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(54) Title: COMPOSITION BASED ON POLYOXYETHYLENE-POLYOXYPROPYLENE BLOCK COPOLYMERS AND CONTAINER CONTAINING IT

(57) Abstract

A sealed pharmaceutically acceptable container which contains in a vacuum or in an inert atmosphere a sterile aqueous injectable solution of a block copolymer of polyoxypropylene/polyoxyethylene, the solution being substantially free from an antioxidant and being buffered at a pH from 5.5 to 6.5.

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COMPOSITION BASED ON POLYOXYETHYLENE POLIOXYPROPYLENE BLOCK COPOLYMERS AND CONTAINER CONTAINING IT

The present invention relates to a stable pharmaceutical formulation of a polyoxypropylene/polyoxyethylene block copolymer.

Certain surface-active polyoxypropylene/polyoxyethylene block copolymers have been found to have beneficial effects in animal and human medicine. In particular, the copolymers may be used for treating circulatory disorders alone or in combination with other agents, such as fibrinolytic enzymes, anticoagulants, free radical scavengers, anti-inflammatory agents, antibiotics, membrane stabilisers and/or perfusion media. These uses are described in US Patent Nos. 3,641,240, 4,801,452, 4,873,083, 4,879,109, 4,837,014, 4,897,263, 4,937,070, 4,997,644, 5,017,370, 5,028,599, 5,030,448, 5,032,394, 5,039,520, 5,041,288, 5,047,236, 5,064,643, 5,071,649, 5,078,995, 5,080,894, 5,089,260, 5,152,979, 5,182,106 and 5,198,211, all of which are incorporated herein by reference.

The surface-active copolymers are effective in circulatory disorders where there is a pathological hydrophobic interaction between cells and/or molecules. These interactions are believed to be caused by 1) a higher than normal concentration of fibrinogen, 2) generation of intravascular or local soluble fibrin, especially high molecular weight fibrin, 3) increased friction in the microvasculature, or 4) mechanical or chemical trauma to blood components. These disorders cause an increase in pathological hydrophobic interactions of blood components such as cells and molecules. It is believed that fibrin, especially soluble fibrin, increases adhesion of cells to one another, markedly increases friction in small blood vessels, and increases viscosity of the blood especially at low shear rates. The effects of the surface-active copolymers are believed to be essentially lubrication effects because they reduce the friction caused by the adhesion.

Commercially available surface-active polyoxypropylene/polyoxyethylene block copolymers generally contain antioxidants . In particular, the preparation of poloxamer 188 that may be purchased from BASF (Parsippany, New Jersey, U.S.A.) contains BHT (butylated hydroxytoluene). This antioxidant is not standardised for pharmaceutical use. In addition, antioxidants tend to be hydrophobic and insoluble in aqueous medium, and some may also present toxicity problems. This is clearly undesirable in an injectable solution for use in medicine. It is therefore an object of the present invention to provide

an aqueous solution of a block copolymer that is substantially free of such antioxidants.

The absence of an antioxidant in solutions of block copolymers tends to result in their oxidation and degradation. This leads to shorter chain molecules and by-products, such as organic acids (for example acetic acid), resulting in a reduction in the pH of the solution to 4 or even lower. It has further been observed that the lower the pH, the faster and more extensive is the degradation of the copolymer. It is therefore an object of the present invention to provide a stable aqueous solution of a block copolymer.

EP-A-103290 describes aqueous pharmaceutical formulations of polyoxypropylene and polyoxyethylene adjusted to a physiologically acceptable pH, preferably from 6 to 8, by addition of electrolytes and buffers. It does not however describe a pharmaceutical formulation of a block copolymer of polyoxypropylene/polyoxyethylene and does not describe or allude to any of the above-mentioned disadvantages associated with such a polymer. Similarly, US Patent No. 4,938,961 describes an aqueous solution of polypropylene glycol but makes no reference to solutions of a block copolymer of polyoxypropylene/polyoxyethylene.

It is a further object of the present invention to provide an aqueous solution of a block copolymer of polyoxypropylene/polyoxyethylene that is suitable for injection, especially intravenous injection.

