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(54) Title: AQUEOUS FORMULATIONS BASED ON SODIUM HYALURONATE FOR PARENTERAL USE

(57) Abstract: An aqueous formulation for parenteral use, comprises sodium hyaluronate having a molecular weight from 500,000 to 5,000,000 D in an amount from 0.01 to 3 % w/v, based on the aqueous formulation, a non saline physiologically acceptable osmogen in an effective amount to impart to the aqueous formulation a physiological osmolarity of from 270-330 mOsm/l, and an amphoter acting as an inhibitor of hyaluronidase activity.

AQUEOUS FORMULATIONS BASED ON SODIUM HYALURONATE FOR PARENTERAL USE

The present invention concerns aqueous formulations based on sodium hyaluronate for parenteral use.

Sodium hyaluronate is the sodium salt of hyaluronic acid, a mucoid polysaccharide of biological origin, which is known as one of the major components of synovial fluid and which is also present in various connective tissues such as skin and cartilage.

Chemically, hyaluronic acid is a member of glycosaminoglycans and it is constituted by alternating and repeating units of D-glucuronic acid and N-acetyl-D-glucosamine, to form a linear chain having a molecular weight up to 13 x 10^6 Daltons.

Formulations containing sodium hyaluronate, inter alia for intra-articular use, are widely described in the literature.

Known aqueous formulations based on sodium hyaluronate for intra-articular use are usually composed of sodium hyaluronate as active ingredient, and further of some salts as sodium chloride for obtaining the physiological osmolarity of 270 - 330 mOsm/l and sodium phosphate as a buffer for maintaining the pH in the range of 6.8 to 7.6, preferably at a physiological pH of 7.4.

WO-A-89 01777 discloses a lubricant composition for intra-articular use, which is useful to reduce the coefficient of kinetic friction imparted to the boundary surface of a joint upon articulation, said lubricant composition comprising at least one phospholipid in a relatively high concentration and hyaluronic acid or a water soluble salt thereof in phosphate-buffered saline solution.

HA with a high molecular weight, in particular with an average molecular weight above 500'000 Daltons, is preferred in many applications in view of the superior visco-elastic properties, residence time and tolerance in the body compared to lower molecular weight HA. Known aqueous HA formulations however suffer from degradation by hyaluronidase enzymes, and as a consequence a deterioration of the sought after properties of the HA.

An object of this invention is to provide an aqueous high molecular weight HA formulation for parenteral uses, such as for intra-articular use or for tissue augmentation, that is stable over a long period of time, in particular that is resistant to degradation by enzymes.

In order to overcome the problem of degradability of hyaluronate polymer by hyaluronidase, the inventors of the present invention have made extensive studies to provide an aqueous formulation based on sodium hyaluronate for parenteral use, such as for intra-articular use or for soft tissue augmentation, which has an improved resistance to degradation of hyaluronate polymer by hyaluronidase and consequently which has, inter alia, an increased residence time at the site of application.

The inventors have found that the presence of sodium chloride in known aqueous HA formulations, which is primarily intended to provide a physiological osmolarity for parenteral use, surprisingly has an adverse influence on the resistance to hyaluronidase degradation of the HA polymer.

Without wishing to be bound by theory, it is believed that the reduced resistance of HA in aqueous saline solution is probably due to a modification in the conformation of the hyaluronate network in aqueous solution when sodium chloride is present, which better exposes the polymer chains to an attack by the enzymes.

The inventors have further found that in the absence of sodium chloride, a wide range of amphoters – which includes fatty acids, fatty acid esters, phospholipids, sphingolipids, and gangliosides – inhibit hyaluronidase enzyme activity very effectively.

Thus, according to the present invention, the object of the invention has been achieved as a result of the unexpected findings that sodium chloride, which is usually contained in known aqueous sodium hyaluronate formulations for parenteral use, may be advantageously replaced by a non saline physiologically

acceptable osmogen, to provide an aqueous formulation having physiological osmolarity. In order to maintain the physiological pH, a suitable buffer can be added, unless the osmogen itself can act as a buffer in the physiological range. In combination with an amphoter, acting as a hyaluronidase activity inhibitor, the hyaluronate polymer has a resistance to hyaluronidase that is, in vitro, more than 30 times greater than hyaluronate polymer contained in the known formulations containing sodium chloride.

