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FORM 1

SPRUSON & FERGUSON

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 11.12.90

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

AUSTRALIAN PATENT OFFICE

SECTION 34(4)(a) DIRECTION SEE FOLIO 3
NAME DIRECTED Cook Imaging Corporation
3555 North Torrey Pines Court, La Jolla,
California 92037. U.S.A.

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which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
011016	UNITED STATES OF AMERICA	5 February 1987

The address for service is:-

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DATED this FIFTH day of FEBRUARY 1988

Biophysica Foundation

By: M.J. Anderson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 49245
S&F CODE: 57361

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Sydney

5845/2

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF AN APPLICATION FOR PATENT

In support of the application made by Cook Imaging Corporation

STERILIZATION OF COMPOSITIONS OF LIMITED STABILITY

I, Charles H. Gifford Jr, of Cook Imaging Corporation, 925 South Curry Pike Bloomington, Indiana 47402, United States of America

do solemnly and sincerely declare as follows:

1. I am authorised by Cook Imaging Corporation, the applicant for the patent to make this declaration on its behalf.

2. Milos Sovak, of PO Box 2494, Rancho Santa Fe, California 92067 United States of America and Stephen J. Foster of 1635 Brookes Avenue, San Diego, California 92103 United States of America, are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:-

3. Biophysica Foundation was the assignee of the invention from the inventors. Biophysica Foundation assigned their rights to Cook Imaging Corporation by virtue of an assignment dated 15 February 1989.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Bloomington, Indiana this 29th day of October 1990

Charles H. Gifford Jr.

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

KWK:896y

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STERILIZATION OF COMPOSITIONS OF LIMITED STABILITY

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(56) Prior Art Documents
AU 47200/85 C07C 103/44 A61K 49/04
AU 20870/88 C07C 103/46 A61K 49/04

(57) Claim

1. A method for heat sterilizing a thermolabile pH sensitive polyiodoaryl composition in an aqueous formulation, said method comprising: preparing said formulation comprising said composition, an aqueous buffered medium of a physiologically acceptable organic carboxylic acid buffer other than an amine nitrogen buffer at a pH of greater than about 5.5 and sufficient CO_2 to reduce the pH below about 5.5; and heating said formulation under sterilizing conditions to sterilize said formulation; and expelling CO_2 from said formulation; whereby said formulation equilibrates to a pH greater than about 5.5.

6. A sterile radiographic non-ionic contrast medium formulation prepared according to the method of any one of claims 1 to 5 comprising a polyiodoaryl non-ionic contrast medium at a concentration in the range of about 150 to 450 mg I/ml, sodium citrate buffer at a concentration in the range of about 0.5 to 24 mM, and at a pH in the range of about 6 to 7.5.

7. A formulation according to Claim 7, wherein said contrast medium is 5-(N-2,3-dihydroxypropylacetamido)-N-(2-hydroxyethyl), N'-(2,3-dihydroxypropyl)-2,4,5-triiodoisophthaldiamide.

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FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

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Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

AUSTRALIAN PATENT OFFICE

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Complete Specification for the invention entitled:

Sterilization of Compositions of Limited Stability

The following statement is a full description of this invention, including the best method of performing it known to me/us

5845/3

24287/BIOP-7

STERILIZATION OF COMPOSITIONS OF LIMITED STABILITY

ABSTRACT OF THE DISCLOSURE

Methods and compositions are provided for producing sterile drug formulations, where drugs are thermolabile and pH sensitive. The method provides formulating the drug with a physiologically acceptable inorganic or organic acidic buffer for buffering at a pH in excess of 6, reducing the pH below about 5 by adding carbon dioxide, and heat sterilizing the formulation in a gas permeable sealed container. The resulting formulation is substantially free of degraded drug and at the desired physiologically acceptable pH. Also, formulations are provided which do not cause clotting during administration.

STERILIZATION OF COMPOSITIONS OF LIMITED STABILITY

TECHNICAL FIELD

Sterilization of drug compositions employing novel protocols and buffer compositions.

BACKGROUND OF THE INVENTION

The preparation of drugs requires that the drugs be sterile. There are a variety of techniques employed for sterilization, including heat, chemicals, such as ethylene oxide, radiation, and the like. One of the most common techniques is the use of heat, particularly steam heat, referred to as autoclaving. In many cases, the drugs are sterilized as liquid formulations. In order for the formulation to be acceptable, it must fulfill a variety of functions.

One of the criteria for many drugs is that the formulation be at an acceptable physiological pH. For some types of drugs, the osmolality of the solution may be significant. In other situations, there may be concern with the particular inorganic cations present, their concentration, and the like. The cations may have pharmacologic effects, for example affecting the stability of the drug, or its physiological acceptability. Thus, in preparing a drug formulation, a number of factors must be considered, not only as to the physiological effect of the components of the drug formulation, but the interaction of the various components, one upon the other, as well as the effect of heat on such interaction and the individual stability of the components.