The present invention accordingly provides a sealed pharmaceutically acceptable container which contains in a vacuum or in an inert atmosphere a sterile aqueous injectable solution of a block copolymer of formula (I):

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \qquad (I)$$

wherein a is an integer such that the hydrophobe represented by (C_3H_6O) has a molecular weight of from 950 to 4000 Daltons, preferably about 1200 to 3500 Daltons, and b is an integer such that the hydrophile portion represented by (C_2H_4O) constitutes from 50% to 95% by weight of the copolymer, the solution being substantially free from an antioxidant and being buffered at a pH from 5.5 to 6.5.

A preferred block copolymer of formula (I) is wherein the molecular weight of the

hydrophobe (C_3H_6O) is approximately 1750 Daltons and the total molecular weight of the copolymer is approximately 8400 Daltons. A particular example of such a block copolymer is that which is referred to as poloxamer 188 (BASF, Parsippany, New Jersey, U.S.A.). A discussion of the structure of poloxamers and poloxamine block copolymers can be found in Schmolka, I.R., "A Review of Block Polymer Surfactants", J. AM. OIL CHEMISTS SOC., 54:110-116 (1977), which is incorporated herein by reference.

Commercially available sources of poloxamer 188 are stated to have a molecular weight of approximately 8400 Daltons. In reality, the block copolymer is composed of molecules having a molecular weight from less than 3000 Daltons to over 20,000 Daltons. The molecular diversity and distribution of molecules of commercial poloxamer 188 can be illustrated by broad primary and secondary peaks detected using gel permeation chromatography, as described in WO 92/16484.

The high molecular weight components, i.e. the components having a molecular weight greater than 15kDaltons, that are present in commercially available poloxamer 188 normally amount to 3%, by weight, of the block copolymer or even more. Such significant amounts may give rise to unwanted side-effects in the clinical application of the block copolymer. In particular, these components have a longer elimination phase half life than the bulk of the block copolymer and thus accumulate in the plasma and kidneys. In addition, these high molecular weight components may be responsible for activation of the complement system. It is thus preferred that the block copolymer of use with the present invention is free, at least to a substantial extent, i.e. less than 1%, preferably 0.5% or 0.2%, by weight, of any molecules having a molecular weight greater than 15kDaltons.

A standard measure of the molecular weight distribution of a polymer is its polydispersity. This is referred to and described in WO92/16484, the contents of which are incorporated herein by reference. Briefly, a polydispersity of 1.0 is indicative of a polymer in which all molecules have the same molecular weight. A typical polymer may have a polydispersity of 2 to 5. The block copolymer of polyoxypropylene/ polyoxyethylene of use with the present invention preferably has a polydispersity less than 1.4, preferably 1.3 or 1.2 or even 1.1.

The surface-active block copolymer may be formed by condensation of ethylene oxide

and propylene oxide at elevated temperature and pressure in the presence of a basic catalyst. However, there is statistical variation in the number of monomer units which combine to form a polymer chain in each copolymer. The molecular weights given are approximations of the average weight of copolymer molecule in each preparation. A more detailed discussion of the preparation of these copolymers is found in U.S. Patent No. 2,674,619, which is incorporated herein by reference. The preferred forms of the block copolymer, that is the forms which are free from any significant amount of molecules having a molecular weight greater than 15kDaltons, or which have a polydispersity of less than 1.4, may be obtained by the process described in WO 92/16484.

Certain commercially available block copolymers, such as poloxamer 188, may be provided in a form containing an antioxidant. Prior to use with the present invention, the antioxidant should be removed from the copolymer, for example, by filtration or by some other means known in the art. Preferably, however, the block copolymer is obtained in a form that is already substantially free from an antioxidant.

The amount of block copolymer contained within the aqueous injectable solution is preferably from 135 to 165 mg/mL, especially about 150 mg/mL (i.e. milligrams per millilitre).

The pH of the aqueous injectable solution is preferably about 6.

The aqueous injectable solution is buffered at the desired pH using a buffering agent. Examples of such buffering agents include citrate (for example sodium citrate/citric acid). The concentration of the buffering agent, in particular citrate buffering agent, should preferably be from 0.005 to 0.05M, particularly about 0.01M.

