



(86) Date de dépôt PCT/PCT Filing Date: 2002/12/13
(87) Date publication PCT/PCT Publication Date: 2003/07/03
(45) Date de délivrance/Issue Date: 2012/02/14
(85) Entrée phase nationale/National Entry: 2004/06/15
(86) N° demande PCT/PCT Application No.: EP 2002/014225
(87) N° publication PCT/PCT Publication No.: 2003/053448
(30) Priorité/Priority: 2001/12/21 (ES P 200102856)

(51) Cl.Int./Int.Cl. *A61K 31/70* (2006.01),
C07H 5/06 (2006.01)
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(54) Titre : PROCEDE POUR PREPARER DES SELS DE GLUCOSAMINE
(54) Title: PROCESS FOR THE PREPARATION OF GLUCOSAMINE SALTS

(57) **Abrégé/Abstract:**

This invention relates to a process for the preparation of glucosamine sulphate or glucosamine hydroiodide or glucosamine pyruvate or glucosamine phosphate, or mixtures thereof with glucosamine hydrochloride by electrodialysis. Starting from glucosamine hydrochloride, the exchange of the Cl^- anion for an anion selected from the group consisting of SO_4^{2-} , I^- , $\text{CH}_3\text{COCOO}^-$ and PO_4^{3-} takes place during the process. The electrodialysis process is carried out in an electrodialyzer or stack of electrodialyses, formed by at least a cathode, anode and a means of separation, composed of anion and cation exchange membranes. The product obtained is suitable to be used in oral, injectable or topical pharmaceutical preparations.

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ABSTRACT

This invention relates to a process for the preparation of glucosamine sulphate or glucosamine hydroiodide or glucosamine pyruvate or glucosamine phosphate, or mixtures thereof with glucosamine hydrochloride by electrodialysis. Starting from glucosamine hydrochloride, the exchange of the Cl^- anion for an anion selected from the group consisting of SO_4^{2-} , I^- , $\text{CH}_3\text{COCOO}^-$ and PO_4^{3-} takes place during the process. The electrodialysis process is carried out in an electrodialyzer or stack of electrodialyses, formed by at least a cathode, anode and a means of separation, composed of anion and cation exchange membranes. The product obtained is suitable to be used in oral, injectable or topical pharmaceutical preparations.

"PROCESS FOR THE PREPARATION OF GLUCOSAMINE SALTS"**DESCRIPTION**5 **Technical sector of the invention.-**

This invention relates to a process for the preparation of glucosamine sulphate, glucosamine hydroiodide, glucosamine pyruvate, glucosamine phosphate or their mixtures with glucosamine hydrochloride. This invention also refers to a glucosamine sulphate containing chlorides obtainable by the process, and its
10 therapeutical use.

State of the art in relation to the invention.-

Electrodialysis is a technique that uses ion exchange membranes and permits to separate dissolved ionic substances when a difference of potential is
15 applied. It is a process widely used to obtain drinking water, generally from salt water, in the treatment of industrial effluents and, in addition, in the food and pharmaceutical industries, where it is being fully developed, it is used, for instance, to separate and purify solutions.

Glucosamine is a well-known substance, used in the treatment of osteoarthritis and arthritis in general, in both acute and chronic forms, as well as in
20 the treatment of pathological conditions affecting the osteo-articular tissue.

The fact that the glucosamine base is an unstable substance has lead to its commercialisation as different salts, which maintain the same pharmacological properties (L. Rovati, US 3,683,076, H. Müller-Faßbender *et al.*, *Osteoarthritis*
25 *Cart.*, 2 (1994)).

Various processes to obtain glucosamine salts are known. Some of them consist of previously obtaining the glucosamine base from glucosamine hydrochloride, later adding the corresponding acid, depending on the salt desired. In general, to obtain the glucosamine base, glucosamine hydrochloride is treated
30 with triethylamine (L.Rovati, CH 525,861), or with sodium methoxide (L. Rovati, US 3,683,076) or by means of anion exchange resins. These processes have the disadvantage of having to previously go through a product as unstable as glucosamine base, and of using, in some cases, toxic substances such as triethylamine. The salts can also be obtained directly, starting from glucosamine hydrochloride and using an anion exchange resin previously treated with the acid that
35 contains the anion of the salt desired, or a metal salt of one of said acids (GB

1,056,331). As this process uses resins it has the disadvantage of giving a low production yield.

In accordance with this, it is necessary to find an alternative method for the preparation of said glucosamine salts, avoiding the above-mentioned disadvantages of the traditional methods.

Until now, no process has been disclosed for the preparation of the glucosamine salts of this invention using an electrochemical technology called electrodialysis.

Disclosure of the invention.-

An embodiment of the invention relates to a process for the preparation of glucosamine sulphate, glucosamine hydroiodide, glucosamine pyruvate, glucosamine phosphate or mixtures thereof, wherein the starting material is glucosamine hydrochloride, said process comprising the step of subjecting the glucosamine hydrochloride to electrodialysis.

A preferred embodiment of the invention relates to a process as defined hereinabove, wherein during said electrodialysis, the Cl^- anion in glucosamine hydrochloride is exchanged for an anion selected from the group consisting of SO_4^{2-} , I^- , $\text{CH}_3\text{COCOO}^-$ and PO_4^{3-} .

Another preferred embodiment of the invention relates to a process as defined hereinabove, wherein during said electrodialysis, the Cl^- anion is exchanged for the SO_4^{2-} anion to thereby obtain a glucosamine sulphate.

