至少一个完全芳环但是一个或多个其它稠合的环可以为芳族或非芳族的。杂芳基可以在任何环的任何可用的氮或碳原子上连接。杂芳基环状系统可含有一个、两个或三个选自下组的取代基:卤代、氨基、氰基、烷基、取代的烷基、三氟甲基、三氟甲氧基、磺酰基、-SO_2(芳基)、-NH(烷基)、-NH(环烷基)、-N(烷基)$_2$、烷氧基、烷基硫基、羟基、硝基、苯基、苄基、苯乙基、苯基氧基、苯基硫基、羧基、-CO_2-烷基、环烷基、-C(=O)H、酰基、-(C = O)NH_2、-(C = O)NH(烷基)、-(C = O)NH(环烷基)、-(C = O)N(烷基)$_2$、-NH-CH_2-羧基、-NH-CH_2-CO_2-烷基、-C(=O)-$(CH_2)_{1-2}NH_2$、-C(=O)-$(CH_2)_{1-2}$NH(烷基)、-C(=O)-$(CH_2)_{1-2}$N(烷基)$_2$、杂环、杂芳基、或(C_3-C_7)环烷基环。杂环可以具有被一个或多个氧(=O)原子取代的硫杂原子。示例性的

单环杂芳基包括吡咯基、吡唑基、吡唑啉基、咪唑基、噁唑基、异噁唑基、噻唑基、噻二唑基、异噻唑基、呋喃基、噻吩基、噁二唑基、吡啶基、吡嗪基、嘧啶基、哒嗪基、三嗪基等。示例性的双环杂芳基包括吲哚基、苯并噻唑基、苯并二氧杂环戊烯基、苯并噁唑基、苯并噻吩基、喹啉基、四氢异喹啉基、异喹啉基、苯并咪唑基、苯并吡喃基、中氮茚基、苯并呋喃基、色酮基、香豆素基、苯并吡喃基、噌啉基、喹喔啉基、吲唑基、吡咯并吡啶基、呋喃并吡啶基、二氢异吲哚基、四氢喹啉基等。示例性的三环杂芳基包括咔唑基、苯并吲哚基、菲咯啉基、吖啶基、菲啶基、呫吨基等。

[0104] 本发明的药物组合物的肽可以呈盐形式或作为游离碱。

[0105] 根据一个优选的实施方案，肽为呈盐形式。

[0106] 优选地，肽的药学上可接受的盐为乙酸盐或庚酸盐。

[0107] 更优选地，肽的药学上可接受的盐为乙酸盐。

[0108] 在一个优选实施方案中，本发明的组合物的活性物质为呈盐形式、优选呈乙酸盐或庚酸盐的下式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽。在更优选的实施方案中，肽 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2为乙酸盐。

[0109] 有利地，相对于组合物的总重量，肽或其盐以按重量计 0.1 至 25％范围的浓度存在。更优选，相对于组合物的总重量，肽或其盐以按重量计 0.1 至 10％范围、甚至更优选地按重量计 0.2 至 6％、甚至仍更优选地 0.3 至 2％的浓度存在。

[0110] 根据本发明，药物组合物包含水溶性或水可分散性胶凝剂。

[0111] 对于本发明目的，术语“胶凝剂”意指当以按重量计 0.5 至 40％的浓度在水溶液中引入时可能在 25℃和 1 至 $10s^{-1}$的剪切速率下实现至少 100cPs、优选至少 500cPs 的动态粘度的试剂。该粘度可使用粘度计例如呈锥－板几何构型的受控应力粘度计、例如来自 Thermo Electron 的 Haake RS1 粘度计测量。

[0112] 作为胶凝剂，可以提及例如多元醇如甘油和丙二醇、聚醚如聚乙二醇、纤维素衍生物如微晶纤维素、羧甲基纤维素钠、甲基纤维素、乙基纤维素、羟乙基纤维素、羟丙基纤维素和羟丙基甲基纤维素、单糖或多糖如透明质酸钠、壳聚糖、淀粉和淀粉衍生物、聚乙烯吡咯烷酮、明胶、乙酸锌及其混合物。