The non saline osmogen may advantageously be an amino acid selected from a group comprising histidine, valine, proline and cysteine. The osmogen may also be: a polyalchohol phosphoric ester such as glycerophosphate; a polyol such as mannitol, sorbitol, glycerol or xylitol; a monosaccharide such as glucose, galactose, xylose, fructose, galactosamine, glucosamine, neuraminic acid, and glucuronic acid; or a disaccharide such as sucrose, maltose and lactose.

An advantage of the use of an amino acid selected from a group comprising histidine, valine, proline and cysteine, and particularly histidine, is that the amino acid itself acts as a buffer in the physiological pH and gives the physiological osmolarity when added in an appropriate amount, thus providing an aqueous formulation for parenteral use comprising sodium hyaluronate having an improved resistance to degradation by hyaluronidase due to the absence of sodium chloride and phosphate buffer and therefore an increased residence time at the site of application.

Thus, the present inventors have surprisingly found that an aqueous formulation for parenteral use, such as intra-articular use or soft tissue augmentation, comprising sodium hyaluronate having a very high resistance to degradation by hyaluronidase, and therefore an optimal residence time at the site of application, may be obtained by adding a small amount of an amphoter (amphoteric compound) such as a phospholipid to a non-saline aqueous formulation comprising sodium hyaluronate,or other salt of hyaluronic acid, and a non saline osmogen such as histidine.

Other objects and advantageous aspects of the present invention will be apparent from the claims and following detailed description and accompanying figure, in which:

Fig. 1 represents a graph showing elastic module kinetics during incubation at 37°C with hyaluronidase in two different formulations, namely a formulation according to the present invention and a comparative formulation.

The aqueous formulation for parenteral use of the present invention comprises between 0.01 to 3 % w/v sodium hyaluronate having a molecular weight from 500,000 to 5,000,000 Daltons. The molecular weight of sodium hyaluronate used in the present invention, which is commercially available, may be determined by known techniques such as gel permeation chromatography or by measuring intrinsic viscosity.

Said aqueous formulation for parenteral use of the present invention is characterized in that it further comprises non saline osmogen in an effective amount to impart to the aqueous formulation a physiological osmolarity of from 270 - 330 mOsm/l and a physiological pH from 6.8 – 7.6, preferably 7.4., or a non saline osmogen plus a suitable buffer capable of maintaining the pH in the physiological range.

Sodium hyaluronate of molecular weights lower than 500,000 D are not appropriate for use in the present invention because of the insufficient visco-elastic properties, the lower residence time and reduced tolerance and increased irritation in the body compared to higher molecular weight HA.

A formulation having a content of sodium hyaluronate greater than 3 % wt/v is not appropriate for parenteral use since it forms a very high viscosity gel that is difficult to administer by injection, for example.

Preferably, the sodium hyaluronate is used in an amount of 0.2 to 2 % wt/v, based on the total aqueous formulation.

Said aqueous formulation for intra-articular use of the present invention comprises both a non saline osmogen in an effective concentration to impart to

the aqueous formulation a physiological osmolarity of from 270-330 mOsm/l and a physiological pH of from 6.8-7.6, or a non saline osmogen plus a suitable buffer. In a first embodiment, the non saline osmogen is preferably an amino acid selected from a group comprising histidine, valine, proline and cysteine, such substances being able to buffer at the physiological pH. In a second embodiment, a suitable buffer such as an amino acid selected from a group comprising histidine, valine, proline, asparagine and cysteine, is associated with an osmogen such as a polyalchohol phosphoric ester such as glycerophosphate; a polyol such as mannitol, sorbitol, glycerol or xylitol; a monosaccharide such as glucose, galactose, xylose, fructose, galactosamine, glucosamine, neuraminic acid, and glucuronic acid; or a disaccharide such as sucrose, maltose and lactose.

It is known that sodium hyaluronate also contributes to the osmolarity of the formulation, said contribution depending on the concentration and molecular weight of sodium hyaluronate present in the formulation.

Therefore, the effective concentration range of osmogen to impart to the aqueous formulation a physiological osmolarity of from 270-330 mOsm/l will depend on the concentration and molecular weight of the sodium hyaluronate present in the formulation.

By way of example, a solution of 36, 40 and 44 g/l of histidine gives an osmolarity of 220, 246 and 268 mOsm/l, respectively. When sodium hyaluronate having a molecular weight of 1'800'000 D is added in an amount of 1 % w/v to the solution, the osmolarity becomes 271, 298 and 310 mOsm/l, respectively.

This means that sodium hyaluronate having an average molecular weight of 1'800'000 D in an amount of 1 % w/v contributes to about 50 mOsm/l.