Another preferred embodiment of the invention relates to a process as defined hereinabove, wherein the electrodialysis is carried out in compartments and comprises the following steps:

(a) preparing

(a_i) an aqueous solution of glucosamine hydrochloride

(a_{ii}) an aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl^- anion; and

(a_{iii}) an aqueous solution of a salt that lends conductivity;

(b) feeding :

(b_i) a diluate compartment with the aqueous solution of glucosamine hydrochloride and the aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl⁻ anion,

(b_{ii}) an electrolyte compartment with the aqueous solution of a salt that lends conductivity, and

(b_{iii}) a concentrate compartment with water or the aqueous solution of a salt that contains the anion to be exchanged for the Cl⁻ anion;

(c) applying an electrical field across said compartments at a constant or variable current intensity or at a controlled potential difference;

(d) verifying the chloride content in the diluate compartment;

(e) discontinuing the electrodialysis once a desired amount of chloride has been obtained;

(f) recovering a solution obtained from the diluate compartment; and

(g) obtaining a solid product by precipitating by adding organic solvents that are miscible with water to said solution of step (f) and subsequently drying the precipitate or by atomising or lyophilising the solution of step (f),

wherein during said process a soluble hydroxide of an alkaline or alkaline earth metal is added to the concentrate compartment in order to maintain a pH greater than 2. More preferably in step (g) a solid product is obtained by atomising or lyophilising the solution of step (f).

Another preferred embodiment of the invention relates to a process as defined hereinabove, wherein the electrodialysis is carried out in compartments and comprises the following steps:

(a) preparing

(a_i) an aqueous solution of glucosamine hydrochloride

(a_{ii}) an aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl⁻ anion; and

(a_{iii}) an aqueous solution of a salt that lends conductivity;

(b) feeding :

(b_i) a diluate 1 compartment with the aqueous solution of glucosamine hydrochloride,

5 (b_{ii}) a diluate 2 compartment with the aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl⁻ anion,

(b_{iii}) an electrolyte compartment with the aqueous solution of a salt that lends conductivity, and

10 (b_{iv}) a concentrate compartment with water or the aqueous solution of a salt that contains the anion to be exchanged for the Cl⁻ anion;

(c) applying an electrical field across said compartments at a constant or variable current intensity or at a controlled potential difference;

(d) verifying the chloride content in the diluate 1 compartment;

15 (e) discontinuing the electrodialysis once a desired amount of chloride has been obtained;

(f) recovering a solution obtained from the diluate 1 compartment; and

20 (g) obtaining a solid product by precipitating by adding organic solvents that are miscible with water to said solution of step (f) and subsequently drying the precipitate or by atomising or lyophilising the solution of step (f). More preferably in step (g) a solid product is obtained by atomising or lyophilising the solution of step (f).

25 Another preferred embodiment of the invention relates to a process as defined hereinabove, wherein the electrodialysis process is carried out in an electrodialyser that comprises a cathode, an anode and means of separation. More preferably, wherein the means of separation are composed of anion exchange membranes, cation exchange membranes or bipolar membranes.

According to a particularly preferred embodiment of the invention, the electrodialysis is carried out at a temperature from 0 to 90°C, and more preferably, said solid product has a chloride content of from 0.5 to 16% or a chloride content of

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less than 0.5%.

Another preferred embodiment of the invention relates to a process as defined hereinabove, wherein the solution of step (f) or the solid product of step (g) is formulated into a product suitable for use in an oral, injectable or topical pharmaceutical preparation.

Another preferred embodiment of the invention relates to a process as defined hereinabove, wherein the solution of step (f) is mixed with a sodium or potassium salt, or with an aqueous solution of a sodium or potassium salt.

The electrodialysis is preferably carried out in an electrodialyser or stack of electrodialysis, which is comprised of a cathode, an anode and means of separation, which are preferably composed of anion exchange membranes, cation exchange membranes, bipolar membranes or by means of other suitable means of separation.

An electrode made of graphite, coal or its derivatives, lead, tin, zinc, copper, platinized titanium, all kinds of steel or alloys of iron, aluminium or its alloys with gallium, indium or thallium, a gas-diffusion cathode, or a DSE cathode are preferably used for the cathode.

A stable electrode selected from Ti-Pt, Ti-Pb, DSA oxygen, DSA chloride, PbO₂, vitreous carbons, graphite, DSE, and a gas-diffusion anode can be used for the anode.

The cathode and the anode should not restrict the invention.

The anion and cation exchange membranes can be chosen from those commercialized, such as, e.g. Nafion®, Neosepta®, Aciplex®, Sybron®, Ionics®, Aqualytic®, or any other one commercialized.

Any bipolar membrane existing on the market can be used, e.g. the BP1* bipolar membrane manufactured by Tokuyama Corporation.

* (Trade name)

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The electrodialysis process is preferably carried out at a temperature from 0 to 90°C.

The final chloride content is preferably from 0.5 to 16% solid product.

Likewise, the final chloride content is preferably lower than 0.5% solid product.

The solution that comes from the diluate of the electrodialyser or the solid product obtained by atomisation, lyophilisation or by other alternative means, can be subjected to any process for the purpose of obtaining a product suitable for use in oral, injectable or topical pharmaceutical preparations.

10

In another preferred embodiment, the solution that comes from the diluate of the electrodialyser is mixed with a sodium or potassium salt or with an aqueous solution of a sodium or potassium salt, and the product is subsequently obtained in a solid form by a drying process, previous precipitation with organic solvents that are miscible with water, by atomisation, by lyophilisation, or by another alternative method.

There are several types of stacks of electrodialysis, which can be used for the preparation of the salts of the present invention, e.g. those of Figures 1 and 2.

