

SPECIFICATION

A process for the preparation of a sterile injectable physiologically acceptable solution of an X-ray contrast agent and solutions of the X-ray contrast agent and a buffer

The present invention relates to the preparation of sterile, injectable physiologically acceptable solutions of X-ray contrast agents by autoclaving and more particularly to the preparation of such solutions at a physiologically acceptable pH which contain substances unstable when autoclaved at physiologically acceptable pH levels.

A difficulty encountered with certain solutions for administration e.g. by injection to human beings is that although the properties of the active compounds are very beneficial it is difficult, if not impossible, to sterilize the solutions by autoclaving at a physiologically acceptable pH e.g. in the range 6.8 to 8.0, without decomposition taking place or without the sterilization process effecting a change which renders the compound unsuitable for use. The term "solution" as used herein refers to aqueous or predominantly aqueous solutions. The extent of this decomposition can often be substantially reduced by autoclaving at a lower pH e.g. pH 5, but a solution at this pH is physiologically unacceptable when injected in substantial quantities. Various methods may be employed to overcome the disadvantage of low pH, for example neutralization after autoclaving or at the time of use, but such *ad hoc* methods have generally proved unsatisfactory.

The use of a buffer in the formulation of the solution to be autoclaved has been considered and has, hitherto, proved unsuccessful. Indeed it has been found that in many cases acid is produced by the decomposition of the active product and, in reducing the pH, eventually stabilises the system; consequently when a buffer is included in the formulation of such a solution in order to maintain its pH constant at pH 7.0 to 7.5 even more decomposition takes place during autoclaving than when the pH is allowed to fall. Thus, for example, conventional buffers such as alkali metal phosphates, citrates, lactates, carbonates and carboxylates have all been found to be unsuccessful in stabilising such solutions against autoclaving.

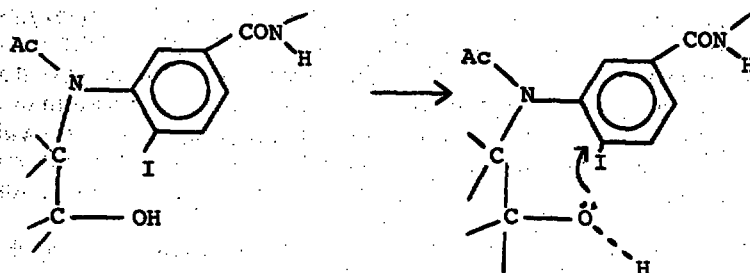
The present invention is directed to the autoclaving of X-ray contrast agents which are required for injection in solution at a physiologically acceptable pH which, at autoclaving temperatures, are unstable at said physiologically acceptable pH but stable at a lower pH. The present invention is based on the discovery that such a solution at a physiologically acceptable pH may successfully be autoclaved without significant decomposition and on cooling to ambient temperature yield a sterile solution at a physiologically acceptable pH, if autoclaving is effected in the presence of a buffer system the pH of which decreases with increasing temperature. In such a system, the pH of the solution is reduced at the high temperature of autoclaving but returns to a physiological pH on cooling.

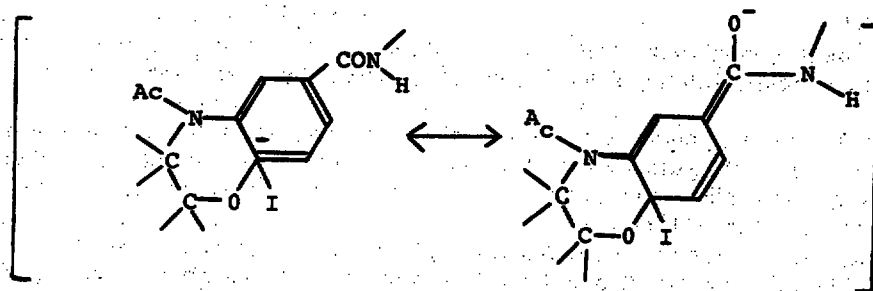
The invention also extends to aqueous solutions containing said unstable X-ray contrast agents together with a buffer system the pH of which decreases with increasing temperature.