Although a pharmaceutically acceptable co-solvent may optionally be present in addition to water, it is preferred that the medium for the aqueous injectable solution is wholly or substantially aqueous.

The aqueous injectable solution is preferably of such tonicity with the blood serum of the patient so as to avoid undesirable side effects. If the tonicity of the aqueous injectable solution needs to be increased, then a substantially isotonic solution may be obtained by

the inclusion of a pharmaceutically acceptable agent that is capable of raising the tonicity of the solution to the required level. Examples of such an agent are well known in the art and include dextrose and sodium chloride and mixtures thereof.

The aqueous injectable solution may be provided in sterile form by filtration or by autoclaving.

The formulation of the aqueous injectable solution and its filling into a pharmaceutically acceptable containers are preferably carried out in accordance with procedures known in the art in which conditions are designed to minimise the oxygen in the formulation solution or headspace.

Examples of a pharmaceutically acceptable container include plastic and glass containers, such as vials, ampoules and bottles. The containers may optionally be coloured, such as amber, to reduce the exposure of the aqueous injectable solution to UV light and possible degradation. Alternatively, the containers may be colourless but packaged in opaque cartons.

Preferably,the aqueous injectable solution is contained in an inert atmosphere which is nitrogen.

The surface-active copolymer may be used in the treatment of circulatory disorders which are caused by or which cause pathological hydrophobic interaction of blood components. Examples of such disorders include myocardial infarction, stroke, bowel or other tissue infarctions, malignancies, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), diabetes, unstable angina pectoris, hemolytic uremic syndrome, red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, sickle cell disease, burns, crush injuries, fractures, trauma producing shock, major surgery, sepsis, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and immediately after any major surgery.

The surface-active copolymer is also effective in increasing the collateral circulation to undamaged tissues with compromised blood supply. Such tissues are frequently adjacent to areas of vascular occlusion. The mechanism appears to be reducing pathological

hydrophobic interactions in small blood vessels. Circulatory disorders in which the surface-active copolymers are effective include cerebral thrombosis, cerebral embolus, myocardial infarction, unstable angina pectoris, transient cerebral ischemic attacks, intermittent claudication of the legs, plastic and reconstructive surgery, balloon angioplasty, peripheral vascular surgery, and orthopedic surgery, especially when using a tourniquet. The copolymer may also be used for the preservation of organs for transplantation.

The aqueous injectable solution of the block copolymer may be administered to the patient by bolus injection or preferably by infusion. A convenient site for administration will normally be a peripheral vein. A bolus injection usually comprises administration over a two minute period. Infusions are normally carried out with the solution contained within an infusion bag or bottle or within an electrically operated infusion pump. The solution may be delivered from the infusion bag or bottle to the patient by gravity feed or by the use of the infusion pump.

An effective amount of the block copolymer to treat a patient with a circulatory disorder will of course depend on a number of factors including, for example, the age and weight of the patient, the precise condition requiring treatment, the route of administration, and will ultimately be at the discretion of the attendant physician. It is likely however that an effective amount will generally be in the range of from 0.2 to 3.0 g/kg, preferably 1.5 to 2.5 g/kg bodyweight, administered to a patient over a period from 1 to 48 hours.

The following examples are provided in illustration of the present invention:

Example 1

For a 5000 litre batch size, the following formulation and manufacturing procedure were employed in which nitrogen protection was used throughout:-

	Per Batch
Poloxamer 188, NF[1]	750.00 kg
Sodium Chloride, USP	15.40 kg
Sodium Citrate (Dihydrate), USP	11.90 kg
Citric Acid Anhydrous, USP	1.83 kg
Water for Injection, USP	q.s
TOTAL	5000.0 litres

1. Collect approximately 4000 litres of preheated water for injection (70^{o}-80^{o}C) into a suitable vessel (vessel No. 1). Collect an additional 1000 litres of preheated water for injection (70^{o}-80^{o}C) into a second vessel (vessel No. 2).

2. Purge water in both vessels with filtered nitrogen gas. Cool to room temperature while continually purging with filtered nitrogen gas.