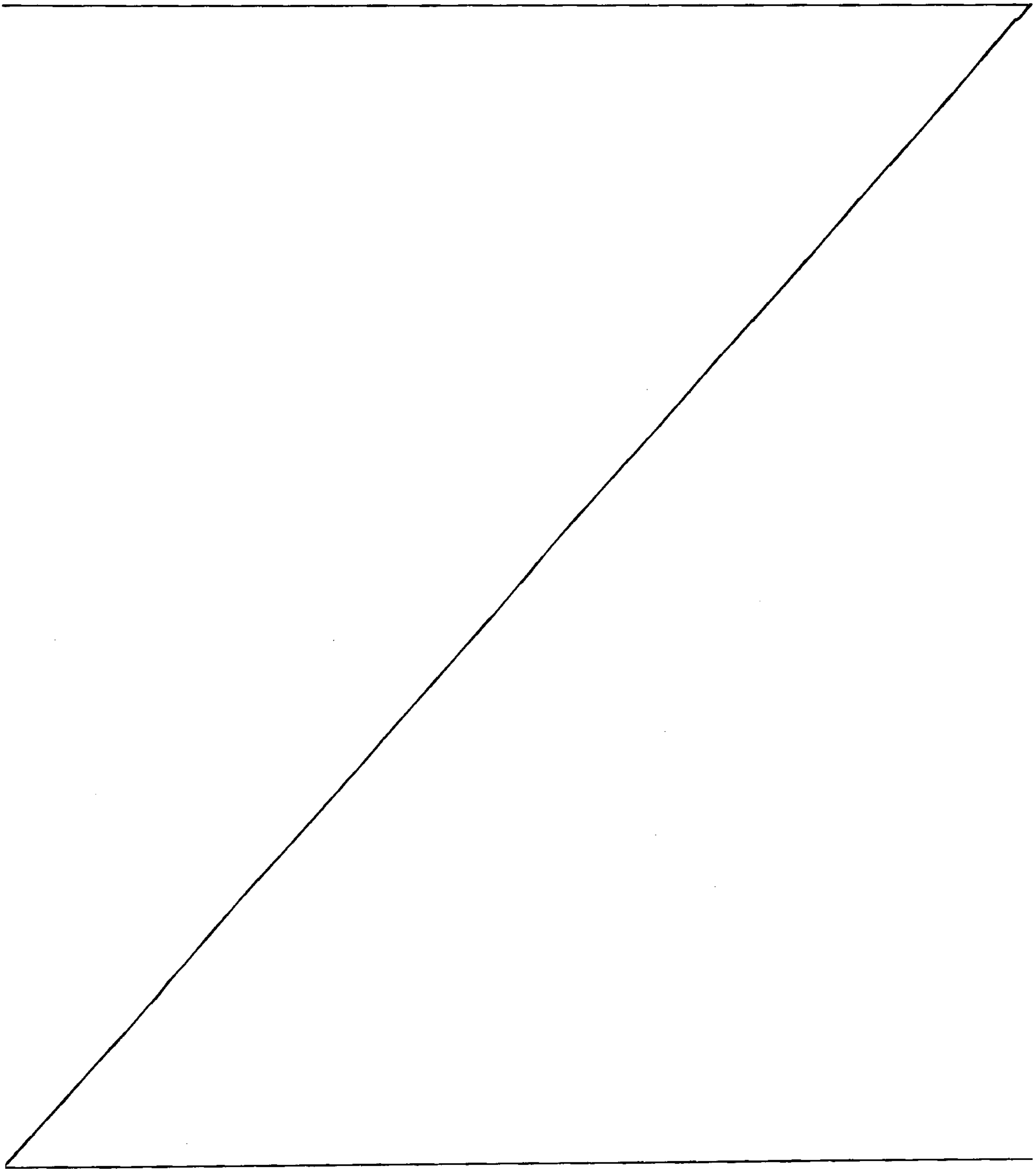
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In Fig. 1, an electrodialyser to be used in the invention is viewed, and Fig. 2 is a diagram of another electrodialyser to be used in the invention. In Figs. 1 and 2, the process of obtaining the glucosamine sulphate is viewed.

In a type of electrodialyser such as that of Fig. 1, to which the steps a) to g) defined hereinabove will be applied, an alternated combination of anion exchange membranes (monoselective or non-monoselective membranes) and cation exchange membranes, or an alternated combination of anion exchange membranes (monoselective or non-monoselective membranes) and bipolar membranes is used. In this case it is a three compartment electrodialysis system: diluate, concentrate and electrolyte. The diluate is fed with a solution prepared from glucosamine hydrochloride and the acid or salt that contains the anion to be ex-

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changed for the chloride, depending on the case. In order to maintain the pH higher than 2, a soluble hydroxide of an alkaline or alkaline earth metal is added to the concentrate. When an electric field is established, the Cl^- anions will leave the diluate solution through the anion exchange membrane. In this manner, if



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desired, a point can be reached at which practically all the chlorides have left the diluate, i.e. the Cl^- anions will be exchanged for the SO_4^{2-} , I^- , $\text{CH}_3\text{COCOO}^-$ or PO_4^{3-} anions.

5 In a type of electrodialyser such as that of Fig. 2, to which the steps of the process of claim 5 will be applied, an alternated combination of cation exchange membranes, monoselective or non-monoselective anion exchange membranes and anion exchange membranes is used. The diluate 1 is fed with a glucosamine hydrochloride solution, which will lose the Cl^- anion through the monoselective or non-monoselective anion exchange membrane and will receive the SO_4^{2-} , I^- ,
10 $\text{CH}_3\text{COCOO}^-$ or PO_4^{3-} anions, depending on the case, through the anion exchange membrane. Thus, the Cl^- anions will be exchanged for the SO_4^{2-} , I^- , $\text{CH}_3\text{COCOO}^-$ or PO_4^{3-} in the diluate.