It will be appreciated that while solutions having a non-physiologically acceptable pH may be injected intravenously in small doses (although this is preferably avoided if possible) it is obviously very important to avoid the intravenous injection of large quantities of a solution which does not have a physiologically acceptable pH. The present invention is thus of particular importance because solutions of X-ray contrast agents are normally administered in relatively large quantities.

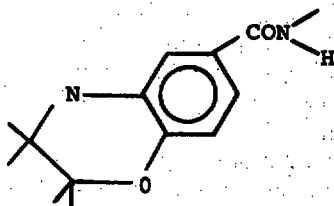
The majority of X-ray contrast agents are in general stable; they may be sterilized by autoclaving without change of pH or liberation of iodide and may be stored subsequently without deterioration. It has been found that the presence of hydroxyalkyl groups, especially alkyl groups with a hydroxy substituent on a carbon atom β to an acylamido nitrogen, in such X-ray contrast agents is particularly advantageous in terms of increased solubility and reduced toxicity. Unfortunately the presence of such groups has been found in certain cases to result in instability at neutral pH and high temperature so that it is difficult to sterilize solutions of such compounds as formulated by conventional pharmaceutical procedures, by autoclaving.

In particular, it is believed that certain X-ray contrast agents containing an m-carboxamido-o-iodo-N-(β -hydroxyalkyl)aniline derivative moiety cyclize during autoclaving at physiologically acceptable pHs or higher pHs according to the general reaction sequence:—



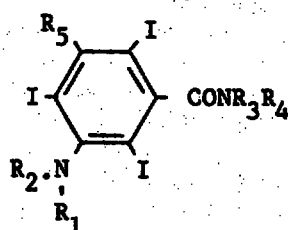


(where Ac represents an acyl group) followed by liberation of iodide and acetate to form a compound of the type

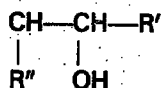


5 with concomitant formation of H_3O^+ and hence reduction of pH. Thus the process of the present invention is especially applicable to such compounds in which the nitrogen atom carries a group capable of intramolecular cyclization to form a stabilized intermediate of the above type.

Thus according to one feature of the present invention there is provided a process for the preparation of a sterile, injectable, physiologically acceptable solution of an X-ray contrast agent which comprises autoclaving a solution of a non-ionic *m*-carboxamido-*o*-iodo-*N*-(β -hydroxyalkyl)aniline derivative X-ray contrast agent in the presence of a physiologically acceptable buffer system the pH of which decreases with increasing temperature said buffer system comprising ammonia or a water soluble amine having a pK_a at 15°C of less than or equal to 9.5. X-ray contrast agents which are of particular interest for use in the process of the present invention, are non-ionic X-ray contrast agents of the formula:—



wherein R_1 represents either (a) the group



10 in which R' and R'' , which may be the same or different, each represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms which may, if desired, carry one or more $-\text{OH}$ groups, or (b) a sugar residue having a OH group at least at the 2-, 3- or 4- position, the said $-\text{OH}$ group being bonded to the carbon atom β to the amido nitrogen atom; R_2 represents an acyl group; R_3 and R_4 , which may be the same or different, each represent a hydrogen atom or an alkyl, hydroxyalkyl or acyloxyalkyl group or a sugar residue; and R_5 represents a hydrogen atom or the group $-\text{CONR}_3\text{R}_4$, $\text{Ac}'\text{NR}^6$ or $-\text{CH}_2\text{NAc}'\text{R}^6$ (in which R_3' and R_4' , which may be the same or different, each represents a hydrogen atom or an alkyl, hydroxyalkyl or acyloxyalkyl group or a sugar residue, R^6 represents a hydrogen atom or an alkyl, hydroxyalkyl, acyloxyalkyl or acyl group, and Ac' represents an acyl group) any hydroxyalkyl group present optionally carrying an aldehyde or acyloxy group as a further substituent and/or any alkyl, hydroxyalkyl or acyl groups present optionally carrying a further non-ionic iodinated hydrocarbon grouping which grouping may carry additional amide groups.