For non-ionic contract media there are a number of problems associated with intravascular administration by needle or catheter. The

hydrophobicity of the contrast media in conjunction with the amino based buffers employed result in clotting. Furthermore, the absence of sodium ions in the medium results in depression of heart function during coronary angiography.

DESCRIPTION OF THE RELEVANT LITERATURE

Radiocontrast Agents, in Handbook of Experimental Pharmacology, ed. M. Sovak, Vol. 73, Springer-Verlag, New York, 1984, provides a broad discussion of contrast media and their properties. U.S. Patent No. 4,278,654 discusses the use of hydroxyamine buffers in sterilizing radiographic non-ionic contrast media.

SUMMARY OF THE INVENTION

According to a first embodiment of the present invention there is provided a method for heat sterilizing a thermolabile pH sensitive polyiodoaryl composition in an aqueous formulation, said method comprising: preparing said formulation comprising said composition, an aqueous buffered medium of a physiologically acceptable organic carboxylic acid buffer other than an amine nitrogen buffer at a pH of greater than about 5.5 and sufficient CO_2 to reduce the pH below about 5.5; and heating said formulation under sterilizing conditions to sterilize said formulation; and expelling CO_2 from said formulation; whereby said formulation equilibrates to a pH greater than about 5.5.

According to a second embodiment of the present invention there is provided a sterile radiographic non-ionic contrast medium formulation prepared by the method of the first embodiment comprising a polyiodoaryl non-ionic contrast medium at a concentration in the range of about 150 to 450 mg I/ml, sodium citrate buffer at a concentration in the range of about 0.5 to 24 mM, and at a pH in the range of about 6 to 7.5.

Novel methods and compositions are provided for the sterilization of thermolabile drugs at physiological pH. The method involves employing a weak acid buffer which provides a physiological pH, reducing the pH with carbonate, and advantageously autoclaving the resulting formulation in a container under sterile conditions, whereby carbon dioxide may be vented. The resulting drug formulation is sterile and has the desired physiologic pH. The method finds particular application with iodaryl thermolabile compounds.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Methods and compositions are provided involving sterilized drug formulations, where the drug is thermolabile or temperature sensitive at physiologic pH at temperatures necessary for sterilization. The method involves buffering the drug with a weak organic or inorganic acid, particularly an organic carboxylic acid, to a pH which is physiologically acceptable, reducing the pH by introducing carbon dioxide, particularly at a reduced temperature, and autoclaving at a temperature in excess of 100°C for sufficient time to

sterilize the formulation and expelling the carbon dioxide under sterile conditions. Under these conditions, upon expelling the carbon dioxide, the pH is returned to the physiologic level, while substantially reduced amounts of degradation or modification of the drug occurs.

The subject method can be used with any thermolabile drug, where the thermolability is evidenced at a pH in excess of 5.5, generally in the range of 6 to 8, but is substantially reduced at a pH below 5.5. Thus, the method relies on the transient presence of carbon dioxide in the form of carbonic acid during the sterilization to substantially reduce the degradation of the drug, while allowing for a return of the formulation to physiologic pH after the sterilization. Of particular interest are formulations containing polyiodoaryl compounds, more particularly, radiographic iodo-containing contrast media, such as non-ionic contrast media particularly non-ionic contrast media having N-hydroxyalkyl substituents. For a description of contrast media, see U.S. Patent Nos. 3,702,866; 4,001,323; 4,021,481, 4,250,113 and 4,341,756.

Contrast media are formulated as aqueous solutions with a pH in the range of about 6-7.5, more usually 6.5-7, desirably 6.7-6.8.

The concentration of the drug in the media may be varied widely. For contrast media, a concentration will generally be about 150-450mg I/ml. The buffers will be free of amino nitrogen and include carboxylates, phosphates or other physiologically acceptable buffers which provide buffering at the desired pH and allow for pH reduction with carbon dioxide. The organic carboxylic acid buffer may be any convenient water soluble organic carboxylic acid which provides the desired physiological pH. Of particular interest are hydroxycarboxylic acids which are stable under the sterilization conditions, where the carboxylic acid may

be mono-or poly-carboxylic acids, particularly of up to about 4, more usually up to about 3 carboxylic acid groups. Illustrative carboxylate buffers include citrate, glycerate, gluconate, glucuronate, saccharate, glucosaccharate, etc. The carboxylate buffers may be substituted or unsubstituted, desirably being substituted with oxy groups, generally having from about 0-5, more usually from about 1-4 oxy groups, particularly hydroxy. In combination with the carboxylate buffer, carbonate, e.g. sodium carbonate, may be added to adjust the pH. The carbonate will generally be in the range of about 0-5mM, usually 0 to 3mM.