In both cases, the electrodialysis is maintained until the chloride content reaches the desired limit. The Mohr method is used to determine the chlorides
15 (I.M. Kolthoff *et al.* "Análisis Químico Cuantitativo", 4th edition, Ed. Nigar, Buenos Aires, 1972).

The present invention also refers to glucosamine sulphate with a chloride content from 0.5 to 16% solid product obtainable by the process of the present invention.

20 Another aspect of the present invention is a pharmaceutical or veterinary composition comprising glucosamine sulphate with a chloride content from 0.5 to 16% solid product, and a pharmaceutically acceptable carrier.

Another aspect of the present invention is the use of glucosamine sulphate with a chloride content from 0.5 to 16% solid product, for the manufacture
25 of a medicament for the treatment or prevention of arthritis.

Preferably the arthritis is osteoarthritis.

One advantage of this process, compared to those known in the art, lies in the fact that a product as unstable as the glucosamine base is not isolated at any time.

30 Another important advantage is that a substance such as triethylamine, that is toxic even in small quantities, is not used.

Another advantage compared to the processes that use ion exchange resins, is that it is a more profitable process, with a lower cost.

35 Detailed description of the preferred embodiments.-

The following examples are not restrictive and illustrate the preparation

process of the salts of this invention.

Example 1: Preparation of glucosamine sulphate according to the process of Figure 2 (current intensity 10A).-

5 A stack of electrodialysis was set up (according to Figure 2) with two electrodes and 10 unit cells, the anode being composed of Ti-Pt and the cathode of stainless steel. The unit cell is comprises of two anion exchange membranes that allow all anions to pass through (NEOSEPTA® AMX anion exchange membrane, manufacture by Tokuyama Corporation) and a cation exchange membrane that
10 allows all cations to pass through (NEOSEPTA® AMX anion exchange membrane, manufactured by Tokuyama Corporation).

Next, the glucosamine hydrochloride and sodium sulphate solutions were prepared.

10 L of a 17% (w/v) glucosamine hydrochloride solution were prepared and loaded in a PVC tank used to feed the diluate 1.

The electrolyte solution, consisting of 2 L of a 1.4 % (w/w) sodium sulphate solution was prepared. Once prepared, it was loaded in a tank used to feed the electrolyte.

The diluate 2 solution, consisting of 20 L of 10% (w/v) sodium sulphate, was prepared. Once prepared, it was loaded in the tank used to feed the diluate 2.

20 L of decalcified water were loaded in the tank used to feed the concentrate.

The solutions contained in the tank were driven by means of a pump and were made to pass through a 10-20 micron filter before feeding the compartments. The flow of the pumps of the concentrate and of both diluates was set to 300 L/h and those of the electrolyte to 150 L/h.

In order to promote the migration of the ions, an electric field was applied, making a current pass between the anode and the cathode. The intensity was maintained constant at 10 A, setting a difference of potential of 40 V between both electrodes. The current was transported through the solution by means of both the anions and the cations, according to their corresponding transport numbers.

The solutions were maintained in recirculation until reaching a chloride concentration of the diluate 1 solution (solution where the glucosamine hydrochloride had been added) lower than 0.085%.

10 The desired chloride levels were reached approximately 9 hours after the start of the reaction.

During the process, samples were taken and the chloride concentration present both in the diluate and in the concentrate, was determined.

After 590 minutes, and because the amount of chlorides of the diluate solution had reached the desired level, the current was turned off.

The diluate solution was subjected to a lyophilisation process in order to obtain the solid product (glucosamine sulphate), a white-coloured solid (yield higher than 95%), with a melting point of 128°C with decomposition being obtained.

20 Assay: 96.6%

Chloride content: 0.48% on dry base

IR (KBr) cm^{-1} : 3600-3100, 3090-3030, 2935, 1610, 1530, 1420, 1420-1070, 1040.

NMR of ^{13}C (D_2O) δ ppm: 95.65 ($\text{C1}\beta$), 92.08 ($\text{C1}\alpha$), 79.08 ($\text{C5}\beta$), 74.89 ($\text{C3}\beta$), 74.55 ($\text{C5}\alpha$), 72.53 and 72.66 ($\text{C4}\alpha$, $\text{C4}\beta$, $\text{C3}\alpha$), 63.44 and 63.30 ($\text{C6}\alpha$, $\text{C6}\beta$), 59.72 ($\text{C2}\beta$) and 57.3 ($\text{C2}\alpha$).

Example 2: Preparation of glucosamine sulphate according to the process of Figure 2 (current intensity 14 A).-

The process in Example 1 was followed, but in this case 10 L of 21% glu-

cosamine hydrochloride, 2 L of a 1.4% (w/w) sodium sulphate solution as electrolyte solution and a current intensity of 14 A were used, setting a difference of potential between both electrodes of 50 V.

The diluate solution was subjected to a lyophilisation process in order to obtain the solid product (glucosamine sulphate), a white-coloured solid (yield higher than 95%), with a melting point of 128°C with decomposition being obtained.

The product obtained, as regards analytical and spectroscopic results, is equivalent to the product obtained in Example 1.

10 Example 3: Glucosamine sulphate preparation according to the process of Figure 1 (monoselective anion exchange membranes and cation exchange membranes).-

A EUR 6-80 stack of electrodialysis manufactured by Eurodia Industrie S.A. was used (according to Figure 1). The stack consisted of 80 unit cells, with a total active surface area of 4.4 m².

20 The cation exchange membrane used was the NEOSEPTA® CMX-SB cation exchange membrane manufactured by Tokuyama Corporation, and the anion exchange membrane was the NEOSEPTA® ACS anion exchange membrane manufactured by Tokuyama Corporation. The anode and the cathode of the electrodialysis stack are dimensionally stable electrodes, provided by Eurodia industrie S.A.