Thus for example R_1 may represent a $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CHOHCH}_2\text{OH}$ or $(\text{CH}_2\text{OH})_2\text{CH}-$ group.

R_2 is preferably a C_{1-8} aliphatic acyl group.

Where R_3 , R_4 , R_3' , R_4' and/or R_6 represents a hydroxyalkyl group this group may carry a single hydroxy group, as in the β -hydroxyethyl group, or more than one hydroxy group as in the

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dihydroxypropyl or tris-(hydroxymethyl)-methyl group or in the polyhydroxyalkyl portion of hexosamines, pentosamines, and sugar amino-alcohols such as glucosamine or glucamines e.g. N-methyl glucamine, 1-glucamine or 2-glucamine. Other non-ionic substituents may also be present, for example, the aldehyde group, as present in glucosamine, or one or more acyloxy groups.

5 The alkyl, hydroxyalkyl and aliphatic acyl groups which are present preferably contain 1—6 carbon atoms. Preferred alkyl groups thus include methyl, ethyl, propyl, butyl and hexyl groups; the methyl group is preferred and an N-methyl substituent often enhances water solubility.

The acyl group R² or Ac may for example, be derived from a carboxylic acid.

10 Preferred acyl groups derived from carboxylic acids, which may be O-attached or N-attached include C₂₋₄ alkanoyl e.g. acetyl, propionyl and butyryl groups, the acetyl group being most preferred. The acyl groups may if desired, carry one or more hydroxy substituents.

The alkyl, hydroxyalkyl and acyl groups which are present may additionally carry a further non-ionic iodinated hydrocarbon grouping which may carry additional amide groups, as stated above and, thus, for example, an alkylene, hydroxyalkylene or a diacyl grouping derived from a dibasic acid may be

15 N-bonded at either end to iodinated hydrocarbons carrying amide groupings. The concentration of radiopaque in solution will normally be for example in the range 100 to 450 mg l per ml.

It is important to ensure that the temperature dependent buffer used has sufficient buffer capacity; in general the pKa of the buffer at room temperature should be near to or in the physiological range 6.8 to 7.6 since the buffer capacity falls off at pH values substantially higher or lower than the pKa. If the buffer capacity is high, less ionic material is required and the osmolality of the solution may thus be kept as low as possible. The pKa value of the buffer system at 15°C should be less than or equal to 9.5. In this connection it should be emphasised that it is the considered opinion among some specialists that certain toxic side effects are due, at least in part, to the osmotic imbalance created by

25 injecting very large concentrations of dissolved material into the body fluids. The osmolality of a solution of a chemical compound is normally approximately directly proportional to the sum of the concentrations of the different molecular or ionic species which are present. A water-soluble salt, for example the sodium salt of an iodinated acid, will normally be almost completely ionised and the osmolality will be proportional to the concentration of both the anion and the cation. The total concentration of ionic species will thus be approximately twice that of the salt considered as a single unionised species. In contrast, the osmolality of a non-ionic compound e.g. of the type described in our British Patent Specification No. 1,321,591, that is a compound which is substantially unionised in aqueous solution, is expected to be approximately proportional simply to the molarity of the compound present, that is approximately half the value for an analogous ionic

30 compound having two ionic species. It is thus important to ensure that the osmolality of the solution of the temperature dependent buffer and the compound to be autoclaved, for example the X-ray contrast agent, is as low as possible. In general, the ionic strength of the buffer should preferably not exceed about 15%, especially 10% of the molar concentration of the substrate is the osmolality or toxicity of the solution is not to be significantly impaired. Some compounds which are used at lower molar concentration for example the bis X-ray contrast agents referred to above, may be capable of tolerating a higher buffer concentration expressed as a percentage of its molar concentration. In general, the concentration of the buffer in the solution is thus preferably not greater than 50 m.molar, more preferably in the range 5 to 25 m.molar.