3. Dissolve the citric acid, sodium citrate and sodium chloride in the nitrogen purged water in vessel No. 1. Continue purging with filtered nitrogen gas.

4. Blanket the headspace with filtered nitrogen gas and discontinue nitrogen purging. Slowly add the block copolymer to the solution. Mix until dissolved. Note: Continue to blanket the headspace with filtered nitrogen gas while mixing.

5. Add sufficient water for injection, previously nitrogen purged (from vessel No. 2) to bring the batch to final volume and mix.

6. Filter solution through a membrane filter, 0.45 micrometers or equivalent, into a suitable, clean, nitrogen-purged reservoir.

7. Under clean conditions, fill approximately 500 mL of solution into previously

washed, 650-mL Type 1 flint glass bottles.

8. Under clean conditions, apply suitable closures to bottles without inserting them into the bottles.

9. Apply vacuum to headspace and insert closures into filled bottles.

10. Apply overseals.

11. Terminally sterilize product.

12. Cool product to room temperature, then mix until uniform.

13. Store bottles in individual cardboard cartons to protect the product from light.

On a mL basis, the amounts of the above components in the formulation are as follows:-

	Per mL
Poloxamer 188, NF[1]	150.0 mg
Sodium Chloride, USP	3.08 mg
Sodium Citrate (Dihydrate), USP	2.38 mg
Citric Acid Anhydrous, USP	0.366mg
Water for Injection, USP	q.s.
TOTAL	1.0 mL

The aqueous injectable solution provided in this way is a clear, colourless solution, free of particulate matter, haze or swirl and is stable, as evidenced by the following data:

[1]Containing less than 0.2% of molecules having a molecular weight greater than 15kDaltons and provided in this form.

Storage		pH	Poloxamer 188 D	Mw	Mn	%l.s.	Degradation Products (PPM) ach	act	pro	met	form
At Storage		5.8	1.21	5718.0	4713.0	99.3	25	<1	21	<1	2
UV:	7 days	5.8	-----NOT DONE -----			98.4	25	3	24	<1	2
	14 days	5.8	-----NOT DONE -----			99.1	20	3	20	<1	2
Fluor:	7 days	5.8	-----NOT DONE-----			100.3	24	7	25	<1	1
	14 days	5.8	-----NOT DONE-----			99.0	19	7	19	<1	1
50°C	1 month	5.8	1.24	5438.0	4408.0	101.6	22	<1	19	<1	4
	4 months	5.8	1.24	5418.0	4369.0	98.3	33	1	29	<1	6
40°C	4 months	5.7	1.26	5437.0	4326.0	98.6	36	<1	33	<1	5
30°C	4 months	5.6	1.25	5429.0	4354.0	99.2	35	1	33	<1	5

PPM: Parts Per Million
D: polydispersity (Mw/Mn)
N/A: Not Available
Fluor: Fluoroscent
l.s.: labelled strength

ach: acetaldehyde
act: acetone
pro: propionaldehyde
met: methanol
form: formaldehyde

Example 2

The procedure of Example 1 was repeated for a 200 litre batch size using the following formulation and collecting 160 litres in vessel No.1 and 40 litres in vessel No.2 :

Poloxamer 188, NF[1]	30.00 kg
Sodium Chloride, USP	0.616kg
Sodium Citrate (Dihydrate), USP	0.476kg
Citric Acid Anhydrous, USP	0.0732kg
Water for Injection, USP	qs
TOTAL	200.0 litres

The resulting aqueous injectable solution was similar in physical appearance as that provided by Example 1. The following stability data were obtained.

