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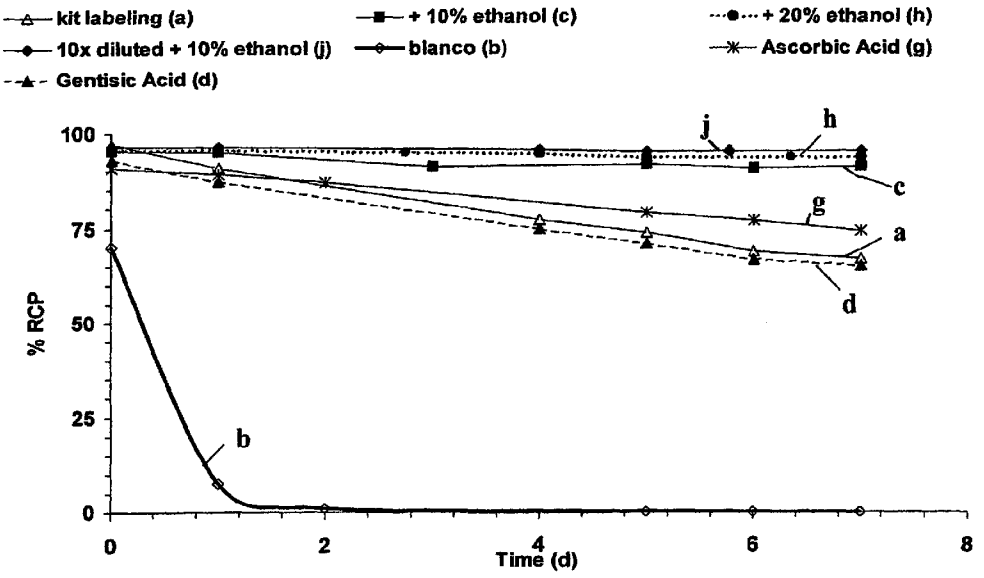
(54) **Title:** USE OF ETHANOL FOR STABILIZING A SINGLE-VIAL LIQUID FORMULATION OF A RADIOLABELED PEPTIDE



(57) **Abstract:** The invention relates to the use of ethanol as a first stabilizer in a single-vial liquid pharmaceutical formulation of a radiolabelled peptide, in a quantity sufficient to prevent radiolysis of said liquid formulation, wherein the formulation comprises in addition a second stabilizer, selected from inositol, ascorbic acid, gentisic acid, gentisyl alcohol, methionine and other suitable HS- or HSe-containing amino acids, and their derivatives, as well as combinations thereof, and wherein the peptide has been labelled with a detectable element, selected from gamma- or positron-emitting radionuclides, or with a therapeutic radionuclide, by using a chelating agent.

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Use of ethanol for stabilizing a single-vial liquid formulation of a radiolabelled peptide

The present invention relates to the use of ethanol in a single-vial liquid pharmaceutical formulation of a radiolabelled peptide, in a quantity sufficient to prevent radiolysis of said liquid formulation.

Radiolabelled peptides are generally stored and transported in the form of multi-vial kit formulations, wherein the radiolabelling component is separated from the peptide to be labeled, to prevent stability problems. Usually the contents of these vials are in a lyophilized or frozen condition. Upon use, the contents of these vials should be brought into solution and subsequently in a mutual reaction to produce the intended radiolabelled peptide. It is comfortable and also more safe for the pharmacists in a clinic or hospital not to have to perform all such handlings with radioactive material. Therefore it is of great importance to be able to store and transport the ready for use liquid formulation of the radiolabelled peptide to allow a pharmacist the administration of the labeled peptide without a radiochemical reaction, so simply by diluting, if necessary, the contents of the vial to a radiopharmaceutical liquid that can be administered by injection. Therefore, the term "vial" also includes injection syringe.

It will be obvious, that such a liquid formulation may be a mono- or multidose formulation, i.e. a dose for one patient or a multidose to be divided into a plurality of doses for administering to a number of patients.

It has now been found, that the use of ethanol for stabilizing a radiolabelled peptide solution, in a quantity sufficient to prevent radiolysis, in combination with a known stabilizer, shows superior stabilizing results, so that this radiolabelled peptide can be stored and transported in a single-vial ready-for-use liquid formulation.

Consequently, the present invention relates to the use of ethanol as a first stabilizer in a single-vial liquid pharmaceutical formulation of a radiolabelled peptide, in a quantity sufficient to prevent radiolysis of said liquid formulation, wherein the formulation comprises in addition a second stabilizer, selected from inositol, ascorbic acid, gentisic acid, gentisyl alcohol, methionine and other suitable HS- or HSe-containing amino acids, and their derivatives, as well as combinations thereof, and wherein the peptide has been labelled with a detectable element, selected from gamma- or positron-emitting radionuclides, or with a therapeutic radionuclide, by using a chelating agent.

The use of ethanol as a quencher or stabilizer is known from literature.

- WO 2005/122712 (Socratech L.L.C. et al.; D1) relates to the binding of a certain protein to Alzheimer's amyloid-β peptide. After labelling with ^{125}I the radioiodinated product is stabilized in ethanol as a quenching agent. For use in animal experiments, the product is purified and analysed, after which the purified product, apparently, is brought into a formulation suitable for infusion into the animal.

- The publication by Pozzi et al. (Applied Radiation and Isotopes 64 (2006), 668-676; D2) relates to the preparation of a special peptide, viz. fNleLFNleYK[^{131}I]BA. After extensive purification the product was dissolved in ethanol and stored (freezer, N_2). This solution did not show radiation damage or self-decomposition up to 7 days. For use in biodistribution studies the solution was evaporated to a small volume and reconstituted in phosphate-buffered saline.

- WO 03/000271 (Univ. of Alberta et al..; D3) relates to a method for the labelling of certain substrates, preferably nucleotides and nucleosides, steroids, or proteins such as antibodies, with radiohalogens. The example and claims disclose the labelling of iododeoxuridine (IudR), a protein (polyclonal anti-TSH antibody) and a steroid (estradiol-6-CMO-histamine), all with ^{125}I. During preparation and storage the radiolabelled products can be stabilized by adding an antioxidant, preferably ethanol or vitamin D (ascorbic acid), or a mixture of both. After purification the radioiodinated products are dissolved in ethanol (Example 3; steroid as substrate), in ethanol plus ascorbic acid (Example 1; IudR as substrate), or in BSA phosphate saline buffer stabilized with ascorbic acid (Example 2; antibody as substrate). In page 5, lines 10-12 it is mentioned, that only vitamin C can be used as an antioxidant for antibodies, "because antibodies and other proteins tend to denature upon contact with ethanol".

