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(54) **AQUEOUS IONIC SOLUTIONS AND THEIR USES IN PARTICULAR IN OPHTHLAMOLOGY**

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(57) **ABSTRACT**

The invention concerns the use for treating and cleaning the eye and is appendages of aqueous ionic solutions obtained from sea water whereof the ionic compositions is qualitatively that of sea water and quantitatively such that their pH ranges between 4 and 9, preferably between 7 and 8 and their osmolality ranges between 150 and 700, preferably between 250 and 350 mOsm/kg.

AQUEOUS IONIC SOLUTIONS AND THEIR USES IN PARTICULAR IN OPHTHLAMOLOGY

[0001] The invention relates to aqueous ionic solutions of the type obtained in particular from seawater and their uses in particular in ophthalmology.

[0002] Some of these aqueous ionic solutions are novel. The invention consequently relates to them as novel industrial products.

[0003] Apart from the latter, aqueous ionic solutions obtained from seawater are known.

[0004] It has already been proposed to apply them in the prevention, cleaning and treatment of the respiratory tracts, the buccal cavities, the skin and the gynecological mucous membranes.

[0005] These indeed appeared to be the only applications which could be envisaged by persons skilled in the art.

[0006] However, the applicant company has had the merit,

[0007] on the one hand, of finding, after extensive research studies, that the already known solutions in question, provided their composition, their pH and their osmolality are adjusted, could be used for the treatment and cleaning of the eye and its appendages, and

[0008] on the other hand, of developing aqueous ionic solutions of the type in question, whose quantitative ionic composition, pH and osmolality are novel.

[0009] The subject of the invention is therefore the use, for treating and cleaning the eye and its appendages, of the aqueous ionic solutions obtained from seawater and whose ionic composition, pH and osmolality have been consequently adjusted.

[0010] From the qualitative point of view, the ionic composition of the solutions used in accordance with the invention is that of seawater.

[0011] By way of illustration, the composition of seawater as it appears on page F 163 of the manual "Handbook of Chemistry and Physics" 63rd edition, 1982-1983, CRC PRESS, is indicated in the table below.

TABLE

Element	Quantity (p.p.m.)
Cl	18.980
Na	10.561
Mg	1.272
S	884
Ca	400
K	380
Br	65
C (inorganic)	28
Sr	13
(SiO_2)	0.01–7.0
B	4.6
Si	0.02–4.0
C (organic)	1.2–3.0
Al	0.16–1.9
F	1.4
N (as nitrate)	0.001–0.7
N (as organic nitrogen)	0.03–0.2
Rb	0.2

TABLE-continued

Element	Quantity (p.p.m.)
Li	0.1
P (as phosphate)	>0.001–0.10
Ba	0.05
I	0.05
N (as nitrite)	0.0001–0.05
N (as ammonia)	>0.005–0.05
As (as arsenic)	0.003–0.024
Fe	0.002–0.02
P (as organic phosphorus)	0.016
Zn	0.005–0.014
Cu	0.001–0.09
Mn	0.001–0.01
Pb	0.004–0.005
Se	0.004
Sn	0.003
Cs	0.002 (approximately)
U	0.00015–0.0016
Mo	0.0003–0.002
Ga	0.0005
Ni	0.0001–0.0005
Th	<0.0005
Ce	0.0004
V	0.0003
La	0.0003
Y	0.0003
Hg	0.00003
Ag	0.00015–0.0003
Bi	0.0002
Co	0.0001
Sc	0.00004
Au	0.000004–0.000008
Fe (as a true solution)	$<10^{-9}$
Ge	Present
Ti	Present
W	Present
Cd	Present in marine organisms
Cr	Present in marine organisms
Ti	Present in marine organisms
Sb	Present in marine organisms
Zr	Present in marine organisms
Pt	Present in marine organisms

[0012] On the same page of the same manual, it is specified that the pH of seawater is 8-9.

[0013] It is moreover known (IFREMER, Department of Coastal Environment and Management of the Marine Environment) that the osmolality of seawater is >1 000 mOsm/kg.