			Poloxamer 188					Degradation Products (PPM)			
Storage		pH	D	Mw	Mn	%l.s.	ach	act	pro	met	form
At Storage		5.8	1.24	5550.0	4482.0	99.8	32	<1	11.0	<1	<1
UV:	7 days	5.7	1.28	5764.5	4509.5	99.7	23	4	24	1	3
	14 days	5.9	1.29	5789.0	4498.0	98.8	22	7	23	1	1
Fluor:	7 days	5.8	1.29	5852.0	4535.5	99.2	24	9	23	2	3
	14 days	5.9	1.29	5873.0	4545.5	98.1	25	12	25	2	4
50°C	1 month	5.8	1.26	5591.5	4428.0	104.8	33	1	29	<1	7
	2 months	5.7	1.35	5411.0	3996.0	101.7	35	1	28	2	10
40°C	3 months	5.8	1.25	5414.0	4327.0	99.6	30	<1	22	<1	8
30°C	3 months	5.9	1.26	5328.0	4228.0	98.6	22	<1	19	<1	4

PPM: Parts Per Million
D: polydispersity (Mw/Mn)
N/A: Not Available
Fluor: Fluoroscent
l.s.: labelled strength

ach: acetaldehyde
act: acetone
pro: propionaldehyde
met: methanol
form: formaldehyde

CLAIMS

1. A sealed pharmaceutically acceptable container which contains in a vacuum or in an inert atmosphere a sterile aqueous injectable solution of a block copolymer of formula (I):

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \qquad (I)$$

wherein a is an integer such that the hydrophobe represented by (C_3H_6O) has a molecular weight of from 950 to 4000 Daltons and b is an integer such that the hydrophile portion represented by (C_2H_4O) constitutes from 50% to 95% by weight of the copolymer, the solution being substantially free from an antioxidant and being buffered at a pH from 5.5 to 6.5.

2. A container according to claim 1, wherein the molecular weight of the hydrophobe is from 1200 to 3500 Daltons.

3. A container according to claim 2, wherein the molecular weight of the hydrophobe is approximately 1750 Daltons and the total molecular weight of the block copolymer is approximately 8400 Daltons.

4. A container according to any of the preceding claims, wherein the block copolymer is substantially free of any molecules having a molecular weight greater than 15000 Daltons.

5. A container according to claim 4, wherein the amount of molecules having a molecular weight greater than 15000Daltons is less than 1%.

6. A containing according to claim 5, wherein the amount is less than 0.5%.

7. A container according to any of the preceding claims, wherein the block copolymer has a polydispersity less than 1.4.

8. A container according to claim 7, wherein the polydispersity is less than 1.3.

9. A container according to claim 8, wherein the polydispersity is less than 1.2.

10. A container according to claim 9, wherein the polydispersity is less than 1.1.

11. A container according to any of the preceding claims, wherein the block copolymer is present in an amount from 135 to 165 mg/mL of solution.

12. A container according to claim 11, wherein the amount is about 150mg/mL of solution.

13. A container according to any of the preceding claims, wherein the pH is about 6.

14. A container according to any of the preceding claims, wherein the solution is buffered using citrate as the buffering agent.

15. A container according to claim 14, wherein the concentration of the citrate buffering agent is from 0.005 to 0.05M.

16. A container according to claim 15, wherein the concentration is about 0.01M.

17. A container according to any of the preceding claims, wherein the solution is substantially isotonic with human blood serum.

18. A container according to any of the preceding claims, wherein the inert atmosphere is nitrogen.

INTERNATIONAL SEARCH REPORT

Inter .onal Application No
PCT/GB 93/02141

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/77

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)
IPC 5 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,90 07336 (EMORY UNIVERSITY) 12 July 1990 cited in the application see claims see page 29, line 3 - line 19	1
Y	US,A,3 641 240 (A.C.HYMES) 8 February 1972 cited in the application see claims see column 1, line 65 - line 70	1
Y	EP,A,0 103 290 (INTERMEDICAT) 21 March 1984 cited in the application see claims see page 4, line 28 - line 32 see page 5, line 1 - line 27	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 938 961 (G.COLLINS) 3 July 1990 cited in the application see claims see column 4, line 11 - line 14 see column 4, line 38 - line 61	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ional Application No
PCT/GB 93/02141

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9007336	12-07-90	US-A-	4879109	07-11-89
		AU-B-	637996	17-06-93
		AU-A-	4849590	01-08-90
		CA-A-	2006953	29-06-90
		EP-A-	0409940	30-01-91
		JP-T-	3505879	19-12-91
		US-A-	4897263	30-01-90
		US-A-	4937070	26-06-90
US-A-3641240	08-02-72	NONE		
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