As will be appreciated a solution of a compound to be autoclaved according to the present invention and a temperature dependent buffer will have a physiologically acceptable pH at room temperature (15°C) e.g. 6.8 to 8.0. As the temperature of the solution is raised in the autoclave the pH of the solution will decrease. Thus if the solution has a pH of 7.4 at room temperature this pH may drop, for example by about 2.5 pH units to a pH of 4.9 at 120°C. On allowing the solution to cool, the pH will increase, but may not necessarily return to as high a pH at room temperature as the solution possessed prior to autoclaving. Thus for example a solution which possesses a pH of 7.6 at room temperature prior to autoclaving may possess a pH of 7.4 at room temperature after autoclaving. This is generally due to a very small amount of acid generating decomposition which is nevertheless acceptable physiologically.

Thus, for example, the pH of the solution at room temperature prior to autoclaving is preferably 55 7.0 to 7.6 falling preferably to 3.5 to 5.5 especially about 4.5, during autoclaving and subsequently returning preferably to a pH of 7.0 to 7.6 at room temperature after autoclaving. The change of pH of the solution at room temperature before and after autoclaving may, for example, be <0.2 of a pH unit in respect of radiopaques autoclaved in accordance with the invention.

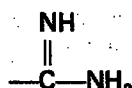
The autoclaving temperature employed for effecting sterilization is correlated with time. Thus, if a relatively low autoclaving temperature is employed, e.g. 110°C, the autoclaving is, in general, conducted for a longer period of time. One advantageous feature of the present invention is that sterilization by autoclaving may be conducted at higher temperatures and for a shorter time than hitherto conventional without decomposing the product to be sterilized. In such processes the pH of the solution at the higher autoclaving temperature will be even lower due to the greater pH reduction

of the buffer, for example, about 0.5 of a pH unit lower at 140°C and about 1.0 pH unit lower at 160°C as compared with the pH at 120°C.

Temperature dependent buffers which may be employed in the solutions to be autoclaved are ammonia and physiologically acceptable water soluble amines having a pKa at 15°C ≤ 9.5. In general, these will be of the formula



wherein R¹, R² and R³, which may be the same or different, each represents a hydrogen atom, a sugar residue, an alkyl group with 1 to 6 carbon atoms which may carry one or more hydroxy, mercapto, carboxyl, carboxamido, imidazolyl, indolyl or hydroxy substituted phenyl groups, alkylthio groups with 1 to 6 carbon atoms and/or groups of the formula: —NR⁴R⁵ (in which R⁴ and R⁵, which may be the same or different, each represents a hydrogen atom, a carboxamido or



groups or an alkyl group with 1 to 6 carbon atoms); or any two of R¹, R² and R³ may, together with the intervening nitrogen atom, represent a pyrrolidine or piperidine ring which may carry hydroxy, carboxyl or carboxamido groups.

Thus, for example, the physiologically acceptable, water soluble amines which may be employed as temperature dependent buffers include amino alcohols and amino sugars. Preferred amines for use in the process of the present invention include "Tris" [tris(hydroxymethyl)methylamine], AMPD [2-amino-2-methylpropane-1,3-diol], diethanolamine, meglumine, triethanolamine and ammonia.

Especially preferred amines for use in the process of the present invention are "Tris" and meglumine in view of their advantageous physiological acceptability. "Bis-Tris" [N,N-bis(2-hydroxyethyl)-tris(hydroxymethyl)methylamine] is an especially preferred amine for use in the process of the present invention in view of its advantageous pKa value of 6.5 at 25°C.

In formulating the solutions for autoclaving it is generally preferred to ensure that no anions such as carboxylates, phosphates and citrates, especially the anions of weak acids having a pKa > 2, are present.