[0113] 胶凝剂含有一种或多种聚醚、一种或多种多元醇及其混合物。

[0114] 根据本发明，胶凝剂选自聚醚、多元醇及其混合物。

[0115] 更优选地，胶凝剂选自聚醚和多元醇。

[0116] 优选地，胶凝剂以相对于组合物的总重量按重量计 0.5 至 70％范围的浓度存在。更优选，胶凝剂以相对于组合物总重量按重量计 10 至 50％、甚至更优选地按重量计 15 至 40％、甚至仍更优选地按重量计 20 至 40％范围的浓度存在。

[0117] 在一个优选实施方案中，本发明涉及水性药物组合物，其包含：

[0118] －作为活性成分的肽，和

[0119] －一种或多种水溶性或水可分散性胶凝剂，

[0120] 所述肽选自一种或多种黑皮质素受体 (MC-R) 的配体或其药学上可接受的盐，和

[0121] 所述胶凝剂以相对于组合物总重量按重量计 10 至 50％范围的浓度存在。

[0122] 在另一优选的实施方案中，本发明涉及水性药物组合物，其包含：

[0123] －作为活性成分的肽，和

[0124] -一种或多种水溶性或水可分散性胶凝剂，

[0125] 所述肽选自一种或多种黑皮质素受体 (MC4-R) 的配体或其药学上可接受的盐，和

[0126] 所述胶凝剂以相对于组合物总重量按重量计 10 至 50％范围的浓度存在。

[0127] 在另一优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2或其药学上可接受的盐，和以相对于组合物总重量按重量计 10 至 50％范围的浓度的胶凝剂。

[0128] 在另一优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐或庚酸盐，和以相对于组合物总重量按重量计 10 至 50％范围的浓度的胶凝剂。在最优选的实施方案中，活性成分为 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐。

[0129] 在一个优选实施方案中，胶凝剂为聚醚或聚醚混合物。

[0130] 优选地，胶凝剂为以相对于组合物总重量按重量计 10 至 50％范围的浓度存在的聚醚。更优选，胶凝剂为聚醚且以相对于组合物总重量按重量计 10 至 40％范围的浓度存在。甚至更优选地，胶凝剂为聚醚且以相对于组合物总重量按重量计 20 至 35％范围的浓度存在。

[0131] 在更优选的实施方案中，胶凝剂为选自聚乙二醇的聚醚。在另一优选的实施方案中，胶凝剂为聚醚 PEG 400。

[0132] 在特定实施方案中，胶凝剂为聚醚 PEG 400 且以相对于组合物总重量按重量计 15 至 40％范围的浓度存在。更优选，胶凝剂为聚醚 PEG 400 且以相对于组合物总重量按重量计 20 至 35％范围的浓度存在。

[0133] 在另一优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2或其药学上可接受的盐，和作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％、更优选按重量计 20 至 35％范围的浓度的聚乙二醇。

[0134] 在另一优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐或庚酸盐，作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％、更优选按重量计 20 至 35％范围的浓度的聚乙二醇。在最优选的实施方案中，活性成分为 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐。

[0135] 在另一优选的实施方案中，胶凝剂为多元醇或多元醇混合物。

[0136] 优选地，胶凝剂为以相对于组合物总重量按重量计 10 至 50％范围的浓度存在的多元醇。更优选地，胶凝剂为以相对于组合物总重量按重量计 15 至 40％范围的浓度存在的多元醇。甚至更优选地，胶凝剂为多元醇且以相对于组合物总重量按重量计 25 至 40％范围的浓度存在。

[0137] 更特别地是，胶凝剂为作为多元醇的甘油。

[0138] 在特定实施方案中，胶凝剂为作为多元醇的甘油且以相对于组合物总重量按重量计 15 至 40％范围的浓度存在。更优选，胶凝剂为作为多元醇的甘油且以相对于组合物总重

量按重量计 25 至 40％范围的浓度存在。

[0139] 在更优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2或其药学上可接受的盐，和作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％、更优选按重量计 25 至 40％范围的浓度的甘油。

[0140] 在更优选的实施方案中，根据本发明的组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐或庚酸盐，和作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％、更优选按重量计 25 至 40％范围的浓度的甘油。在最优选的实施方案中，活性成分为 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐。