The higher the concentration of sodium hyaluronate, the lower is the amount of osmogen (for example histidine) needed to impart to the aqueous formulation a physiological osmolarity of from 270-330 mOsm/l, and the higher the molecular weight of sodium hyaluronate, the lower the amount of histidine is needed to impart to the aqueous formulation a physiological osmolarity of from 270-330 mOsm/l.

An advantage of using an amino acid, and in particular histidine, as an osmogen, is that it results in a physiological pH at all concentrations of histidine if the physiological osmolarity is achieved in the formulation containing sodium hyaluronate. An additional buffer is thus not needed.

Presence of histidine in an effective amount to impart a physiological osmolarity in the aqueous formulation containing sodium hyaluronate allows to improve the resistance of hyaluronate to hyaluronidase by 2 - 3 times compared with classical formulations containing sodium chloride and phosphate buffer instead of histidine.

In an embodiment of the invention, the aqueous formulation of the present invention may be prepared according to conventional techniques by adding histidine in water previously heated at a temperature up to 40°C and stirring until complete dissolution of histidine into water, and then by further adding thereto sodium hyaluronate and stirring until complete dissolution of sodium hyaluronate into the histidine solution.

In a preferred embodiment of the present invention, the aqueous formulation further contains up to 1 % w/v phospholipid based on the total aqueous formulation.

Phospholipids which can be used in the present invention may be any naturally or artificially synthesized phospholipids and are preferably selected from phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, sphingomyelin and derivatives thereof.

Presence of a small amount of phospholipid in the aqueous formulation of the present invention containing sodium hyaluronate and histidine is advantageous in the sense that it allows to impart to hyaluronate a drastically improved resistance to degradation by hyaluronidase.

The aqueous formulation of the present invention further containing phospholipid may be prepared according to conventional techniques by adding a suspension of phospholipid, previously prepared by adding phospholipid to water heated at a

temperature up to 50°C, to the aqueous formulation according to the present invention containing histidine and sodium hyaluronate and stirring until the formulation be homogeneous.

In case the non-saline osmogen added to the formulation does not act as a buffer, various physiologically acceptable buffers may be added to the formulation, these buffers including: common buffers such as citric acid, cacodylic acid Sodium salt-HCl, and imidazole-HCl; peptides such as carnosine, amino acid such as histidine, proline, valine or cysteine; and Zwitterionic buffers such as Glycyl-glycine-piperazine-2HCl-NaOH, MES-NaOH-NaCl, TRIS-malic acid-NaOH, ADA-NaOH-NaCl, ACES-NaOH-NaCl, BES-NaOH-NaCl, MOPS-NaOH-NaCl, TES-NaOH-NaCl, MOPS-KOH, HEPES-NaOH-NaCl, TRIS-HCl, HEPPSO-NaOH, and BICINE-NaOH-NaCl.

The aqueous formulation for parenteral use of the present invention is particularly useful for intra-articular administration or soft tissue augmentation and has the advantage of showing an increased residence time at the site of application for the reason that hyaluronate polymer contained in the formulation has an improved resistance to degradation by hyaluronidase.

EXAMPLES

Example 1: Preparation of a formulation according to a preferred embodiment of the present invention containing 1 % w/v of sodium hyaluronate, in which the formulation contains a single substance that acts as an osmogen and as a buffer.

1 liter of an aqueous solution of sodium hyaluronate with 1% concentration are prepared using the following substances:

- L-histidine provided by FLUKA assay 99.5%.
- Sodium hyaluronate provided by H.T.L s.a.r.l.

- 1,2-Dipalmitoyl-sn-glycero-3-phosphate monosodium salt provided by FLUKA assay 98%

The formulation is prepared as follows:

1. 49 g of histidine are added to 800 ml of water for injection preheated at 40°C under stirring conditions
2. After dissolution of histidine is complete, 10 g of sodium hyaluronate are added to the histidine solution and stirred until complete dissolution of sodium hyaluronate is achieved (Solution A).
3. In parallel, a suspension of 1 g of 1,2-Dipalmitoyl-sn-glycero-3-phosphate monosodium salt in 200 ml of warm water for injection (40-50°C) was prepared (Solution B).
4. Solution B is poured into Solution A under stirring conditions, to prepare 2 liter of a formulation according to an embodiment of the present invention.

Example 2: Preparation of a formulation according to a preferred embodiment of the present invention containing 2 % w/v of sodium hyaluronate, in which the the formulation contains a substance that acts as an osmogen and another substance which acts as a buffer.