The solutions for autoclaving will generally possess conventional adjuvants such as chelating agents e.g. ethylenediamine tetraacetate.

According to a further feature of the present invention there is provided a solution of a non-ionic *m*-carboxamido-*o*-iodo-N-(β-hydroxyalkyl)aniline derivative X-ray contrast agent and a physiologically acceptable buffer system the pH of which decreases with increasing temperature said buffer system comprising ammonia or a water soluble amine having a pKa at 15°C of less than or equal to 9.5.

The buffer is preferably an amine buffer of formula II as hereinbefore defined. The amine buffer is conveniently the sole buffer present in the system.

The solution preferably comprises meglumine or tris(hydroxymethyl)methylamine as the amine buffer.

The concentration of the buffer in the solution is advantageously no greater than 50 m.molar especially in the range 5 to 25 m.molar.

The *m*-carboxamido-*o*-iodo-N-(β-hydroxyalkyl)aniline derivative X-ray contrast agent is preferably of formula I as hereinbefore defined especially 5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-triiodo-N',N''-bis(2,3-dihydroxypropyl)isophthalamide.

The following Examples 1—7 illustrate the invention:—

Comparative example

The stability of various radiopaques to autoclaving in the absence of a buffer is shown in the following Table I in which both the pH and the iodide ion concentration is noted before and after autoclaving. Solutions were prepared using conventional adjuvants, in particular 0.2 mg/ml of ethylenediamine tetraacetate; the concentration of X-ray contrast agent was 300 mg/ml:

Compound I=5-N-(2-hydroxyethyl)acetamido-2,4,6-triiodo-N',N''-bis(2,3-dihydroxypropyl)isophthalamide;

Compound II=5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-triiodo-N',N''-bis(2-hydroxyethyl)isophthalamide;

Compound III=3,5-bis-N',N''-(2,3-dihydroxypropyl)acetamido-2,4,6-triiodo-N-(2-hydroxyethyl)benzamide;

Compound IV=5-N-(2-hydroxyethyl)acetamido-2,4,6-triiodo-N',N''-dimethyl-N',N''-bis(2,3-dihydroxypropyl)isophthalamide;

Compound V=5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-triiodo-N',N''-bis(2,3-dihydroxypropyl)isophthalamide.

Table I

Compound/buffer	pH			I ⁻ µg/ml			
	before	after	change	before	after	change	
A) Compound I/8 mM phosphate	7.39	7.04	-0.35	4	130	+126	5
5 B) Compound I/5 mM bicarbonate	7.57	6.75	-1.0	4	108	+104	
C) Compound II/10 mM phosphate	7.53	6.89	-0.64	3	310	+307	
D) Compound II/10 mM HCO ₃ ⁻	7.51	6.81	-0.70	3	266	+263	

Examples

Compounds previously found to be unstable at autoclaving temperatures were subjected to autoclaving in the presence of certain temperature dependent buffers.

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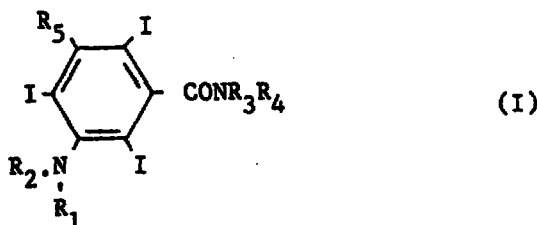
Table II

Effect of various buffers on autoclaving stability								
No.	Compound	Buffer	pH before	pH after	Γ before	Γ after		
15	1	Compound I	10 mM TRIS	7.34	7.34	4	8	15
	2		20 mM meglumine	7.65	7.53	2	10	
	3	Compound II	10 mM TRIS	7.45	7.41	3	13	
	4		10 mM meglumine	7.42	7.13	3	15	
	5	Compound III	10 mM TRIS	7.50	7.35	≤8	23	
20	6	Compound IV	10 mM TRIS	7.49	7.60	14	14	20
	7	Compound V	10 mM TRIS	7.53	7.43	5	11	

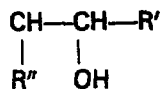
As will be seen from the above results the compounds could be sterilized by autoclaving without substantial change of pH and iodide ion concentration.