- The publication by Chen et al. (2006 Annual Meeting – Society of Nuclear Medicine; D4) relates to the evaluation of radiostabilizers for formulated ^{177}Lu-AMBA, a bombesin-like peptide. A large number of radiostabilizers, among which methionine, cysteine, mercaptoethanol, selenomethionine, ascorbic acid, gentisic acid and ethanol, are mentioned for testing in frozen formulations of radiolabelled AMBA. Selenomethionine, ascorbic acid, cysteine, methionine and gentisic acid were the most effective, but no single compound completely prevented radiolysis of ^{177}Lu-AMBA. A combination of selenomethionine and ascorbic acid has shown to be superior as a stabilizer. Under optimised conditions this combination could stabilize a robust two-vial frozen formulation for preparing ^{177}Lu-AMBA that could maintain an RCP (radiochemical purity) of over 90% for 5 days. It should be remarked, that ethanol apparently has not attracted the particular attention of the investigators.

In sum, the stabilized radiolabelled products of documents 1,2,3 and 4 are not ready for use, with the exception of the radioiodinated protein of Example 2 of D3; this product, however, could not be stabilized with a mixture of ascorbic acid and ethanol. Further, there is not any indication, neither in D3 nor in D4, that a mixture of ethanol with e.g. ascorbic acid could have superior radiostabilizing properties over other combinations or over the separate stabilizers.

In fact ethanol, in combination with a second stabilizer, stabilizes a liquid formulation of said radiolabelled peptides so superbly, that such a formulation can be protected completely against deterioration during the desired storage and transport period. It is indeed beyond expectation, that ethanol has a generally superior stabilizing effect on radiolabelled peptide solutions, stabilized with well-known stabilizers such as gentisic acid, ascorbic acid and methionine or combinations thereof, compared with these stabilizers or combinations as such.

The radiolabelled peptide to be stabilized according to the invention can be characterized in more detail as a product destined for tumour localization and therapy (see in this connection the review article of Reubi: Endocrine Reviews 24(4), 389-427 (2003)). Suitable peptides for this purpose – after labelling – are: CCK, gastrin, substance P, bombesine, VIP, PACAP, NPY, neurotensine and somatostatin, as well as derivatives and analogues of these peptides. Eight amino acid moieties containing somatostatin derivatives or analogues, so-called octreotides and octreotates, have attracted the most interest of the scientific world to date, and are, after radiolabelling, pre-eminently suitable substrates to be stabilized according to the present invention.

More in particular, the peptide to be stabilized according to the present invention has been labelled by use of a chelating agent with a detectable element selected from gamma- or positron-emitting radionuclides, or with a therapeutic radionuclide. Suitable chelating agents are selected from: (i) N_2S_2-, N_3S- and N_4-tetradentate ring structure containing agents, (ii) isocyanate, carbonyl, formyl, diazonium, isothiocyanate and alkoxycarbimidoyl containing agents, (iii) agents derived from N-containing di- and polyacetic acids and their derivatives, and (iv) 2-iminothiolane and 2-iminothiacyclohexane containing agents. Suitable specific examples of such chelating agents are: ethylenediamine tetraacetic acid (EDTA), diethylenetriamine pentaacetic acid (DTPA), ethyleneglycol-O,O'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), substituted EDTA or DTPA,

1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), 1,4,7-triazacyclonane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), or derivatives of any of these chelators.

The peptide to be stabilized may be labelled with a detectable element such as ^{99m}Tc, ^{203}Pb, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113m}In, ^{97}Ru, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{51}Cr, ^{24}Na, ^{157}Gd, ^{52m}Mn, ^{162}Dy and ^{201}Tl. Preferred detectable elements are: ^{111}In, ^{99m}Tc, ^{67}Ga and ^{68}Ga.

It is a particular aspect of the present invention, that the use of ethanol as a co-stabilizer in radiostabilizing liquid formulations of radiolabelled peptides is very suitable also for therapeutically applicable compositions. It is well-known in the art, that the stabilization of such formulations is generally very difficult because of the high level of radioactivity thereof. Therefore the present invention relates in particular to the use of ethanol in liquid formulations comprising a peptide labelled with a therapeutic radionuclide.
Suitable therapeutically active radionuclides are: ^{186}Re, ^{188}Re, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{109}Pd, ^{165}Dy, ^{177}Lu, ^{161}Tb, ^{123m}Rh, ^{111}In, ^{166}Ho, ^{89}Sr, ^{105}Rh and ^{153}Sm. Preferred radionuclides are: ^{67}Cu, ^{177}Lu, ^{153}Sm, ^{90}Y and ^{166}Ho.

The above compositions can generally be stabilized adequately by ethanol as a first stabilizer, if used in a quantity sufficient to prevent radiolysis, if this formulation comprises in addition a second stabilizer, such as: inositol, ascorbic acid, gentisic acid, gentisyl alcohol, methionine and other suitable HS- and HSe-containing amino acids, and their derivatives, as well as combinations of two or more of these second stabilizers.

The present invention further relates to a stabilized single-vial liquid formulation of a radiolabelled peptide comprising ethanol in a quantity sufficient to prevent radiolysis of said formulation, in combination with a second stabilizer as defined above.

Preferably, such a composition comprises a radiolabelled peptide to be used for tumour localization or therapy. More in particular, such a peptide is labelled by use of a chelating agent with a detectable element selected from gamma- or positron-emitting radionuclides, or with a therapeutic radionuclide. Suitable chelating agents and radionuclides are listed hereinbefore. Preferred therapeutic radionuclides are selected from ^{67}Cu, ^{177}Lu, ^{153}Sm, ^{90}Y and ^{166}Ho, which have superior characteristics as labels for therapeutic application.