1 liter of an aqueous solution of sodium hyaluronate with 2% concentration are prepared using the following substances:

- DL-α-Glycerol phosphate Disodium salt provided by FLUKA assay 90%.
- L-histidine provided by FLUKA assay 99.5%.
- Sodium hyaluronate provided by H.T.L s.a.r.l.
- 1,2-Dipalmitoyl-sn-glycero-3-phosphate monosodium salt provided by FLUKA assay 98%

The formulation is prepared as follows:

1. 28g of Glycerol phosphate and 5g of L-histidine are dissolved in 800 ml of water for injection (Solution A).

2. 1 g of 1,2-Dipalmitoyl-sn-glycero-3-phosphate monosodium salt are dissolved in 200 ml of water for injection at a temperature of 60°C (Solution B).
3. Solution A and solution B are mixed together and the pH is adjusted at 7.4 with sulfuric acid 10% in water for injection.
4. Finally, 20g of sodium hyaluronate are added to the solution, and stirred, to prepare 2 liter of a formulation according to an embodiment of the present invention.

A solution with an osmolarity of 300 [mOsm/lt] and a pH of 7.4 is obtained. The resistance to hyaluronidase degradation of the formulation obtained is significantly increased as illustrated in Figure 1. In Figure 1, the elastic module kinetics of the formulation according to the above example (IF), and a conventional HA saline aqueous formulation (CF) is measured during incubation with hyaluronidase at 37 degrees celsius. The known formulation is a formulation at 2% concentration of sodium hyaluronate in a saline aqueous solution commercialised by the firm TRB Chemedica SA (Switzerland) under the tradename "VISIOL".

CLAIMS

1. An aqueous formulation for parenteral use, comprising sodium hyaluronate having a molecular weight from 500,000 to 5,000,000 D in an amount from 0.01 to 3 % w/v, based on the aqueous formulation, characterized in that it further comprises a non saline physiologically acceptable osmogen in an effective amount to impart to the aqueous formulation a physiological osmolarity of from 270-330 mOsm/l, and an amphoter acting as an inhibitor of hyaluronidase activity.

2. An aqueous formulation according to claim 1 further comprising a physiologically acceptable buffer in an effective amount to impart to the aqueous formulation a physiological pH from 6.8-7.6.

3. The formulation according to claim 2 wherein the physiologically acceptable buffer is selected from the groups comprising: common buffers including citric acid, cacodylic acid Sodium salt-HCl, and imidazole-HCl; peptides including carnosine; amino acid such as histidine, proline, valine or cysteine and Zwitterionic buffers inluding Glycyl-glycine-piperazine-2HCl-NaOH, MES-NaOH-NaCl, TRIS-malic acid-NaOH, ADA-NaOH-NaCl, ACES-NaOH-NaCl, BES-NaOH-NaCl, MOPS-NaOH-NaCl, TES-NaOH-NaCl, MOPS-KOH, HEPES-NaOH-NaCl, TRIS-HCl, HEPPSO-NaOH, and BICINE-NaOH-NaCl.

4. An aqueous formulation according to claim 1, 2 or 3, wherein the non saline osmogen is an amino acid selected from the group comprising histidine, valine, proline and cysteine.

5. An aqueous formulation according to any one of the preceding claims wherein the non saline osmogen is selected from the groups comprising: a polyalchohol phosphoric ester such as glycerophosphate; a polyol such as mannitol, sorbitol, glycerol or xylitol; a monosaccharide such as glucose, galactose, xylose, fructose, galactosamine, glucosamine, neuraminic acid, and glucuronic acid; and a disaccharide such as sucrose, maltose and lactose.

6. The formulation according to any one of the preceding claims wherein said amphoter is selected from a group of compounds comprising unsaturated fatty acids, fatty acid esters, phospholipids, sphingolipids, and gangliosides.

7. The formulation according to claim 6 wherein the amphoter is a phospholipid selected from a group comprising phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, sphingomyelin and derivatives thereof.