[0014] From the quantitative point of view, the ionic composition of the solutions in question, obtained from seawater, is chosen such that their pH is from 4 to 9, preferably from 7 to 8, and that their osmolality is from 150 to 700, preferably from 250 to 350 mOsm/kg.

[0015] Among the solutions which have given particularly encouraging results in the use in accordance with the invention, there may be mentioned:

[0016] the aqueous ionic solutions obtained by diluting seawater, in particular with distilled water, especially at the rate of 2 to 5 fold,

[0017] the aqueous ionic solutions obtained from seawater by techniques known by the term desalination and, optionally, enriched with at least one of their ions,

[0018] the aqueous ionic solutions artificially obtained from sea salts.

[0019] The aqueous ionic solutions in accordance with the invention, which constitute novel industrial products and which are in particular obtained from seawater, are characterized by:

[0020] a pH value preferably less than or at most equal to the lowest pH values of seawater,

[0021] an osmolality lower than that of seawater, and

[0022] a composition, from the ionic point of view, which is qualitatively and quantitatively that of seawater, with the exception from the quantitative point of view, on the one hand, of the potassium concentration which is greater than that of seawater and, on the other hand, of the Na, Mg, Ca and Cl concentrations which are less than those of seawater, said concentrations being

[0023] for Na^+, from 1 300 to 1 500, preferably from 500 to 1 000 mg/l,

[0024] for K^+, from 4 500 to 6 500, preferably from 5 000 to 6 000 mg/l,

[0025] for Mg^{++}, from 50 to 1 300, preferably from 100 to 500 mg/l,

[0026] for Ca^{++}, from 20 to 350, preferably from 40 to 200 mg/l,

[0027] for Cl^-, from 4 000 to 6 000, preferably from 4 500 to 5 000 mg/l.

[0028] In the case of seawater, the corresponding values are exemplified by the ranges reflecting the results of 134 measurements carried out on seawater collected off Saint-Malo from August 1998 to July 1999, namely:

[0029] pH: 7.70 to 8.30

[0030] osmolality: >1 000 mOsm/kg

[0031] $[Na^+]$: $^{10\ 500}$-11 500 mg/l

[0032] $[K^+]$: ^{365}-420 mg/l

[0033] $[Mg^{++}]$: $^{1\ 200}$-1 450 mg/l

[0034] $[Ca^{++}]$: ^{380}-435 g/l

[0035] $[Cl^-]$: $^{18\ 900}$-20 500 mg/l

[0036] The novel aqueous ionic solutions in accordance with the invention are particularly appropriate for treating and cleaning the eye and its appendages.

[0037] However, they can also be used in the treatment and cleaning of the respiratory tracts, the buccal cavities, the skin and the mucous membranes, in particular gynecological mucous membranes, optionally after adjusting the pH and the osmolality as necessary.

[0038] The aqueous ionic solutions in accordance with the invention as defined above, when they are used for treating and cleaning the eye and its appendages, are remarkable in that

[0039] they have the physiological pH and osmolality of tears, and

[0040] they are free of preservatives.

[0041] The latter advantage is of great importance.

[0042] Indeed, the preservatives present in most medicaments for the eye are considered harmful for the cornea.

[0043] For the preparation of the aqueous ionic solution in accordance with the invention, seawater was used which was taken off Saint-Malo and collected at a depth of 5 to 10 meters in a zone with strong movements of current; this water is characterized by a salt content greater than 32 g/l; it is naturally rich in calcium, magnesium and trace elements.

[0044] This water is subjected to selective electrodialysis; in a first instance, only sodium chloride is removed in order to reach the desired osmolality, then the ionic concentrations are adjusted depending on the therapeutic use; the desired pH is preferably obtained by exchanging the Na^+ ions against protons.

[0045] Selective electrodialysis may be carried out with an EUR 6B type apparatus marketed by the company EURODIA Industrie SA under the trademark EURODIA.