During the last decade there is a growing interest in radiolabelled peptides, such as somatostatin derivatives and analogs, for diagnostic purposes as well as for tumor therapy. Suitable somatostatin analogs that are in the centre of interest are octapeptides having a high somatostatin receptor affinity, generally called octreotides and octreotates.
Such octapeptides may be represented by the general formula

$$H\text{-}(A^0)_n\text{-}(D)A^1\text{-}cyclo[Cys^2\text{-}A^3\text{-}A^4\text{-}A^5\text{-}A^6\text{-}Cys^7]\text{-}A^8 \quad (I)$$

wherein:
n is 0 or 1,
A^0 is optionally halogenated Tyr or Phe, or wherein
A^0 is a trifunctional amino acid residue to which an additional peptide part, comprising 3 to 12 amino acid residues which form at least once the Arg-Gly-Asp sequence, is covalently linked,
A^1 is optionally halogenated Tyr, or optionally halogenated or methylated Phe or Nal,
A^3 is Tyr, Phe, Nal or benzothienylalanyl,
A^4 is Trp, optionally N-methylated in its side-chain,
A^5 is Lys, optionally N-methylated in its side-chain,
A^6 is Thr, Val, Ser, Phe or Ile, and
A^8 is Thr, Trp or Nal, wherein the terminal carboxy group may be modified to an alcohol or an , optionally C1-C3 alkylated, amide group.

Suitable examples of the above peptides of formula I are:

(1) H-(D)Phe-*cyclo*[Cys-A^3-(D)Trp-Lys-Thr-Cys]-Thr-ol

(2) H-(D)Nal-*cyclo*[Cys-A^3-(D)Trp-Lys-Val-Cys]-Thr-NH_2

(3) H-(D)Phe-*cyclo*[Cys-A^3-(D)Trp-Lys-Thr-Cys]-Thr-OH

Consequently, the present invention relates even more preferably to a composition as described hereinbefore, wherein the radiolabelled peptide is an octreotide or octreotate, as defined above, labelled with a suitable metal radionuclide by use of a chelating agent selected

from ethylenediamine tetraacetic acid (EDTA), diethylenetriamine pentaacetic acid (DTPA), ethyleneglycol-O,O'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), substituted EDTA or DTPA, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), 1,4,7-triazacyclonane-1,4,7-triacetic acid (NOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), and derivatives of any of these chelators.

The present invention relates to a stabilized liquid formulation which is ready for use, i.e. which can be administered as such to the patient, e.g. intravenously (as an infusion fluid). If necessary or desired, this liquid formulation can be diluted with a physiologically acceptable liquid, e.g. buffered saline. Such a stabilized formulation comprises, in addition to a radiolabelled peptide and a second stabilizer, both as defined hereinbefore, a stabilizing quantity of ethanol as a first stabilizer, which quantity is physiologically acceptable to the human body. In general, the quantity of ethanol in the injection liquid, is 1 to 20 % v/v, preferably approx. 5 to 20% v/v. Generally approx. 10% v/v of ethanol is sufficient for an adequate stabilization. The second stabilizer is used in a usual molar quantity, dependent on the character of the peptide to be stabilized. Normally approx. 1 to 100 mM of second stabilizer (including stabilizer combination) per mL liquid to be stabilized is sufficient. It will be obvious, that the volume of the liquid depends strongly on the purpose of the radiolabelled peptide formulation. For diagnostic purposes in general a few millilitres are sufficient, e.g. to be administered by injection; for therapeutic purposes approx. 100 mL per treatment is frequently necessary, to be administered by infusion. The term treatment means the administration of the liquid to a human being of approx. 70 kg of body weight. Under all such different conditions the use of ethanol as a first stabilizer has appeared to be necessary to obtain a pharmaceutically acceptable and stable single-vial liquid formulation. The quantity of second stabilizer (including stabilizer combination), of course, also depends on the radioactivity of the liquid to be stabilized. In general 0.1 to 40 mM second stabilizer is sufficient per 100 MBq activity.

The invention will now be described with reference to the following specific Examples.

Example 1

A concentrated labelled peptide solution is prepared in a manner known per se, e.g. as described for ^{111}In labelled DTPA-octreotide in EP 0600992, viz. by diluting a frozen formulation of the chelated peptide, stabilized with a mixture of ascorbic acid and gentisic acid salts, as delivered by the producer, with buffered saline, followed by labelling with a ^{177}Lu solution ("kit labelling").

To this solution 10% v/v ethanol is added. The second stabilizer combination is present in the same amount as in commercially available kit formulation, viz. 1 mM for both ascorbic and gentisic acid. The stability of the ethanol containing solutions is compared with that of solutions of radiolabelled peptides, comprising in addition second radiostabilizers, selected from gentisic acid and ascorbic acid as salts, and methionine, as well as mixtures thereof, instead of ethanol as a stabilizer. The liquid formulations (solutions) are stored at room temperature (21-22° C) during a certain period. At regular time intervals the radiochemical purity (RCP) is determined. The results are presented in the graphs appended as figures 1-3.

In Figure 1 the influence of ethanol on the RCP of solutions of ascorbic/gentisic acids-stabilized ^{177}Lu labelled DOTA- octreotate (60MBq + 2 μg in 0.10 mL) is shown, in comparison with the addition of quantities of these second stabilizers instead of ethanol. Ethanol in an amount of 10% v/v stabilizes the solution completely against degradation during at least 7 days; additional ethanol is not necessary. The stabilizing effect is significantly greater than without this first stabilizer ("kit labelling": a). Dilution of the solution has no negative influence on the stability. Comparable results are obtained at the level of a therapeutical patient's dose, viz. 7400 MBq, in 100 mL. Addition of gentisic acid (d) and ascorbic acid (g) is not or hardly effective. The results of the unstabilized formulation (blanco) is shown as graph b.

In Figure 2 comparable effects are obtained by using solutions of ^{111}In labelled DOTA-octreotate (60MBq + 2 μg in 0.14 mL). Ethanol has a superior influence on the stability of these solutions during the test period, i.e. 24 hours, whereas addition of gentisic acid and L-methionine show no or less stabilizing effect, respectively; dilution of the unstabilized solution has only a slightly positive effect.

In Figure 3 the influence of ethanol on the RCP of solutions of ^{111}In labelled DTPA-octreotide during storage is shown. The stability of these solutions is compared with the commercially available (as Octreoscan) kit formulation after reaction of their ingredients; this commercial kit contains a mixture of gentisic acid and ascorbic acid as stabilizers. According to these experiments, addition of a mixture of ethanol and ascorbic acid, first and second stabilizer, respectively, prevents radiolysis of ^{111}In labelled DTPA-octreotide solutions completely.