Claims

1. A process for the preparation of a sterile, injectable, physiologically acceptable solution of an X-ray contrast agent which comprises autoclaving a solution of a non-ionic *m*-carboxamido-*o*-iodo-N-(β-hydroxyalkyl)aniline derivative X-ray contrast agent in the presence of a physiologically acceptable buffer system the pH of which decreases with increasing temperature said buffer system comprising ammonia or a water soluble amine having a pKa at 15°C of less than or equal to 9.5.
2. A process as claimed in claim 1 wherein the *m*-carboxamido-*o*-iodo-N-(β-hydroxyalkyl)aniline X-ray contrast agent is of the formula:—



[wherein R₁ represents either (a) the group



- in which R' and R'', which may be the same or different, each represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms which may, if desired, carry one or more —OH groups, or (b) a sugar residue having a OH group at least at the 2-, 3- or 4-position, the said —OH group being bonded to the carbon atom β to the amido nitrogen atom; R₂ represents an acyl group; R₃ and R₄, which may be the same or different, each represent a hydrogen atom or an alkyl, hydroxyalkyl or acyloxyalkyl group or a sugar residue; and R₅ represents a hydrogen atom or the group —CONR₃R₄, Ac'NR⁶ or —CH₂NAc' R⁶ (in which R₃' and R₄', which may be the same or different, each represents a hydrogen atom or an alkyl, hydroxyalkyl or acyloxyalkyl group or a sugar residue, R⁶ represents a hydrogen atom or an alkyl, hydroxyalkyl, acyloxyalkyl or acyl group and Ac' represents an acyl group) any hydroxyalkyl group present optionally carrying an aldehyde or acyloxy group as a further substituent and/or any alkyl, hydroxyalkyl or acyl groups present optionally carrying a further non-ionic iodinated hydrocarbon grouping which grouping may carry additional amide groups].

3. A process as claimed in claim 2 wherein an X-ray contrast agent of formula I is used in which R₁ represents a —CH₂CH₂OH, —CH₂CHOHCH₂OH or (CH₂OH)₂CH— group.



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Table I

Compound/buffer		pH before	pH after	change	I ⁰ µg/ml before	I ⁰ µg/ml after	change
5	A) Compound I/8 mM phosphate	7.39	7.04	-0.35	4	130	+126
	B) Compound I/5 mM bicarbonate	7.57	6.75	-1.0	4	108	+104
	C) Compound II/10 mM phosphate	7.53	6.89	-0.64	3	310	+307
	D) Compound II/10 mM HCO ₃ ⁻	7.51	6.81	-0.70	3	266	+263

Examples

Compounds previously found to be unstable at autoclaving temperatures were subjected to autoclaving in the presence of certain temperature dependent buffers.

Table II

Effect of various buffers on autoclaving stability

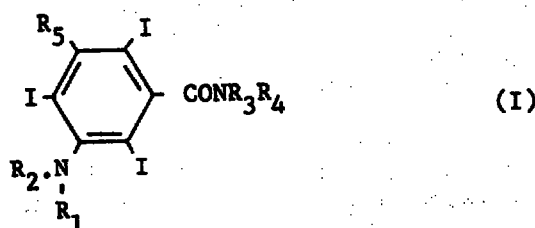
No.	Compound	Buffer	pH before	pH after	I ⁰ before	I ⁰ after
15	Compound I	10 mM TRIS	7.34	7.34	4	8
		20 mM meglumine	7.65	7.53	2	10
	Compound II	10 mM TRIS	7.45	7.41	3	13
		10 mM meglumine	7.42	7.13	3	15
	Compound III	10 mM TRIS	7.50	7.35	≤8	23
20	Compound IV	10 mM TRIS	7.49	7.60	14	14
	Compound V	10 mM TRIS	7.53	7.43	5	11

As will be seen from the above results the compounds could be sterilized by autoclaving without substantial change of pH and iodide ion concentration.