The resulting system has three compartments: diluate, concentrate and electrolyte.

Next, the solutions to feed the diluate and electrolyte were prepared.

A solution with 9.2 Kg of glucosamine hydrochloride and 38.4 Kg of water, and sulphuric acid until reaching 4.9% (w/w), was used for the diluate. 500 L of decalcified water were initially used for the concentrate. A 1.4% (w/w) solution of sodium sulphate was used for the electrolyte.

The experiment was carried out at room temperature with the following program of difference of potential against time:

From 0 to 0.8 h 100 V

From 0.8 h to the end 75 V

Sodium hydroxide was added to the concentrate so that its pH was higher than 2.

The solutions were maintained in recirculation until the desired chloride concentration was obtained in the diluate. The detection of the final point was carried out by means of a chloride analysis according to the Mohr method.

The experiment lasted 4.3 hours, obtaining a 0.004% (w/w) chloride concentration in the diluate.

The monitoring of the reaction can be observed in Table 1.

The glucosamine sulphate was obtained by lyophilisation, white-coloured solid (yield higher than 95%) being obtained.

Assay: 97.7%

Chloride content: 0.02% on dry base

TABLE 1

Time (h)	Voltage (V)	% Cl ⁻ (diluate)	% Cl ⁻ (dry base) (diluate)	% SO ₄ ²⁻ (diluate)	pH (diluate)
0	96	2.670		4.79	0.5
0.3	98	1.540	8.9	4.55	0.8
1.0	74	0.860	5.0	4.15	1.5
1.6	74	0.190	1.1	3.77	2.0
2.2	74	0.082	0.49	3.69	2.5
2.8	74	0.030	0.18	3.67	2.6
4.3	74	0.004	0.02	3.46	3.2

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Example 4: Preparation of glucosamine sulphate according to the process of Figure 1 (monoselective anion exchange membranes and bipolar membranes).-

A EUR TS-2-10-P stack of electrodialysis manufactured by Eurodia Industrie S.A. was used. The stack consisted of 10 unit cells, with a total active surface area of 0.2 m².

The bipolar membrane used was the Tokuyama Soda BP1 and the anion exchange membrane used was the Tokuyama Soda ACS. Stainless steel was used as a cathode and Ti/Pt as the anode.

Next, the solutions to feed the diluate, concentrate and electrolyte were prepared.

An aqueous solution of 18% (w/w) glucosamine hydrochloride and 7.3% (w/w) sulphuric acid was used for the diluate. A 0.44% (w/w) sodium sulphate solution was used for the concentrate. A 1.4% (w/w) sodium sulphate solution was used for the electrolyte.

The experiment was carried out at a temperature below 40°C and at a controlled intensity, applying the following program of intensity against time:

From 0 to 0.32 h	3.3 A
From 0.32 to 2.4 h	4.0 A
From 2.4 to 2.7 h	3.0 A
From 2.7 to 3.6 h	2.3 A
From 3.6 to 4.6 h	2.0 A
From 4.6 to 6.0 h	1.4 A
From 6.0 to 7.5 h	1.0 A
From 7.5 to 13.2 h	0.8 A

When the specific conductivity of the concentrate reached 20 mS/cm, half of the concentrate was unloaded and replaced by the same quantity of water.

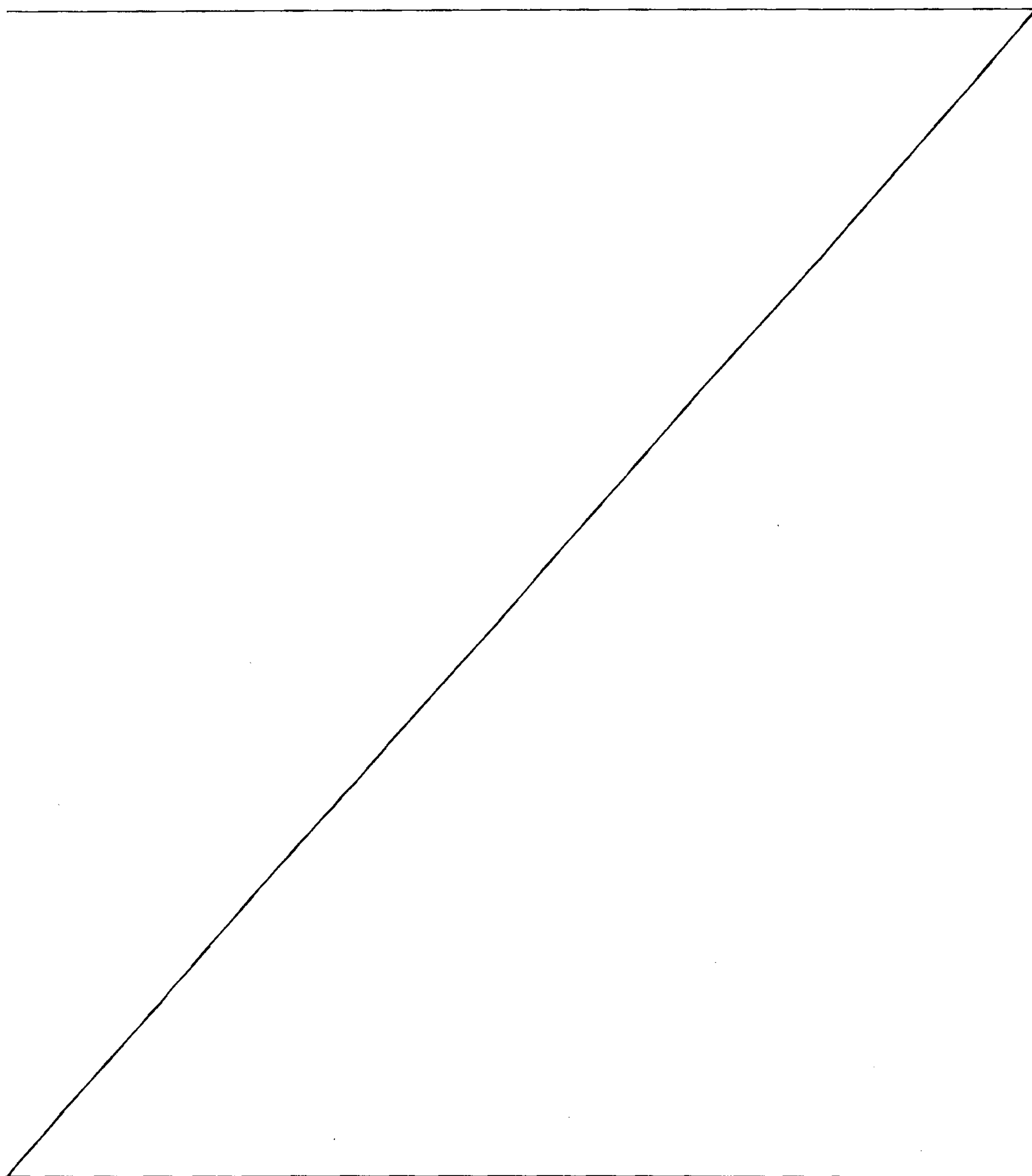
The experiment lasted 13.2 hours, obtaining a 0.029% (w/w) chloride concentration in the diluate. The monitoring of the reaction can be observed in Table 2.