Example 2

In this Example a number of ^{111}In-labelled peptides are prepared by labelling these peptides with ^{111}In at different specific activities and concentrations of radioactivity (up to 100MBq per nmol in 100μL), while varying t, T and stabilizers. The RCP on a HPLC reverse phase C_{18} column is determined at t=0 up to 7 days after labelling. The peptides used are DOTA-octreotate [DOTA-DF-C-Y-DW-K-T-C-T], DTPA-octreotide [DTPA-DF-C-F-DW-K-T-C-T(ol)], DTPA-bombesine [DTPA-P-Q-R-Y-G-N-W-A-V-G-H-L-M-NH_2] and DOTA-MG11 [DOTA-DGlu-A-Y-G-W-M-D-NH_2]; the two last compounds have a methionin amino acid moiety in their molecules.

At t=0 the RCP of the radiopeptides prepared varied between 97% for DTPA-octreotide (highest) and 93% for DOTA-MG11 (lowest). The stability of the radiopeptide solutions in buffered saline is measured by HPLC, in the presence / absence of a number of stabilizers, viz. ethanol, ascorbic acid, gentisic acid and methionin, in different combinations. Under optimised conditions and by adding 10% v/v ethanol and 1 mM ascorbic acid, the RCP could be maintained at between 85% and 93% for all radiolabelled peptides up to 7 days.

Example 3

Stability experiments of a number of peptides.

Peptides: DOTA-MG11 [DOTA-DGlu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2], including methionin-sulfoxide; DOTA-CCK [DOTA-DAsp-Tyr-Nle-Gly-Trp-Nle-Asp-Phe-NH_2; and Demogastrin-2 [N4-Gly-(D)Glu-$(Glu)_5$-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2.

12μg DOTA-MG11 is radiolabelled with ^{111}In at 80° C, yielding the radiolabelled product in a RCP of 90%, as measured directly after labelling. The RCP decreased after 24 hours at room temp. to 60%. Figure 4 shows the C18 HPLC chromatograms of ^{111}In-DOTA-MG11 at 24 h after radiolabelling, without (chromatogram A) and with stabilizers. Addition of 10% v/v ethanol, 4 mM L-methionin and 4 mM ascorbic acid, resp. does not show satisfactory improvement: chromatograms B,C and D respectively. Enhancement of the methionin and ascorbic acid concentrations up to 50 mM does not improve the chromatographic results, shown in C and D, substantially. The chromatograms, shown as E and F, are obtained after addition of 10% v/v ethanol and 10% ethanol v/v plus 50 mM L-methionin, respectively. The RCP of A and F are 60% and 94% respectively, 94% being also the RCP of the radiolabelled peptide in the presence of these stabilizers immediately after radiolabelling: 5

min. at 80° C in the presence of ascorbate, methionin and ethanol. Similar results are obtained with DOTA-CCK.

Demogastrin 2 is labelled with 99mTc to the labelled peptide up to a specific activity of 250 MBq per nmol, with a RCP of approx 83%. A combination of ascorbic acid and ethanol stabilizes this product adequately against radiolysis: no significant reduction of radiolabelled peptide according to RCP during storage.

Claims

1. Use of ethanol as a first stabilizer in a single-vial liquid pharmaceutical formulation of a radiolabelled peptide, in a quantity sufficient to prevent radiolysis of said liquid formulation, wherein the formulation comprises in addition a second stabilizer, selected from inositol, ascorbic acid, gentisic acid, gentisyl alcohol, methionine and other suitable HS- or HSe-containing amino acids, and their derivatives, as well as combinations thereof, and wherein the peptide has been labelled with a detectable element, selected from gamma- or positron-emitting radionuclides, or with a therapeutic radionuclide, by using a chelating agent.

2. The use according to claim 1, wherein the radiolabelled peptide is a peptide compound to be used for tumour localisation or therapy.

3. The use according to any of claims 1-2, wherein the peptide is an octreotide or an octreotate.

4. The use according to any of claims 1-3, wherein the peptide has been labelled by use of a chelating agent, selected from: (i) N_2S_2-, N_3S- and N_4-tetradentate ring structure containing agents, (ii) isocyanate, carbonyl, formyl, diazonium, isothiocyanate and alkoxycarbimidoyl containing agents, (iii) agents derived from N-containing di- and polyacetic acids and their derivatives, and (iv) 2-iminothiolane and 2-iminothiacyclohexane containing agents.

5. The use according to any of claims 1-4, wherein the peptide has been labelled with a detectable element, selected from the group consisting of ^{99m}Tc, ^{203}Pb, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{72}As, ^{111}In, ^{113m}In, ^{97}Ru, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{51}Cr, ^{24}Na, ^{157}Gd, ^{52m}Mn, ^{162}Dy and ^{201}Tl, preferably from ^{111}In, ^{99m}Tc, ^{67}Ga and ^{68}Ga.

6. The use according to any of claims 1-4, wherein the peptide has been labelled with a therapeutic radionuclide, selected from the group consisting of ^{186}Re, ^{188}Re, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{109}Pd, ^{165}Dy, ^{177}Lu, ^{161}Tb, ^{123m}Rh, ^{111}In, ^{166}Ho, ^{89}Sr, ^{105}Rh and ^{153}Sm, preferably from ^{67}Cu, ^{177}Lu, ^{153}Sm, ^{90}Y and ^{166}Ho.

7. A stabilized single-vial liquid pharmaceutical formulation of a radiolabelled peptide, comprising ethanol as a first stabilizer in a quantity sufficient to prevent radiolysis of said liquid formulation, and comprising in addition a second stabilizer, selected from inositol, ascorbic acid, gentisic acid, gentisyl alcohol, methionine and other suitable HS- or HSe-containing amino acids, and their derivatives, as well as combinations thereof, in which formulation the peptide has been labelled with a detectable element, selected from gamma- or positron-emitting radionuclides, or with a therapeutic radionuclide, by using a chelating agent.

8. The liquid formulation as claimed in claim 7, wherein the radiolabelled peptide can be used for tumour localisation or therapy.