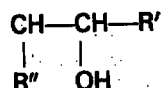
Claims

1. A process for the preparation of a sterile, injectable, physiologically acceptable solution of an X-ray contrast agent which comprises autoclaving a solution of a non-ionic *m*-carboxamido-*o*-iodo-N-(β-hydroxyalkyl)aniline derivative X-ray contrast agent in the presence of a physiologically acceptable buffer system the pH of which decreases with increasing temperature said buffer system comprising ammonia or a water soluble amine having a pKa at 15°C of less than or equal to 9.5.

2. A process as claimed in claim 1 wherein the *m*-carboxamido-*o*-iodo-N-(β-hydroxyalkyl)aniline X-ray contrast agent is of the formula:—



[wherein R₁ represents either (a) the group



in which R' and R'', which may be the same or different, each represents a hydrogen atom or an alkyl group with 1 to 4 carbon atoms which may, if desired, carry one or more —OH groups, or (b) a sugar residue having a OH group at least at the 2-, 3- or 4-position, the said —OH group being bonded to the carbon atom β to the amido nitrogen atom; R₂ represents an acyl group; R₃ and R₄, which may be the same or different, each represent a hydrogen atom or an alkyl, hydroxyalkyl or acyloxyalkyl group or a sugar residue; and R₅ represents a hydrogen atom or the group —CONR₃R₄, Ac'NR⁶ or —CH₂NAc' R⁶ (in which R₃ and R₄, which may be the same or different, each represents a hydrogen atom or an alkyl, hydroxyalkyl or acyloxyalkyl group or a sugar residue, R⁶ represents a hydrogen atom or an alkyl, hydroxyalkyl, acyloxyalkyl or acyl group and Ac' represents an acyl group) any hydroxyalkyl group present optionally carrying an aldehyde or acyloxy group as a further substituent and/or any alkyl, hydroxyalkyl or acyl groups present optionally carrying a further non-ionic iodinated hydrocarbon grouping which grouping may carry additional amide groups].

3. A process as claimed in claim 2 wherein an X-ray contrast agent of formula I is used in which R₁ represents a —CH₂CH₂OH, —CH₂CHOHCH₂OH or (CH₂OH)₂CH— group.

4. A process as claimed in claim 2 or claim 3 wherein an X-ray contrast agent of formula I is used in which R_2 represents a C_{1-6} aliphatic acyl group.

5. A process as claimed in any one of claims 2 to 4 wherein an X-ray contrast agent of formula I is used in which R_3 , R_4 , R_5 , R_6 and/or R_7 represents a β -hydroxyethyl, dihydroxypropyl, tris(hydroxymethyl)-methyl group or the polyhydroxyalkyl portion of a hexosamine, pentosamine or sugar amino alcohol.

6. A process as claimed in claim 5 wherein the hydroxyalkyl group is derived from N-methyl glucamine, 1-glucamine, 2-glucamine or glucosamine.

7. A process as claimed in any one of claims 2 to 6 wherein any alkyl groups present are methyl groups.

8. A process as claimed in any one of claims 2 to 7 wherein any acyl groups present are acetyl, propionyl or butyryl groups.

9. A process as claimed in any one of the preceding claims wherein the concentration of X-ray contrast agent in the solution to be autoclaved is 100 to 450 mg I per ml.

10. A process as claimed in any one of the preceding claims wherein the concentration of the buffer in the solution is no greater than 50 m.molar.

11. A process as claimed in claim 10 wherein the concentration of the buffer in the solution is in the range 5 to 25 m.molar.

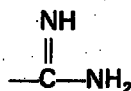
12. A process as claimed in any one of the preceding claims wherein the pH of the solution prior to autoclaving is 7.0 to 7.6.