[0046] The various stages of the selective electrodialysis corresponding to the adjustment of each of the different parameters (pH, osmolality, ion concentration) are carried out in a known manner.

EXAMPLE

[0047] The characteristics of the solution examined are as follows:

[0048] pH: 7.45

[0049] osmolality: 309 mOsm/kg

[0050] $[Na^+]$: 680 mg/l

[0051] $[K^+]$: 5 818 mg/l

[0052] $[Mg^{++}]$: 128 mg/l

[0053] $[Ca^{++}]$: 54 mg/l

[0054] $[Cl^-]$: 4 850 mg/l

[0055] It was with the aid of a test derived from the Draize test that it was shown that this solution was not very irritant toward the eye and, in any case, less irritant than physiological serum or physiological saline.

[0056] The Draize test makes it possible to evaluate eye irritation after multiple applications; it can be carried out on the eye of albino rabbits.

[0057] The reference solution used in this test consists, as indicated above, of physiological saline, that is to say a solution of sodium chloride (0.9% NaCl); physiological saline is traditionally used to rinse the eyes in the event of an accidental chemical spillage, to clean the eyes of unweaned babies and also as solvent for artificial tears, as collyrium or as ophthalmic washing solution; it is the reference solution in ophthalmology for the French Agency for the Safety of Health Products.

[0058] According to the Draize test, 12 albino rabbits are divided into two groups (a reference group and a group for the test solution).

[0059] There are administered, six times consecutively at intervals of 1 hour into the conjunctival cul-de-sac of the right eye

[0060] on the one hand, 50 μl of physiological saline in the case of the rabbits of the reference group, and

[0061] on the other hand, 50 μl of the test solution in the case of the rabbits of the other group.

[0062] The treated eyes of the rabbits are examined using a slit lamp (Slit lamp AIT-20, Topcon, Topcon France—F-92300 Levallois-Perret), before instillation, and then 1 hour after the 1st and 6th instillations, respectively, and then 1, 2 and 3 days after the sixth instillation.

[0063] The effects produced on the conjunctiva, the iris and the cornea are observed.

[0064] As regards the conjunctiva, the following were noted:

[0065] (a) the edematous infiltration, awarding a score of 0 to 4, the score 0 denoting the absence of infiltration and the score 4 the complete closure of the eyelids,

[0066] (b) the discharge, awarding a score of 0 (no discharge) to 3 (eyelids and hair wet over a large area around the eye),

[0067] (c) the redness (c), awarding a score of 0 to 3, the score 0 denoting normal vessels and the score 3 an intense redness of the conjunctiva.

[0068] For the evaluation of the effect on the conjunctiva, there is selected the figure obtained by applying the formula:

$$(a+b+c)\times 2.$$

[0069] In the case of the iris, there is awarded a score ranging from 0 to 2, the score 0 corresponding to a normal iris and the score 2 corresponding to an iris exhibiting no reaction to light but exhibiting, on the other hand, hemorrhages and severe impairments. For the evaluation of the effect on the iris, there is chosen the figure given by the formula:

$$(d)\times 5.$$

[0070] Finally, as regards the cornea, there are evaluated, on the one hand, the intensity (e) of the opaqueness, knowing that the score 0 is awarded for the absence of opaqueness and the score 4 for complete corneal opaqueness with an invisible iris, and, on the other hand, the area of opaqueness (f), the scores ranging from 0 to 4, the latter score corresponding to an opacification of more than ¾ of the total area.

[0071] For the evaluation, there is selected the value given by the formula:

$$e\times f\times 5.$$

[0072] The sum of the values obtained for the conjunctiva, the iris and the cornea, at each measurement and for each animal, represents the individual ocular irritation index (IOI) which is 110 maximum.

[0073] The arithmetic mean of the values found for the 6 rabbits represents the mean ocular irritation index (MOI).

[0074] The maximum ocular irritation index (MOI max) is the maximum individual value obtained at each measurement.