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The glucosamine sulphate was obtained by lyophilisation, a white-coloured solid (yield higher than 95%) being obtained.

Assay: 97.6%

Chloride content: 0.16% on dry base



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TABLE 2

Time (h)	Voltage (V)	% Cl ⁻ (diluate)	% Cl ⁻ (dry base) (diluate)	% SO ₄ ²⁻ (diluate)	pH (diluate)
0	16.0	2.900		7.62	0.0
1.2	19.7	2.140	12	6.61	0.1
2.1	19.0	1.650	8.9	6.34	0.3
3.3	14.6	1.190	6.3	5.81	0.6
4.6	12.3	0.740	4.0	5.12	0.9
7.5	11.4	0.290	1.5	4.24	1.5
13.2	11.3	0.029	0.16	4.01	2.8

WHAT IS CLAIMED IS:

1. A process for the preparation of glucosamine sulphate, glucosamine hydroiodide, glucosamine pyruvate, glucosamine phosphate or mixtures thereof, wherein the starting material is glucosamine hydrochloride, said process comprising
5 the step of subjecting the glucosamine hydrochloride to electrodialysis.

2. The process according to claim 1, wherein during said electrodialysis, the Cl^- anion in the glucosamine hydrochloride is exchanged for an anion selected from the group consisting of SO_4^{2-} , I^- , $\text{CH}_3\text{COCOO}^-$ and PO_4^{3-} .
10

3. The process according to claim 2, wherein during said electrodialysis, the Cl^- anion in the glucosamine hydrochloride is exchanged for the SO_4^{2-} anion to thereby obtain glucosamine sulphate.

4. The process according to any one of claims 1 to 3, wherein the electrodialysis is carried out in compartments and comprises the following steps:
15

(a) preparing

(a_i) an aqueous solution of glucosamine hydrochloride

(a_{ii}) an aqueous solution of a salt or of an acid that contains an anion
20 to be exchanged for the Cl^- anion; and

(a_{iii}) an aqueous solution of a salt that lends conductivity;

(b) feeding :

(b_i) a diluate compartment with the aqueous solution of glucosamine hydrochloride and the aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl^- anion,
25

(b_{ii}) an electrolyte compartment with the aqueous solution of a salt that lends conductivity, and

(b_{iii}) a concentrate compartment with water or the aqueous solution of

a salt that contains the anion to be exchanged for the Cl^- anion;

(c) applying an electrical field across said compartments at a constant or variable current intensity or at a controlled potential difference;

(d) verifying the chloride content in the diluate compartment;

5 (e) discontinuing the electrodialysis once a desired amount of chloride has been obtained;

(f) recovering a solution obtained from the diluate compartment; and

10 (g) obtaining a solid product by precipitating by adding organic solvents that are miscible with water to said solution of step (f) and subsequently drying the precipitate or by atomising or lyophilising the solution of step (f),

wherein during said process a soluble hydroxide of an alkaline or alkaline earth metal is added to the concentrate compartment in order to maintain a pH greater than 2.

15 5. The process according to any one of claims 1 to 3, wherein the electrodialysis is carried out in compartments and comprises the following steps:

(a) preparing

(a_i) an aqueous solution of glucosamine hydrochloride

20 (a_{ii}) an aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl^- anion; and

(a_{iii}) an aqueous solution of a salt that lends conductivity;

(b) feeding :

(b_i) a diluate 1 compartment with the aqueous solution of glucosamine hydrochloride,

25 (b_{ii}) a diluate 2 compartment with the aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl^- anion,

(b_{iii}) an electrolyte compartment with the aqueous solution of a salt that lends conductivity, and

(b_{iv}) a concentrate compartment with water or the aqueous solution of

a salt that contains the anion to be exchanged for the Cl^- anion;

(c) applying an electrical field across said compartments at a constant or variable current intensity or at a controlled potential difference;

(d) verifying the chloride content in the diluate 1 compartment;

5 (e) discontinuing the electrodialysis once a desired amount of chloride has been obtained;

(f) recovering a solution obtained from the diluate 1 compartment; and

10 (g) obtaining a solid product by precipitating by adding organic solvents that are miscible with water to said solution of step (f) and subsequently drying the precipitate or by atomising or lyophilising the solution of step (f).