13. A process as claimed in any one of the preceding claims wherein the buffer is a physiologically acceptable water soluble amine of the formula:—



(II)

wherein R^1 , R^2 and R^3 , which may be the same or different, each represents a hydrogen atom, a sugar residue, an alkyl group with 1 to 6 carbon atoms which may carry one or more hydroxy, mercapto, carboxyl, carboxamido, imidazolyl, indolyl or hydroxy substituted phenyl groups, alkylthio groups with 1 to 6 carbon atoms and/or groups of the formula:— NR^4R^5 (in which R^4 and R^5 , which may be the same or different, each represents a hydrogen atom, a carboxamido or



group or an alkyl group with 1 to 6 carbon atoms); or any two of R^1 , R^2 and R^3 may, together with the intervening nitrogen atom, represent a pyrrolidine or piperidine ring which may carry hydroxy, carboxyl or carboxamido groups.

14. A process as claimed in claim 13 wherein the water soluble amine comprises an amino alcohol or amino sugar.

15. A process as claimed in claim 13 or claim 14 wherein the water soluble amine comprises 2-amino-2-methylpropane-1,3-diol, diethanolamine, triethanolamine or ammonia.

16. A process as claimed in claim 13 or claim 14 wherein the water soluble amine comprises tris(hydroxymethyl)methylamine.

17. A process as claimed in claim 13 or claim 14 wherein the water soluble amine comprises meglumine.

18. A process as claimed in claim 13 or claim 14 wherein the water soluble amine comprises N,N-bis(2-hydroxyethyl)tris(hydroxymethyl)methylamine.

19. A process as claimed in any one of the preceding claims wherein the solution to be autoclaved contains a chelating agent.

20. A process as claimed in claim 19 wherein the chelating agent comprises ethylenediamine tetraacetate.

21. A process as claimed in claim 1 or claim 2 wherein the *m*-carboxamido-*o*-iodo-N-(β -hydroxyalkyl)aniline derivative X-ray contrast agent is 5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-tri-iodo-N',N''-bis(2,3-dihydroxypropyl)isophthalamide.

22. A process as claimed in claim 1 substantially as herein described.

23. A process for the preparation of a sterile, injectable, physiologically acceptable solution of an X-ray contrast agent substantially as herein described in any one of Examples 1 to 7.

24. A sterile injectable physiologically acceptable solution of a *m*-carboxamido-*o*-iodo-N-(β -hydroxyalkyl)aniline derivative X-ray contrast agent when prepared by a process as claimed in claim 1.

25. A solution of a non-ionic *m*-carboxamido-*o*-iodo-N-(β -hydroxyalkyl)aniline derivative X-ray contrast agent and a physiologically acceptable buffer system the pH of which decreases with increasing temperature said buffer system comprising ammonia or a water soluble amine having a pKa of less than or equal to 9.5.

26. A solution as claimed in claim 25 wherein the buffer is an amine buffer of formula II as defined in claim 13.
27. A solution as claimed in claim 26 in which the amine buffer is the sole buffer present in the system.
- 5 28. A solution as claimed in any one of claims 25 to 27 wherein the amine buffer is meglumine or tris(hydroxymethyl)methylamine.
29. A solution as claimed in any one of claims 25 to 28 wherein the concentration of the buffer in the solution is no greater than 50 m.molar.
- 10 30. A solution as claimed in claim 29 wherein the concentration of the buffer in the solution is in the range 5 to 25 m.molar.
31. A solution as claimed in any one of claims 25 to 30 wherein the *m*-carboxamido-*o*-iodo-N-(β -hydroxyalkyl)aniline derivative X-ray contrast agent is of formula I as defined in claim 2.
32. A solution as claimed in claim 31 wherein the *m*-carboxamido-*o*-iodo-N-(β -hydroxyalkyl)aniline derivative X-ray contrast agent is 5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-tri-15 iodo-N',N''-bis(2,3-dihydroxypropyl)isophthalamide.
33. A solution as claimed in claim 25 substantially as herein described.

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