9. The liquid formulation as claimed in any of claims 7-8, wherein the peptide is an octreotide or an octreotate.

10. The liquid formulation as claimed in any of claims 7-9, comprising as the radiolabelled peptide a peptide labelled by use of a chelating agent, selected from: (i) N_2S_2-, N_3S- and N_4-tetradentate ring structure containing agents, (ii) isocyanate, carbonyl, formyl, diazonium, isothiocyanate and alkoxycarbimidoyl containing agents, (iii) agents derived from N-containing di- and polyacetic acids and their derivatives, and (iv) 2-iminothiolane and 2-iminothiacyclohexane containing agents.

11. The liquid formulation as claimed in any of claims 7-10, wherein the peptide has been labelled with a radionuclide as defined claim 5.

12. The liquid formulation as claimed in any of claims 7-10, wherein the peptide has been labelled with a radionuclide as defined in claim 6.

13. The liquid formulation as claimed in any of claims 7-12, comprising, in addition to a radiolabelled peptide, as defined in any of claims 8-12, and a second stabilizer, as claimed in claim 7, a stabilizing quantity of ethanol as a first stabilizer, which quantity is physiologically acceptable to the human body and is preferably 1-20% v/v, more preferably 5-20% v/v.

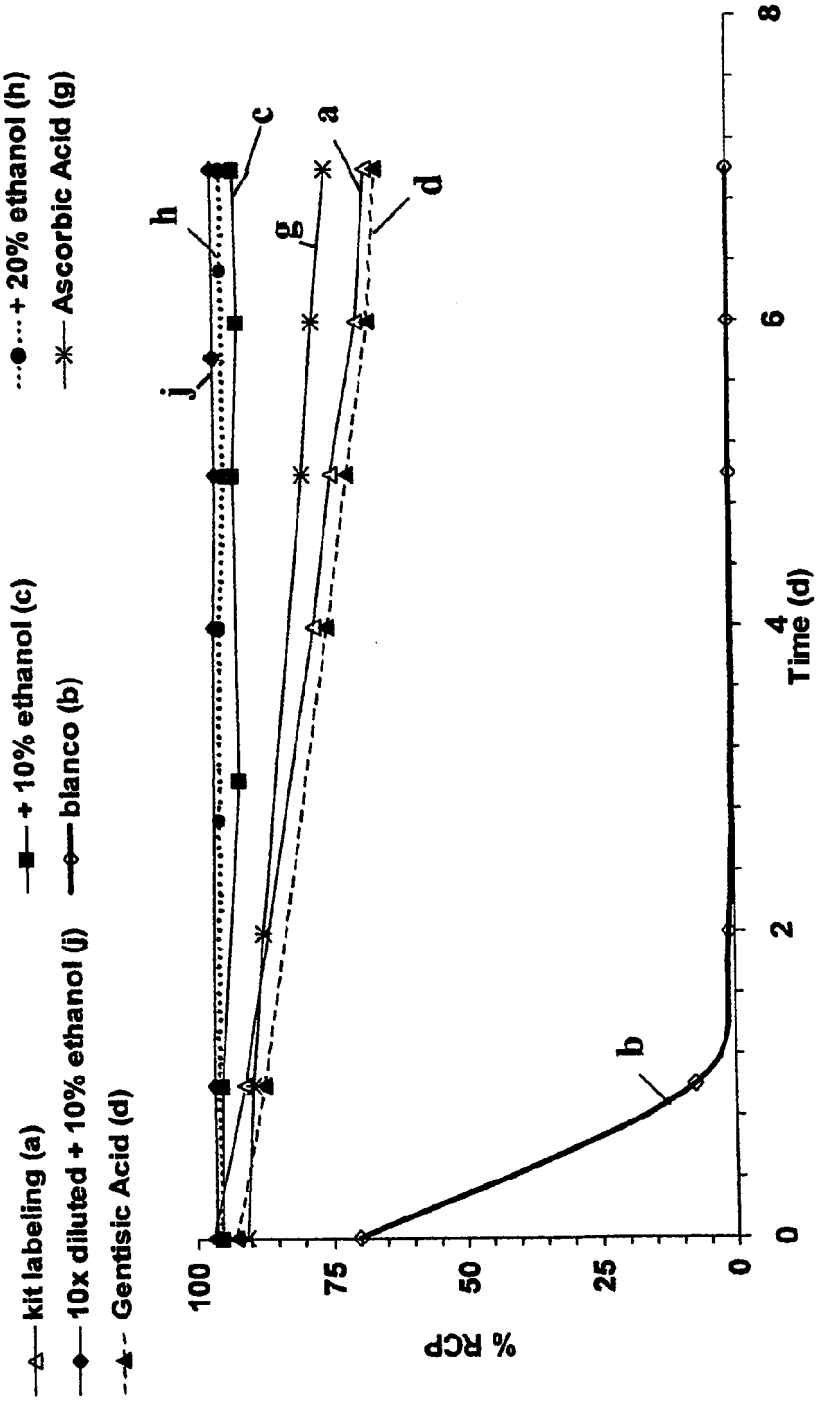
kit labeling (a)
+ 10% ethanol (c)
+ 20% ethanol (h)
10x diluted + 10% ethanol (j)
blanco (b)
Ascorbic Acid (g)
Gentisic Acid (d)
% RCP
100
75
50
25
0
0
2
4
6
8
Time (d)
a
b
c
d
g
h
j