6. The process according to any one of claims 1 to 3, wherein the electrodialysis is carried out in compartments and comprises the following steps:

(a) preparing

15 (a_i) an aqueous solution of glucosamine hydrochloride

(a_{ii}) an aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl^- anion; and

(a_{iii}) an aqueous solution of a salt that lends conductivity;

(b) feeding :

20 (b_i) a diluate compartment with the aqueous solution of glucosamine hydrochloride and the aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl^- anion,

(b_{ii}) an electrolyte compartment with the aqueous solution of a salt that lends conductivity, and

25 (b_{iii}) a concentrate compartment with water or the aqueous solution of a salt that contains the anion to be exchanged for the Cl^- anion;

(c) applying an electrical field across said compartments at a constant or variable current intensity or at a controlled potential difference;

(d) verifying the chloride content in the diluate compartment;

(e) discontinuing the electrodialysis once a desired amount of chloride has been obtained;

(f) recovering a solution obtained from the diluate compartment; and

(g) obtaining a solid product by atomising or lyophilising the solution of step

(f),

wherein during said process a soluble hydroxide of an alkaline or alkaline earth metal is added to the concentrate compartment in order to maintain a pH greater than 2.

7. The process according to any one of claims 1 to 3, wherein the electrodialysis is carried out in compartments and comprises the following steps:

(a) preparing

(a_i) an aqueous solution of glucosamine hydrochloride

(a_{ii}) an aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl⁻ anion; and

(a_{iii}) an aqueous solution of a salt that lends conductivity;

(b) feeding :

(b_i) a diluate 1 compartment with the aqueous solution of glucosamine hydrochloride,

(b_{ii}) a diluate 2 compartment with the aqueous solution of a salt or of an acid that contains an anion to be exchanged for the Cl⁻ anion,

(b_{iii}) an electrolyte compartment with the aqueous solution of a salt that lends conductivity, and

(b_{iv}) a concentrate compartment with water or the aqueous solution of a salt that contains the anion to be exchanged for the Cl⁻ anion;

(c) applying an electrical field across said compartments at a constant or variable current intensity or at a controlled potential difference;

(d) verifying the chloride content in the diluate 1 compartment;

(e) discontinuing the electrodialysis once a desired amount of chloride has

been obtained;

(f) recovering a solution obtained from the diluate 1 compartment; and

(g) obtaining a solid product by atomising or lyophilising the solution of step (f).

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8. The process according to any one of claims 4 to 7, wherein the electrodialysis process is carried out in an electrodialyser that comprises a cathode, an anode and means of separation.

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9. The process according to claim 8, wherein the means of separation are composed of anion exchange membranes, cation exchange membranes or bipolar membranes.

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10. The process according to claim 9, wherein the electrodialysis is carried out at a temperature from 0 to 90°C.

11. The process according to claim 10, wherein said solid product has a chloride content of from 0.5 to 16% w/w.

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12. The process according to claim 10, wherein said solid product has a chloride content of less than 0.5% w/w.