[0141] 根据本发明的组合物还可包含一种或多种添加剂如表面活性剂。这些添加剂包括脂肪酸及其盐、多元醇、聚氧醚、泊洛沙姆、聚山梨酯和聚氧乙烯脂肪酸酯。

[0142] 在一个优选实施方案中，根据本发明的组合物仅包含作为活性物质的肽和水溶性或水可分散性胶凝剂。

[0143] 优选地，根据本发明的组合物仅包含式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的一种或多种多元醇。

[0144] 更优选地，根据本发明的组合物仅包含式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的甘油。

[0145] 甚至更优选地，根据本发明的组合物仅包含以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％范围的浓度的甘油。当然，存在水（注射级用水）用来完成配制至 100％ (w/w)（适量 100％）。

[0146] 在更优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2或其药学上可接受的盐，作为胶凝剂的以相对于组合物总重量按重量计 25 至 40％范围的浓度的甘油，和水（注射用水适量至 100％）。

[0147] 在更优选的实施方案中，根据本发明的水性组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐或庚酸盐，作为胶凝剂的以相对于组合物总重量按重量计 25 至 40％范围的浓度的甘油，和水（注射用水适量至 100％）。在最优选的实施方案中，活性成分为 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐。

[0148] 仍更优选地，根据本发明的组合物仅包含以相对于组合物总重量按重量计 0.3 至 2％范围的浓度的式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的以相对于组合物总重量按重量计 25 至 40％范围的浓度的甘油。当然，存在水（注射级用水）用来完成配制至 100％ (w/w)（适量 100％）。

[0149] 在另一优选的实施方案中，根据本发明的组合物仅包含式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的一种或多种聚醚。

[0150] 优选地，根据本发明的组合物仅包含式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp

-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的一种或多种聚乙二醇。

[0151] 在另一优选的实施方案中，根据本发明的组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2或其药学上可接受的盐，作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％、更优选按重量计 20 至 35％范围的浓度的聚乙二醇，和水（注射用水适量至 100％）。

[0152] 在另一优选的实施方案中，根据本发明的组合物包含作为活性成分的以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐或庚酸盐，作为胶凝剂的以相对于组合物总重量按重量计 20 至 35％范围的浓度的聚乙二醇，和水（注射用水适量至 100％）。在最优选的实施方案中，活性成分为 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的乙酸盐。

[0153] 更优选地，根据本发明的组合物仅包含式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐和作为胶凝剂的 PEG 400。

[0154] 甚至更优选，根据本发明的组合物仅包含以相对于组合物总重量按重量计 0.1 至 10％范围的浓度的式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐，和作为胶凝剂的以相对于组合物总重量按重量计 15 至 40％范围的浓度的 PEG 400。仍更优选，根据本发明的组合物仅包含以相对于组合物总重量按重量计 0.3 至 2％范围的浓度的式 Ac-Arg-c(Cys-D-Ala-His-D-Phe-Arg-Trp-Cys)-NH_2的肽或其药学上可接受的盐，和作为胶凝剂的以相对于组合物总重量按重量计 20 至 35％范围的浓度的 PEG 400。当然，存在水（注射级用水）用来完成配制至 100％ (w/w)（适量 100％）。

[0155] 本发明的组合物可通过将肽、一种或多种水溶性或水可分散性胶凝剂和任选的添加剂（如果有的话）在水中混合来制备。

[0156] 根据本发明的药物组合物通过胃肠外途径施用。在一个优选实施方案中，本发明的组合物通过皮下途径、优选通过皮下输注来施用。

[0157] 根据本发明的药物组合物通过胃肠外途径、经由 27Gauge(G) 针头、更优选经由 29G 针头容易地施用。

[0158] 在一个优选实施方案中，根据本发明的组合物被配制使得肽在需要其的对象体内释放延长的时间段。

[0159] 根据本发明的组合物可用于胃肠外施用，以使肽持续释放至少 2 小时、3 小时、4 小时、5 小时、6 小时、8 小时、10 小时、12 小时或 24 小时。