Figure 1

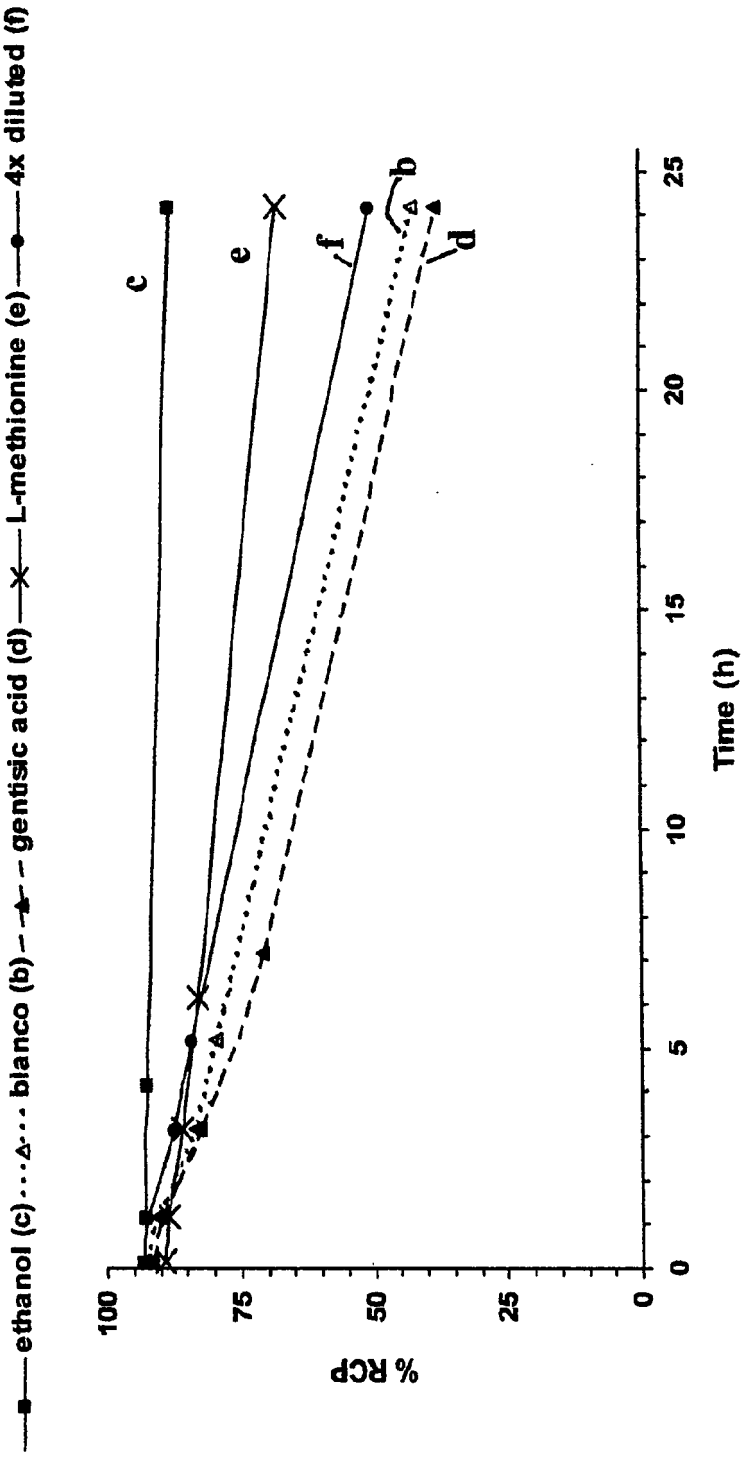
ethanol (c)
blanco (b)
gentisic acid (d)
L-methionine (e)
4x diluted (f)
% RCP
100
75
50
25
0
Time (h)
0
5
10
15
20
25
c
e
f
b
d

Figure 2

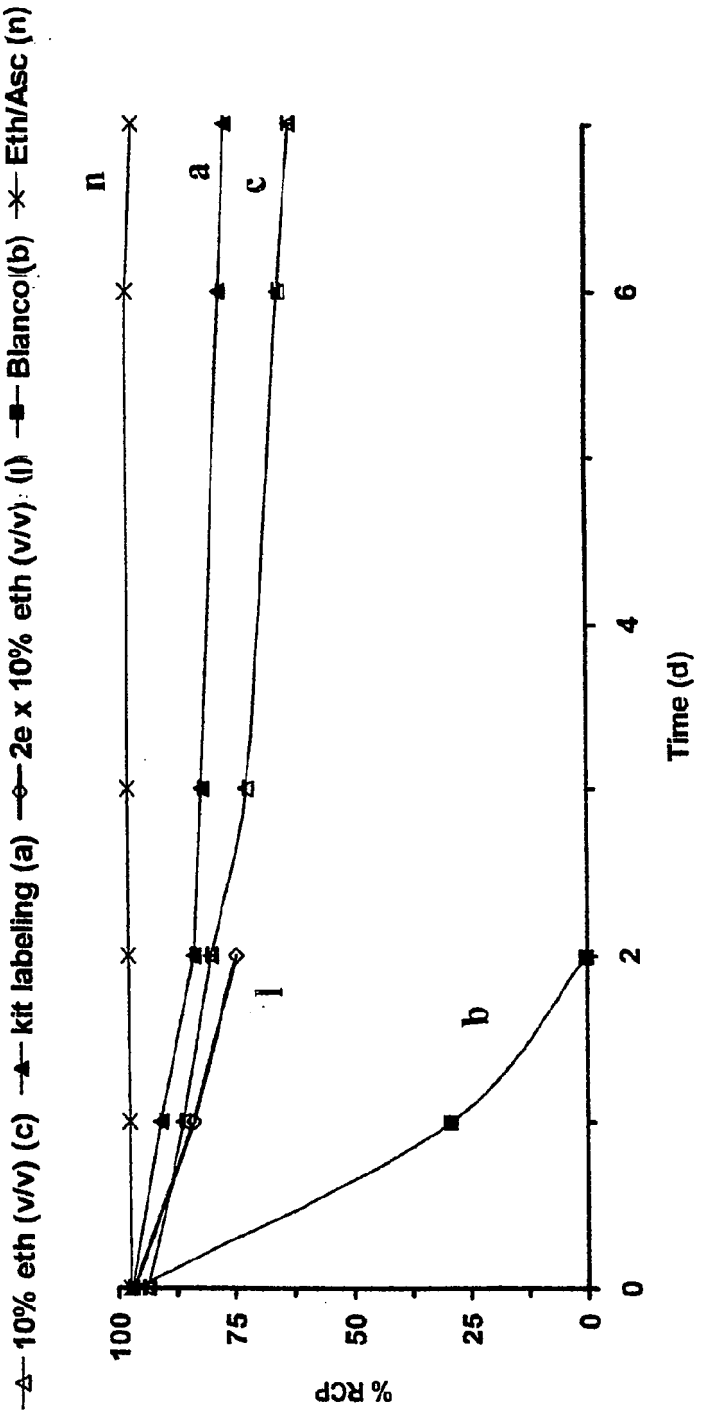
10% eth (v/v) (c)
kit labeling (a)
2e x 10% eth (v/v) (l)
Blanco(b)
Eth/Asc (n)
% RCP
100
75
50
25
0
Time (d)
0
2
4
6
n
a
c
l
b