8. The formulation according to claim 7 wherein there is less than 1 % w/v of phospholipid, based on the aqueous formulation.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/728 A61K47/18 A61K47/24

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, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 89/01777 A (MACNAUGHT PTY. LIMITED) 9 March 1989 (1989-03-09) cited in the application page 3, line 5 - line 12; claims	1-8
Y	AU 23208 88 A (MACNAUGHT PTY. LIMITED) 31 March 1989 (1989-03-31) examples	1-8
Y	US 2001/041671 A1 (NAPOLI GUIDO DI ET AL) 15 November 2001 (2001-11-15) paragraphs [0037] - [0042]; table 1	1-8
Y	EP 0 138 572 A (FIDIA SPA; FIDIA S.P.A) 24 April 1985 (1985-04-24) examples 11,14	1-8

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

[X] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003918

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 499 164 A (C.R. BARD, INC) 19 August 1992 (1992-08-19) examples 4,5,7,11	1-8
X	US 5 234 914 A (GALLINA ET AL) 10 August 1993 (1993-08-10) column 6, line 55 - column 7, line 25	1-8
X	US 5 679 655 A (GALLINA ET AL) 21 October 1997 (1997-10-21) examples D,G,H	1-8
A	US 4 957 744 A (DELLA VALLE ET AL) 18 September 1990 (1990-09-18) column 8, line 24 - line 33	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/003918

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8901777 A	09-03-1989	CA 1325595 C	28-12-1993
		CN 1033239 A	07-06-1989
		DE 3884622 T2	28-04-1994
		EP 0387252 A1	19-09-1990
		JP 3501250 T	22-03-1991
		US 5403592 A	04-04-1995
AU 2320888 A	31-03-1989	NONE	
US 2001041671 A1	15-11-2001	AT 250924 T	15-10-2003
		AU 778858 B2	23-12-2004
		AU 3340401 A	11-10-2001
		BR 0101332 A	06-11-2001
		CA 2342133 A1	07-10-2001
		CN 1317342 A	17-10-2001
		CZ 20011229 A3	14-11-2001
		DE 60100866 D1	06-11-2003
		DE 60100866 T2	29-07-2004
		DK 1142566 T3	09-02-2004
		EP 1142566 A1	10-10-2001
		ES 2206363 T3	16-05-2004
		JP 2001316284 A	13-11-2001
		PL 346926 A1	08-10-2001
		PT 1142566 T	27-02-2004
		SK 4602001 A3	06-11-2001
		TR 200302105 T4	23-02-2004
		ZA 200102769 A	05-10-2001
EP 0138572 A	24-04-1985	AR 231992 A1	30-04-1985
		AU 575861 B2	11-08-1988
		AU 3414884 A	18-04-1985
		BE 900810 A2	11-04-1985
		CA 1205031 A1	27-05-1986
		CH 666897 A5	31-08-1988
		DE 3482812 D1	30-08-1990
		DK 485384 A	12-04-1985
		ES 8507573 A1	16-12-1985
		FI 843990 A	12-04-1985
		FR 2553099 A1	12-04-1985
		HK 66091 A	30-08-1991
		HU 36834 A2	28-10-1985
		IE 57931 B1	19-05-1993
		IN 163192 A1	20-08-1988
		KR 8601148 B1	18-08-1986
		LU 85582 A1	04-06-1985
		NO 844054 A	12-04-1985
		PT 79339 A	01-11-1984
		SG 59491 G	23-08-1991
EP 0499164 A	19-08-1992	AU 652022 B2	11-08-1994
		AU 1055292 A	20-08-1992
		CA 2060223 A1	13-08-1992
		JP 6048948 A	22-02-1994
US 5234914 A	10-08-1993	AU 2161392 A	12-01-1993
		WO 9222585 A1	23-12-1992
US 5679655 A	21-10-1997	US 5583118 A	10-12-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/003918

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5679655 A		US 5624915 A	29-04-1997
		US 5583119 A	10-12-1996
		US 5529987 A	25-06-1996
		US 5583120 A	10-12-1996
		US 5631242 A	20-05-1997
US 4957744 A	18-09-1990	AR 247406 A1	29-12-1994
		AT 163942 T	15-03-1998
		AU 610087 B2	16-05-1991
		AU 7960087 A	21-04-1988
		CA 1317287 C	04-05-1993
		CN 87106919 A	24-08-1988
		DE 3752176 D1	16-04-1998
		DE 3752176 T2	29-10-1998
		DK 536087 A	14-04-1988
		EP 0265116 A2	27-04-1988
		ES 2115583 T3	01-07-1998
		FI 874504 A	14-04-1988
		HU 45734 A2	29-08-1988
		IE 872618 L	13-04-1988
		IL 84032 A	20-11-1997
		IN 170801 A1	23-05-1992
		IT 1198449 B	21-12-1988
		JP 2648308 B2	27-08-1997
		JP 63105003 A	10-05-1988
		KR 9202702 B1	31-03-1992
		NO 874251 A	14-04-1988
		NZ 221994 A	26-07-1990
		PH 26025 A	29-01-1992
		PT 85908 A	01-11-1987
		ZA 8707559 A	13-04-1988