[0160] 在一个优选实施方案中，根据本发明的组合物允许持续释放至少 2 小时。在另一优选的实施方案中，根据本发明的组合物允许持续释放至少 3 小时。在另一优选的实施方案中，根据本发明的组合物允许持续释放至少 6 小时。在更优选的实施方案中，根据本发明的组合物允许持续释放至少 8 小时。在另一更优选的实施方案中，本发明的组合物允许持续释放至少 10 小时，更优选 12 小时。

[0161] 根据本发明的药物组合物特别可用于治疗体重病症如肥胖和恶病质。

[0162] 提供下列实施例以说明上述程序并且不应被认为限制本发明的范围。

[0163] 实验部分

[0164] 实施例 1：制备工艺

[0165] 根据下列工艺、用作为活性成分的肽 1 来制备根据本发明的各种组合物：

[0166] 于室温在磁力搅拌下将胶凝剂掺混（当可混溶时）或溶解（当可溶时）于注射用水中至少 15min。对肽盐精确称量，在磁力搅拌下将其溶解于先前制备的组合物中直到获得澄清溶液。配制组合物的实例于表 1 中报道：

[0167] 表 1

[0168]

组合物 #	肽 1 盐	肽 1 盐的含量	胶凝剂	胶凝剂含量	注射用水 (1) 含量
1	乙酸盐	0.4%	PEG 400	32%	适量至 100%
2	乙酸盐	0.4%	PEG 400	22%	适量至 100%
3	乙酸盐	0.4%	甘油	38%	适量至 100%
4	庚酸盐	0.4%	PEG 400	32%	适量至 100%

[0169] (1) 意指注射用水。

[0170] 肽盐含量以产物相对于组合物总重量的重量百分比表示。胶凝剂含量以试剂相对于组合物总重量的重量百分比表示。

[0171] 在以下实施例 2、4 和 5 所述的不同试验中使用表 1 的四种制剂。

[0172] 实施例 2：可滤性测试

[0173] 使用配备有 1mL Terumo 注射器的 Millex GV PVDF（低蛋白结合 **Durapore®** 聚偏二氟乙烯）0.22 μm 滤器手动评价组合物 1-4 的可滤性。

[0174] 显示所有制剂为可滤的。

[0175] 实施例 3：溶解度测试

[0176] 在过滤后使用 HPLC 分析来评价表 1 的胶凝组合物中肽 1 盐的溶解度。表 2 中给出用于这种评价的方法 1 和 2 的技术参数。

[0177] 表 2

[0178]

	HPLC 方法 1	**HPLC 方法 2**
柱	**YMC-ODS-AM 250x4.6mm 5μm**	**YMC-ODS-AM 150x4.6mm 3μm**
温度	**30℃**	**40℃**
流动相	**A: NaH_2PO_4 (50 mM, pH 2.5)** **B: 乙腈**	**A: H_2O + TFA (0.05 %)** **B: 乙腈+ TFA (0.05 %)** **C: 甲醇+ TFA (0.05 %)**

[0179]

流速	1.0mL/min				1.0mL/min				
UV 检测	220 nm				220 nm				
保留时间	~31.5min				~24.6min				
分析持续时间	60min				60min				
标准(100 %)	0.6mg/mL				0.6mg/mL				
注入体积	10μL				10μL				
稀释溶剂	乙酸 0.1 N				乙酸 0.1 N				
梯度	时间	%A	%B	曲线	时间	%A	%B	%C	曲线
	0	90	10	/	0	85	5	10	/
	35	83	17	6	45	70	15	15	6
	50	70	30	6	47	85	5	10	6
	51	90	10	6	60	85	5	10	6
	60	90	10	6					

[0180] 在所有制剂中，肽盐呈现至少 4mg/mL 的溶解度。更精确地，肽 1 乙酸盐显示于 32% PEG 400 和于 38%甘油中的至少 100mg/mL 的溶解度。肽 1 庚酸盐显示于 32% PEG 400 中的 28.1mg/mL 的溶解度。这意指在表 1 的所有制剂中，肽盐完全溶解。