Figure 3

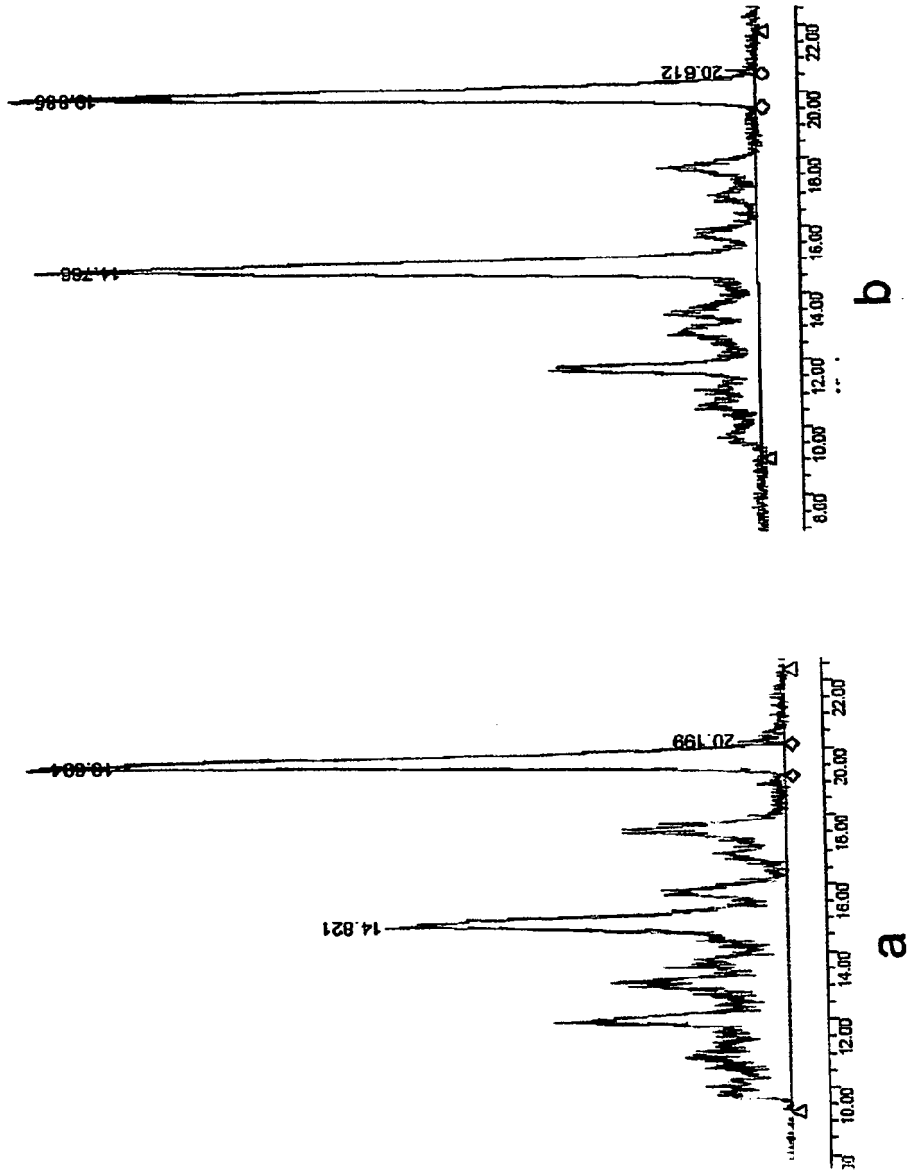

Figure 4

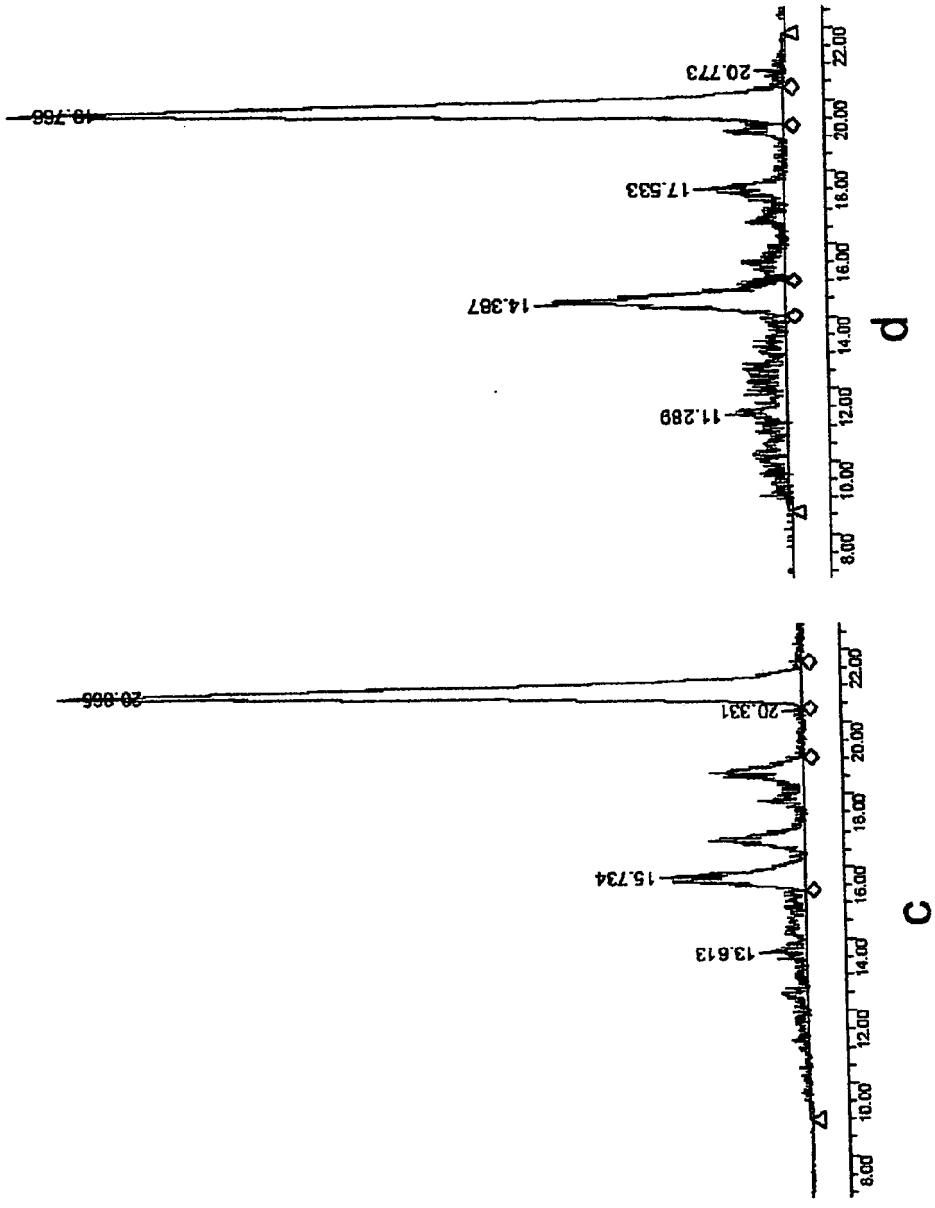
d
18.766
20.773
17.533
14.387
11.289
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00
c
20.866
20.331
15.734
13.613
8.00
10.00
12.00
14.00
16.00
18.00
20.00
22.00