The concentration of the buffer will be selected so as to be physiologically acceptable and provide the desired stability of the drug. Conveniently, depending upon the buffer, the concentration may range as high as 50mM, more usually not greater than about 30mM, usually ranging from about 0.5-25mM, more usually from about 2-25mM, particularly 2-5mM. With non-ionic contrast media, employing citrate as buffer, a particularly desirable concentration is about 3mM.

The buffer will be desirably present as the sodium salt, although other physiologically acceptable salts may be present, e.g., potassium, so that mixtures may be employed. Preferably, the counterion will be sodium. Usually, the sodium ion concentration will be somewhere in the range of about 2-20mN.

The presence of the sodium counterion in non-ionic contrast media is particularly important because of pharmacological benefit. Without sodium, constrast media depress the heart function at the time of coronary angiography. By contrast, amine-based buffers do not provide the necessary sodium and the addition of sodium to the formulation would undesirably increase

the osmolality of the formulation resulting in increased vascular pain during angiography.

In addition to the buffer, a physiologically acceptable metal chelating agent may be present, such as ethylenediaminotetraacetic acid (EDTA). EDTA is conveniently employed, generally at a concentration of about 0.5-1.5mM.

Other additives may also be present for a variety of purposes, depending upon the nature of the drug, the formulation, the manner of administration, or other considerations.

The osmolality of the contrast medium will generally be in the range of about 100-1000 mOs/kg, usually about 150-1000 mOs/kg.

The amount of carbon dioxide which is added to the medium will generally reduce the pH to below about 5.5, preferably below about 5, and usually not less than about 4, mainly ranging from about 4-5, preferably from about 4.3-4.9. The temperature of the solution may be reduced or the pressure raised to dissolve the desired amount of carbon dioxide. Conveniently, the temperature can be reduced, either internally by employing dry ice as the source of CO_2 or externally by cooling with an appropriate cooling medium, e.g. ice, ice-saline, etc. Usually, the temperature will be dropped to below 10°C, and can be reduced to just above the freezing point of the medium.

For sterilization, the formulation may be introduced into a container, which is gas permeable, conveniently employing a gas permeable membrane, stopper or the like, depending upon the nature of the container. The container will be capable of withstanding the pressure and temperature of the autoclaving or other heat sterilization. The container may be a permeable plastic bag, plastic or glass vial used in conjunction with stoppers made of teflon, natural or semi-synthetic rubber, silicone rubber, or other conventional gas per-

meable rubber or stopper. Alternatively, unstoppered containers may be used and the CO_2 expelled under sterile conditions, e.g., a sterile room. Syringe needles through a gas-impermeable stopper may be employed to expel the CO_2. Other techniques may also be employed.

The autoclaving will normally be carried out under standard conditions as defined by the U.S. Pharmacopeia, i.e., 121°C for 20 min. During this time, a significant proportion of the carbon dioxide is vented from the formulation and further equilibration is permitted as required to obtain the final pH. Depending upon whether ambient pressures or reduced pressures are employed, equilibration may take as long as twelve days. The equilibration may be greatly speeded up by placing the containers in a vacuum while still at an elevated temperature shortly after the autoclaving or other heat sterilization. At the end of the equilibration, the pH of the product will generally be in the range of about 5.5-8, more usually in the range of about 6-7.5, preferably in the range of about 6.5-7.5.

Of particular interest are contrast media which are polyiodoaryl compounds, particularly benzene derivatives, where the positions which are not iodinated are substituted with amino or carboxy groups. The carboxy groups may be the carboxylic acid, ester, amide, particularly N-alkyl or N-hydroxyalkyl amides and amines, particularly N-hydroxyalkyl acetylamines. Illustrative compounds include 3-N(β-hydroxyethyl) acetamido-5-acetamido-2,4,6-triiodobenzoic acid; 3-(N-hydroxyethylcarbamyl)-5-acetylamino-triiodobenzoic acid; Iohexol; Metrizamide; Iopamidol; 5-(N-2,3-dihydroxypropylacetamido)-N-(2-hydroxyethyl), N'-(2,3-dihydroxypropyl)-2,4,6-triiodoisophthaldiamide (Ioxitol); MP-328 (Mallinckrodt); and 5-N-(2,3-dihydroxypropylacetamido)-2,4,6-triiodo-(N-methyl)-N'-(1,3,4-trihydroxyerythrobut-2-yl) isophthaldiamide.

Formulations of particular interest are the following:

Formulations

	Range	
	Broad	Narrow
Na citrate	1-5mM	1-4mM
EDTA, 2Na	0.5-1.5mM	1-1.5 mM
Non-ionic contrast medium	150-450mg I/ml	200-400mg I/ml
Deionized H_2O	q.i.d	q.i.d

The non-ionic contrast media formulation provides a large number of advantages. The osmolality of the compositions minimize the pain associated with intravascular administration of the compositions. The sodium citrate buffer inhibits clotting during intravascular administration. The presence of the sodium avoids heart function depression. Thus, the subject method of sterilization, not only protects labile compounds from thermal degradation, but in the the use of non-ionic contrast media provides a formulation which has many advantages in administration and physiological properties.