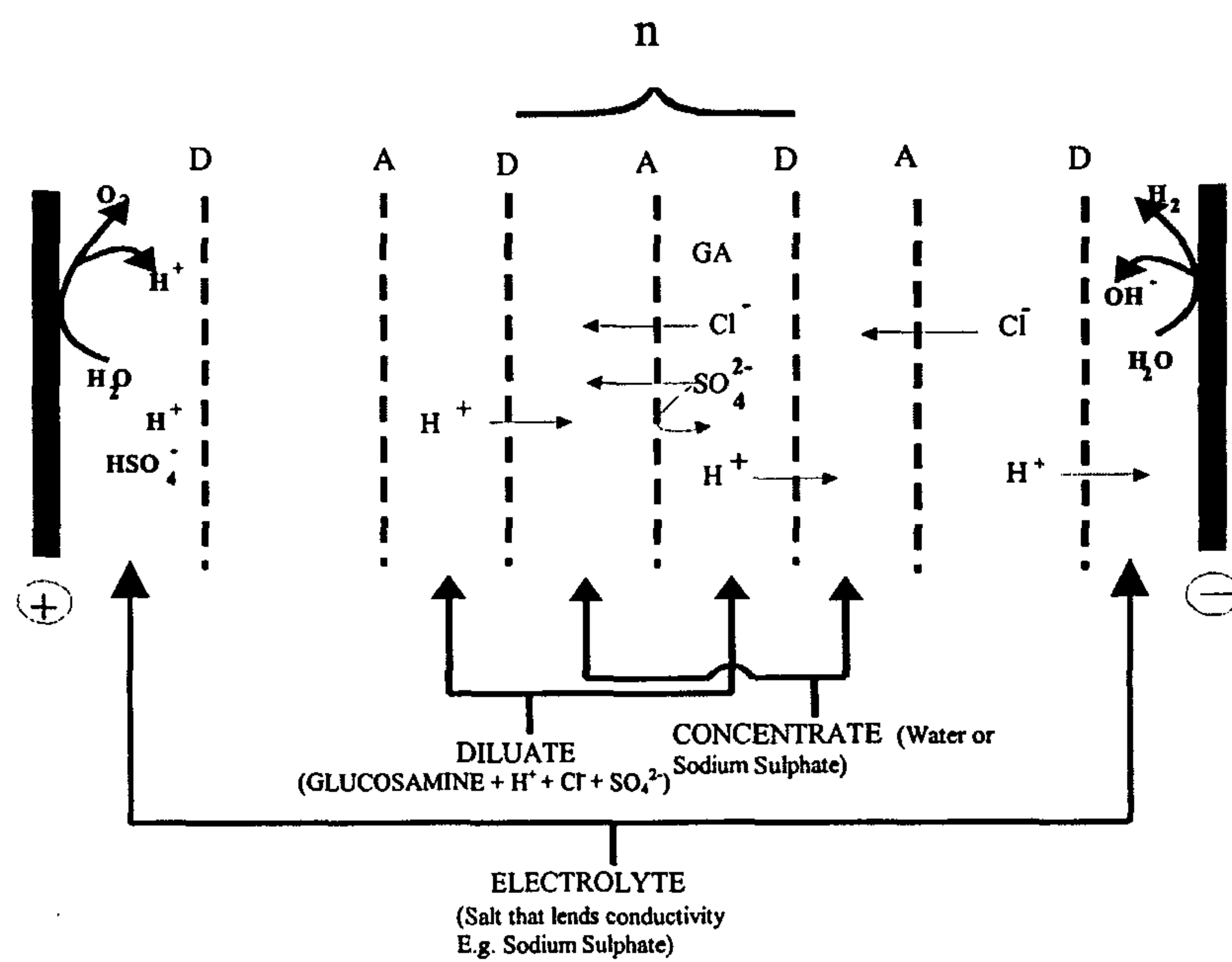
25

13. The process according to any one of claims 4 to 12, wherein the solution of step (f) or the solid product of step (g) is formulated into a product suitable for use in an oral, injectable or topical pharmaceutical preparation.

14. The process according to any one of claims 4 to 12, wherein the solution of step (f) is mixed with a sodium or potassium salt, or with an aqueous solution of a sodium or potassium salt.

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FIGURE 1



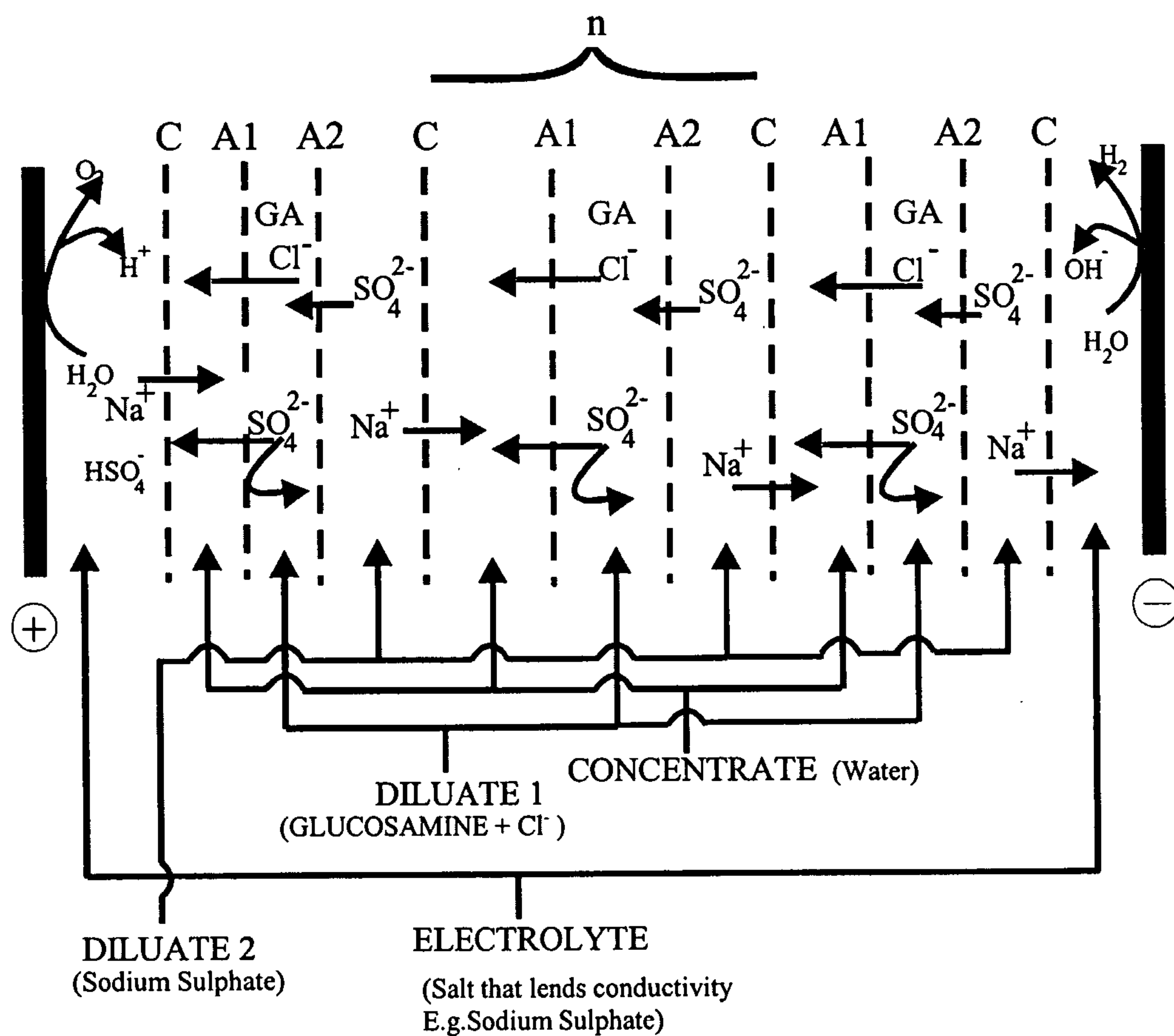
A= Monoselective or non-monoselective anion exchange membrane

D= Cation exchange membrane or bipolar membrane

GA= Glucosamine

2 / 2

FIGURE 2



A1= Monoselective or non-monoselective anion exchange membrane

A2= Anion exchange membrane

C= Cation exchange membrane

GA= Glucosamine