Figure 4

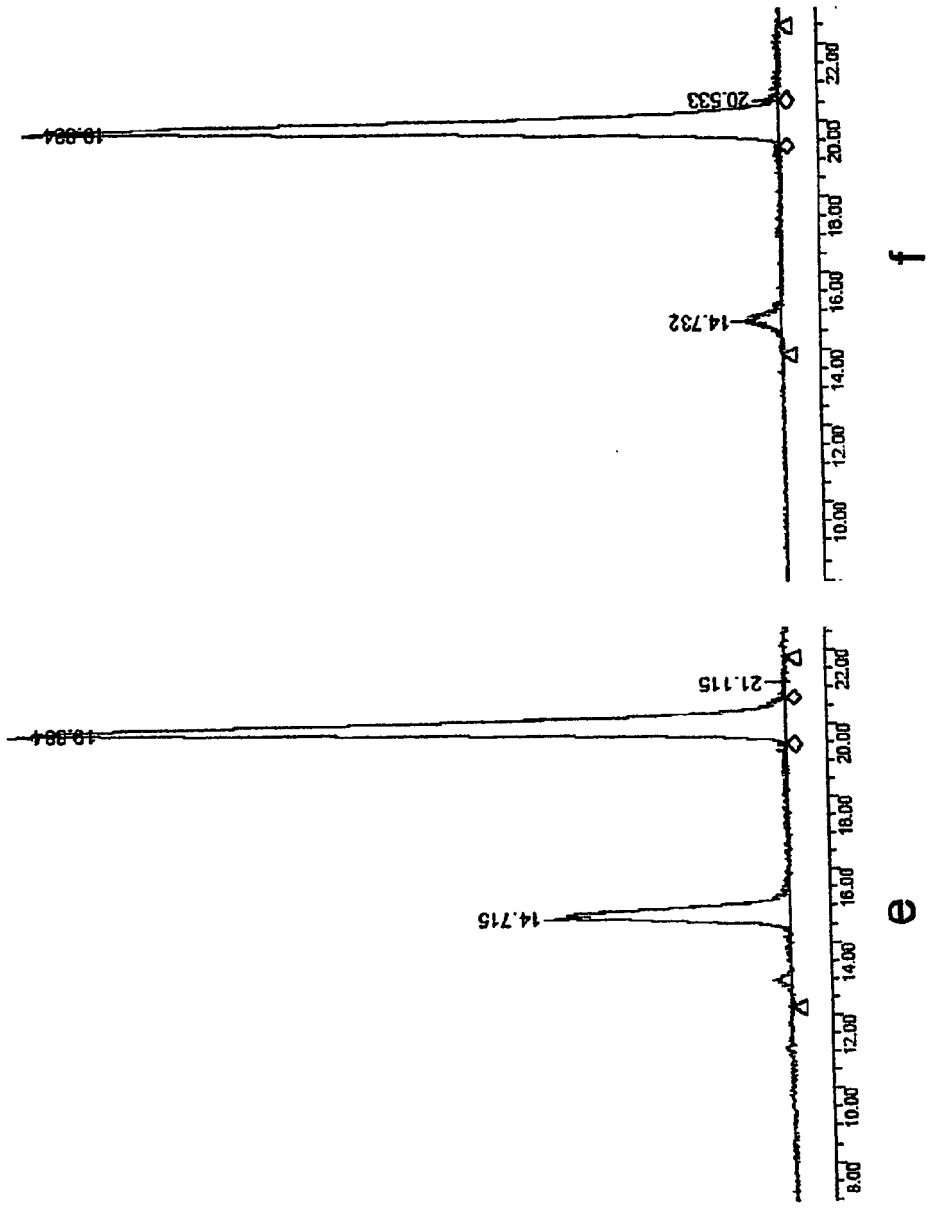
f
20.533
18.884
14.732
22.00
20.00
18.00
16.00
14.00
12.00
10.00
e
21.115
18.884
14.715
22.00
20.00
18.00
16.00
14.00
12.00
10.00
8.00

Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/006405

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/10 A61K47/12 A61K47/18 A61K47/26 A61K51/08
A61K51/04

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 practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/180918 A1 (CYR JOHN E [US] ET AL) 18 August 2005 (2005-08-18) paragraph [0013] paragraph [0031]; examples 5,6	1-13
X	WO 03/092743 A (BRACCO IMAGING SPA [IT]; CHEN JIAQING [US]; LINDER KAREN [US]; WANG NA) 13 November 2003 (2003-11-13) examples 3,4,6	1-13
X	WO 03/000271 A (UNIV ALBERTA THE UNIVERSITY OF [CA]) 3 January 2003 (2003-01-03) cited in the application page 1, line 8 - line 15 page 5, line 6 - line 12	1-13

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

☒ See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2007	27/11/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bendl, Ernst

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/006405

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1406636 A2	14-04-2004
		JP 2004536092 T	02-12-2004
		US 7238338 B1	03-07-2007