[0181] 实施例 4：可注射性测试

[0182] 使用牵引 / 压缩机评价组合物 1-4 的可注射性，该牵引 / 压缩机在从配有针头的 1mL 注射器模拟注入制剂的期间测量注射强度。

[0183] 最大耐受强度为 15N，且对于每日皮下注射而言，最适合的针头直径不小于 27Gauge。

[0184] 所有制剂已显示可经由 27G 针头注射。

[0185] 实施例 5：体外测试

[0186] 开发体外测试试验并将其用于评价水性制剂 1-4 对肽释放曲线的影响。该试验是基于肽从制剂经由琼脂糖层扩散到保持在 37℃的磷酸盐缓冲液盐水 pH 7.4。

[0187] 在磁力搅拌下将 100mg 琼脂糖在 80℃溶解于 5mL 水中。在总琼脂糖溶解后，将溶液于 60℃冷却。

[0188] 将对应于 800 μg 肽的 200 μL 制剂引入小瓶中。将制剂用 300 μL 在 60℃加热的温热琼脂糖溶液悬浮。然后将掺混物混合并在室温冷却 10min，产生第一凝胶层。

[0189] 将 300 μL 60℃温热琼脂糖制剂 - 游离加入到第一凝胶层的顶部以形成第二层。然后将第二凝胶层在室温冷却 10min。

[0190] 将第二琼脂糖层用作为释放介质的 3.4mL 保持在 37℃的 PBS 缓冲液覆盖。

[0191] 将小瓶用搅拌棒塞住并在 37℃置于 200rpm 的水平旋转振荡器中。

[0192] 在开始试验后的下列时间，在小瓶的上半部分中取出 500 μL 释放介质用于 UV 分析：15min、30min、1h、3h、5h、9h、16h、24h 和 30h。

[0193] 取出用于分析的等分试样用等体积的新鲜 PBS 缓冲液替换。在 UV 分析前将各样品用新鲜 PBS 缓冲液稀释 1/2。

[0194] 使用 UV 分光光度计（Perkin **Elmer®**）在 280nm 测量肽含量。以每个时间点计算肽浓度，考虑先前取出的各肽量。

[0195] 于介质中释放的肽的浓度被报道为时间的函数。

[0196] 用图示评价 50％肽从制剂中释放至释放介质的时间（$T_{50\%}$），并且用于比较各种制剂。

[0197] 图 1 中给出显著地改变肽释放的胶凝制剂的体外释放曲线。

[0198] 与盐水中的参考相比，制剂 1 和 3 表明肽释放放缓非常明显。对于制剂 1 和 3，$T_{50\%}$ 值分别等于 17.7h 和 19.9h，而于盐水中的参考的值为 7.8h。

[0199] 也确认制剂 2 和 4 的释放放缓，其中 $T_{50\%}$ 等于 20.7h（对于制剂 4）且等于 16.2h（对于制剂 2）。

[0200] 实施例 6：化学稳定性

[0201] 将作为胶凝剂的 PEG 400 或甘油制备的制剂在 40℃储存 3 个月且在 5℃和 25℃储存 6 个月。

[0202] 使用表 2 中描述的 HPLC 方法 1 和 2，在不同时间点执行 HPLC 分析以评价这些化合物的化学稳定性。

[0203] 以最大耐受赋形剂含量和以下各项制备选定制剂：

[0204] - 以针对人的最大估算剂量，如下：

[0205] • 100mg 肽 1 乙酸盐 /mL 30％ PEG 400（制剂 A），

[0206] • 100mg 肽 1 乙酸盐 /mL 32.5％甘油（制剂 B），

[0207] - 或以于 30％ PEG 400 中的最大庚酸盐溶解度，如下：

[0208] • 28mg 肽 1 庚酸盐 /mL 30％ PEG 400（制剂 C）。

[0209] 上述制剂的支持性稳定性数据分别示于表 3、4 和 5 中。

[0210] 表 3（制剂 A）

[0211]

	T0	温度	T1M	Δ(%)	T2M	Δ(%)	T3M	Δ(%)	T6M	Δ(%)
估算含量 (mg/mL)	88.1	40℃			73.3	-16.8	67.6	-23.3		
		25℃	89.7	1.9	89.2	1.3	87.6	-0.5	87.5	-0.6
		5℃					89.9	2.0	92.7	5.2
总杂质总和 (%)	4.3	40℃			16.0	11.7	21.1	16.8		
		25℃	4.9	0.6	5.6	1.3	6.1	1.8	7.9	3.6
		5℃					5.1	0.8	4.8	0.5