[0075] The results obtained with the solution in accordance with the invention and with physiological saline are assembled in tables I and II which follow and in which:

[0076] Day 1/0 denotes the measurement made 1 day before the instillation,

[0077] Day 1/1 denotes the measurement made 1 hour after the 1st instillation,

[0078] Day 1/6 denotes the measurement made 1 hour after the 6th instillation,

[0079] Day 2 denotes the measurement made 24 hours after the last instillation,

[0080] Day 3 denotes the measurement made 48 hours after the last instillation,

[0081] Day 4 denotes the measurement made 72 hours after the last instillation.

TABLE I

(solution in accordance with the invention)

	Day 1/0	Day 1/1	Day 1/6	Day 2	Day 3	Day 4
MOI	0.00	0.67	0.00	0.00	0.00	0.00
MOI max	0	4	0	0	0	0

[0082]

TABLE II

(physiological saline)

	Day 1/0	Day 1/1	Day 1/6	Day 2	Day 3	Day 4
MOI	0.00	0.00	1.00	0.33	0.67	0.00
MOI max	0	0	4	2	2	0

[0083] On comparing these values, it is observed that the superiority of the solution in accordance with the invention manifests itself from the measurement made on Day 1/6 and becomes beneficial on Days 2 and 3, which means that the solution defined above is particularly beneficial for long-term treatments and for those requiring multiple applications.

[0084] This being the case, and from a general point of view, the products, in particular the ophthalmic products, prepared using the aqueous ionic solutions in accordance with the invention or more generally any aqueous ionic solutions obtained from seawater may be provided, for example, in the form of lotions intended for washing the eye, in the form of collyria, ophthalmological gels, or to replace the water in ocular inserts.

[0085] The composition of such a lotion may be as follows:

aqueous ionic solution:	qsp 100%
salicylic acid:	0.1%
distilled water of hamamelis	0.4%

[0086] The lotions in question may be administered using, more preferably, devices of the type according to the French patent application filed in the name of the applicant on Oct. 13, 1999 under No. 99 12782 under the title "Device for washing and bathing the eye".

[0087] By way of example, it is reported that it is possible to carry out 2 or 3 eye washes or baths per day.

1. The use, for treating and cleaning the eye and its appendages, of aqueous ionic solutions obtained from seawater whose ionic composition is, from the qualitative point of view, that of seawater, and from the quantitative point of view such that, on the one hand, their pH is from 4 to 9, preferably from 7 to 8, and, on the other hand, their osmolality is from 150 to 700, preferably from 250 to 350 mOsm/kg.

2. The use as claimed in claim 1, in which the aqueous ionic solution is obtained by diluting seawater, in particular with distilled water, especially at the rate of 2 to 5 fold.

3. The use as claimed in claim 1, in which the aqueous ionic solution is obtained from seawater by techniques known by the term desalination and, optionally, enriched with at least one of its ions.

4. The use as claimed in claim 1, in which the aqueous ionic solution is artificially obtained from sea salts.

5. A novel aqueous ionic solution obtained from seawater, characterized by:

a pH value preferably less than or at most equal to the lowest pH values of seawater,

an osmolality lower than that of seawater, and

a composition, from the ionic point of view, which is qualitatively and quantitatively that of seawater, with the exception from the quantitative point of view, on the one hand, of the potassium concentration which is greater than that of seawater and, on the other hand, of the Na, Mg, Ca and Cl concentrations which are less than those of seawater, said concentrations being

for Na^+, from 1 300 to 1 500, preferably from 500 to 1 000 mg/l,

for K^+, from 4 500 to 6 500, preferably from 5 000 to 6 000 mg/l,

for Mg^{++}, from 50 to 1 300, preferably from 100 to 500 mg/l,

for Ca^{++}, from 20 to 350, preferably from 40 to 200 mg/l,

for Cl^-, from 4 000 to 6 000, preferably from 4 500 to 5 000 mg/l.

6. An ophthalmic product for treating and cleaning the eye and its appendages based on an aqueous ionic solution as claimed in claim 5 or as used in one of claims 1 to 4.

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