EXPERIMENTAL

The following examples are offered by way of illustration and not by way of limitation.

A number of solutions were prepared having different formulations, where the solutions were adjusted with carbon dioxide prior to autoclaving, to bring the pH of the solution to less than 5 or no carbon dioxide was introduced. The amount of Ioxitol (5-(N-2,3-dihydroxypropylacetamido)-N-(2-hydroxyethyl), N'-(2,3-dihydroxypropyl)-2,4,6-triiodoisophthaldiamide) was 300 mg I/ml. The remaining components and the results are listed in the following table.

Table 2

A. pH of solution adjusted to less than 5 with carbon dioxide prior to autoclaving.

Buffer Solution Na citrate (mM)[1]	pH before[2]	pH after[3]	Iodide release µg/ml
1	6.8	6.6	8
	6.8	6.5	9
	7.1	6.9	2
	7.1	6.9	1.5
2	6.8	6.4	9
	6.8	6.4	9
	7.1	6.9	4
	7.1	6.9	5
3	7.1	6.7	8
4	6.8	6.2	11
	7.1	7.0	9

B. pH of solution not adjusted with CO_2

2[4]	6.3	5.9	94
	6.5	6.0	122
	6.8	6.3	179
	7.1	6.2	165
2[5]	6.0	5.8	53
	6.3	5.9	91
	6.5	6.0	135
	6.8	6.0	112

1/ Solution contains 1.5mM EDTA, 2Na.

2/ Adjusted with Na_2CO_3; before autoclaving and addition of CO_2.

3/ After autoclaving and CO_2 equilibration.

4/ 2.0mM citrate, 1.5mM EDTA to given pH with Na_2CO_3.

5/ 2.0mM citrate, 1.5mM EDTA, 1.5mM Na_2CO_3. The pH was adjusted upwards or downwards with NaOH or HCl, respectively.

It is evident from the above results, that the subject invention provides the ability to sterilize thermolabile pH-sensitive materials at elevated temperatures and substantially prevent their degradation. The procedure is simple, effective, and can be readily employed with a large variety of drugs without adverse effects and provide for physiologically acceptable products.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

The claims defining the invention are as follows:

1. A method for heat sterilizing a thermolabile pH sensitive polyiodoaryl composition in an aqueous formulation, said method comprising: preparing said formulation comprising said composition, an aqueous buffered medium of a physiologically acceptable organic carboxylic acid buffer other than an amine nitrogen buffer at a pH of greater than about 5.5 and sufficient CO_2 to reduce the pH below about 5.5; and heating said formulation under sterilizing conditions to sterilize said formulation; and expelling CO_2 from said formulation; whereby said formulation equilibrates to a pH greater than about 5.5.

2. A method according to Claim 1, wherein said buffer provides a pH in the range of 6 to 7.5 and said CO_2 reduces the pH to the range of 4 to 5.

3. A method according to Claim 1 or Claim 2, wherein said buffer is citrate.

4. A method according to any one of claims 1 to 3, wherein said buffer is an organic carboxylate buffer at a concentration of up to about 50 mM.

5. A method according to any one of claims 1 to 4, wherein said sterilization is at a temperature of about 121°C for about 20 minutes.

6. A sterile radiographic non-ionic contrast medium formulation prepared according to the method of any one of claims 1 to 5 comprising a polyiodoaryl non-ionic contrast medium at a concentration in the range of about 150 to 450 mg I/ml, sodium citrate buffer at a concentration in the range of about 0.5 to 24 mM, and at a pH in the range of about 6 to 7.5.

7. A formulation according to Claim 7, wherein said contrast medium is 5-(N-2,3-dihydroxypropylacetamido)-N-(2-hydroxyethyl), N'-(2,3-dihydroxypropyl)-2,4,5-triiodoisophthaldiamide.

8. A formulation according to Claim 7 or Claim 8, wherein said formulation has a sodium ion concentration in the range of about 2 to 20 mN.

9. A formulation according to any one of claims 6 to 8, comprising in addition a physiologically acceptable chelating agent at a concentration in the range of about 0.5 - 1.5 mM.

10. A method for heat sterilizing a thermolabile pH sensitive compositions in an aqueous formulation which method is substantially as herein described with reference to any one of the Examples but excluding any comparative examples.

11. A formulation as defined in Claim 6 and substantially as herein described with reference to any one of the Examples but excluding any comparative examples.

DATED this TWENTY-NINTH day of NOVEMBER 1990
Cook Imaging Corporation

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

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