[0212] 表 4(制剂 B)

[0213]

	T0	温度	T1M	Δ(%)	T2M	Δ(%)	T3M	Δ(%)	T6M	Δ(%)
估算含量(mg/mL)	88.5	40℃			70.7	-20.1	65.6	-25.9		
		25℃	89.7	1.4	88.9	0.4	87.0	-1.7	88.6	0.1
		5℃					88.3	-0.2	93.0	5.1
总杂质总和(%)	4.2	40℃			18.7	14.7	23.6	19.4		
		25℃	4.7	0.5	5.4	1.2	6.2	2.0	8.0	3.8
		5℃					4.7	0.5	4.7	0.5

[0214] 于 25℃ 6 个月后总杂质的增加是适度的且不超过 5%。于 5℃ 6 个月后,这些制剂未呈现总杂质水平的任何显著性增加。

[0215] 表 5(制剂 C)

[0216]

	T0	温度	T1M	Δ(%)	T2M	Δ(%)	T3M	Δ(%)	T6M	Δ(%)
估算含量(mg/mL)	27.5	40℃			23.6	-14.1	21.7	-21.2		
		25℃	26.3	-4.3	28.7	4.5	28.6	4.2		
		5℃					23.1	-16.0		
总杂质总和(%)	5.6	40℃			14.4	8.8	23.8	18.2		
		25℃	6.9	1.3	7.3	1.7	9.0	3.4	12.9	7.3
		5℃					7.0	1.4	8.5	2.9

[0217] 制剂 C 于 25℃ 3 个月后也呈现总杂质的适度增加,不超过 5%。

[0218] 于 5℃ 6 个月后,该制剂呈现总杂质水平的适度增加;总杂质的这种增加倾向于大幅高于具有乙酸盐的先前制剂所获得的增加,但仍保持低于 5%。

[0219] 然后制备选定制剂以评价在较低剂量下注射的可能性:

[0220] • 10mg 肽 1 乙酸盐 /mL 30% PEG 400(制剂 D),

[0221] • 7.5mg 肽 1 庚酸盐 /mL 22.5% PEG 400(制剂 E)。

[0222] 上述制剂的支持性稳定性数据分别示于表 6 和 7 中:

[0223] 表 6(制剂 D)

[0224]

	T0	温度	T1M	Δ(%)	T3M	Δ(%)
估算含量(mg/mL)	10.0	40℃	9.9	-0.5	9.1	-9.1
		25℃			10.1	1.3
总杂质总和(%)	2.4	40℃	4.7	2.3	6.9	4.5
		25℃			3.0	0.6

[0225] 表 7(制剂 E)

[0226]

	T0	温度	T3M	Δ(%)
估算含量(mg/mL)	6.3	40℃	5.5	-12.8
		25℃	6.3	0.5
总杂质总和(%)	7.7	40℃	10.6	2.9
		25℃	7.1	0.6

[0227] 在 40℃ 3 个月后,这些制剂呈现总杂质的适度增加趋向于 5%,而在 25℃ 3 个月后,未呈现总杂质水平的任何显著性增加。

[0228] 实施例 7:体内测试

[0229] 在大鼠中评价根据本发明制剂的 PK 曲线。每种制剂使用四只一组分成两组的八只大鼠。每只动物以 0.5mg/kg 的剂量接受皮下 (SC) 注射,然后在不同时间点经由颈静脉导管交替地对每组执行血液取样。通过 LC-MS 分析确定血浆浓度。通过 WinNonLin 分析计算 PK 参数。

[0230] 将将 PK 值与在相同条件下注射于盐水溶液中的肽后获得的 PK 值相比较。PK 曲线呈现于图 2(大鼠中的 PK 曲线 -450nmole/kg,0.5mg/kg,SC) 中。

[0231] 制剂 2 和盐水参考的 PK 参数示于表 8 中。

[0232] 表 8

[0233]

	参考	制剂 2
T_{max}(min)	30	60
C_{max}(ng/ml)	346	164
$T_{1/2}$(min)	49.4	52.4
MRT(min)	74.5	102
AUC(min.ng/ml)	29.6	20.1

[0234] C_{max}:于 PK 曲线中出现的最大药物血浆浓度 ;AUC :曲线下面积 ;MRT :介质滞留时间 ;T_{max}:对应于 C_{max}值的时间 ;$T_{1/2}$:半衰期。

[0235] 这些结果证实 :对于 22% PEG 400 的浓度而言,C_{max}显著性降低以及 T_{max}增加 2 倍。在大鼠中,制剂 2 看似足够有效地显著降低 C_{max}并增加 T_{max}。

[0236] 制剂 4 的 PK 曲线和参数分别呈现于图 3(大鼠中的 PK 曲线 -450nmole/kg,0.5mg/kg,SC) 和表 9(制剂 4 和 DMA/ 盐水参考的 PK 参数) 中。

[0237] 表 9

[0238]

	参考	制剂 4
T_{max}(min)	60	120
C_{max}(ng/ml)	362	163
$T_{1/2}$(min)	186	189
MRT(min)	145	191
AUC(min.ng/ml)	71.7	35.9

[0239] 与制剂 2 类似,制剂 4 呈现 C_{max}降低超过 2 倍以及 T_{max}增加 2 倍。

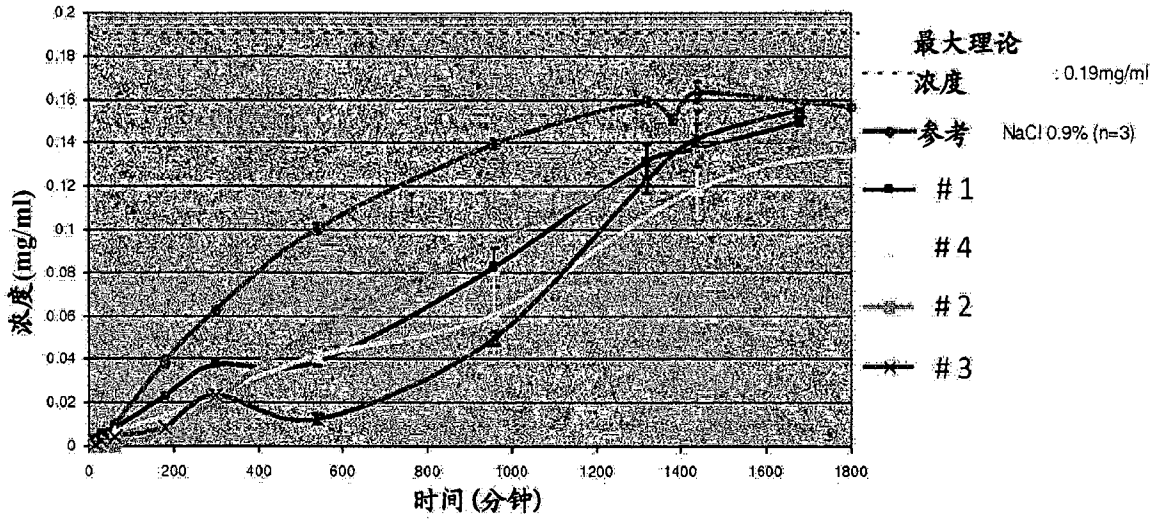

浓度(mg/ml)
时间(分钟)
最大理论浓度 : 0.19mg/ml
参考 NaCl 0.9% (n=3)
#1
#4
#2
#3

图 1

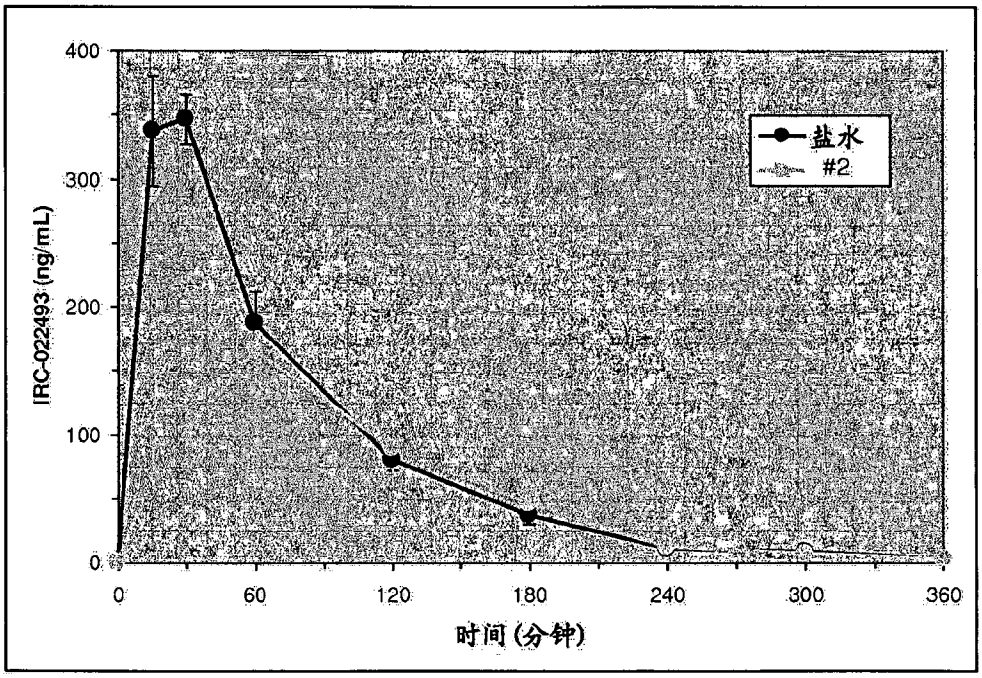

IRC-022493 (ng/mL)
时间(分钟)
盐水
#2

图 2

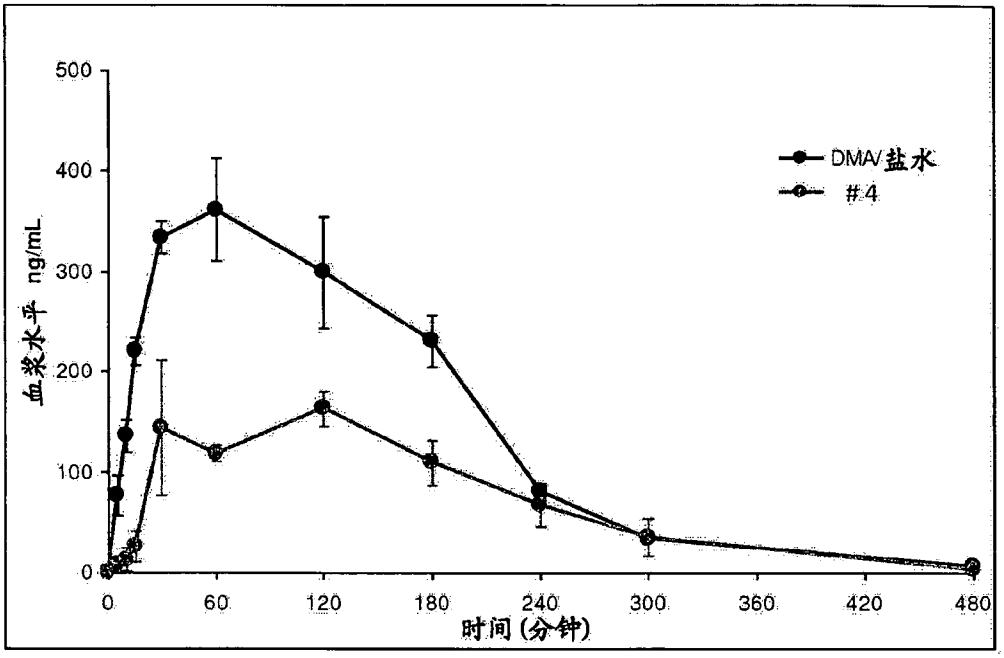

500
400
300
200
100
0
血浆水平 ng/mL
0
60
120
180
240
300
360
420
480
时间(分钟)
DMA/盐水
#4

图 3

Abstract

The present invention relates to an aqueous pharmaceutical composition comprising a peptide as the active ingredient, and one or more water-soluble or water-dispersible gelling agents.