

- 1 -

"Disinfectant solution based on sodium hypochlorite,
and process for preparing it"

5 The present invention relates to a disinfectant solution based on sodium hypochlorite and to a process for preparing it.

Throughout the present description and the claims, unless otherwise specified, the term "solution" always refers to an aqueous solution.

10 The bactericidal properties of sodium hypochlorite solutions have been known since 1820. Above all in France, in the period of the First World War, they were also widely used for the medical treatment of war injuries.

Even today, they are widely used as disinfectants for environments, surfaces, surgical instruments, various objects and injuries.

15 The disinfectant activity of sodium hypochlorite solutions depends to a large extent on the bactericidal activity of hypochlorous acid and, thus, on its presence in the solutions.

20 The efficiency of the activity is influenced by the temperature, the contact time, the type and concentration of the micro-organisms and, above all, the pH. Since the dissociation constant of hypochlorous acid to 25°C is $pK_a = 7.49$, it results that when the hypochlorite solution comes into contact with bodily fluids, the pH is modified and tends to approach neutrality, and thus the ratio between the ionized species and neutral species tends to become equal. Now, although hypochlorite is a bland disinfectant compared with hypochlorous acid, it acts as a
25 reserve.

EP-A-0 471 129 relates to a solution of sodium hypochlorite which is useful as an antiseptic. The solution contains sodium hypochlorite in a quantity sufficient for 4 to 6 grams per liter of active chlorine, a pH regulator in a quantity sufficient to yield a pH greater than 10 and less

- 1a -

than or equal to 10.5 and purified water in a quantity sufficient to yield 1 liter of solution.

US-A-5 624 636 aims at improving the disinfection of dental impressions following removal from the patient's mouth and before
5 entering the dental laboratory to prevent contamination. It involves the use of a pH-adjusted hypochlorite solution, which is highly effective in killing microorganisms, and also relatively inexpensive. The disinfectant solution causes no damage to the impression, no loss of accuracy, and does not destroy the details on the impression surface. The solution
10 has a pH of from 9 to 11 and has a sodium hypochlorite content of from 0.05% to about 1.05%.

US-A-4 990 334 discloses a germicidal solution for sanitizing the human epidermis without irritation. The solution is a homogenous blend of glycerol, sodium hypochlorite, inert ingredients, soft water, scented
15 oil, and isopropyl alcohol, having a pH of 9.8 to about 10.1. The solution may be applied to a towlette and sealed in a hermetically sealed pouch for later use.

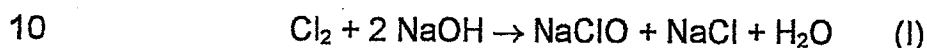
One of the problems associated with sodium hypochlorite disinfectant solutions is that their composition cannot be predetermined
20 at will since the industrial methods for producing hypochlorite give solutions in which the sodium hypochlorite is accompanied by side products and starting materials. Thus, since the said industrial

- 2 -

solutions are the only sources of hypochlorite that are available for preparing the said disinfectant solutions, the said disinfectant solutions will necessarily also contain a certain amount of the said side products and starting materials already present in the industrial hypochlorite solution used.

The production of sodium hypochlorite is based on the dismutation of molecular chlorine in sodium hydroxide solution.

This reaction, also known as "chlorination of alkali", proceeds according to the following reaction scheme (I):



The industrial process more commonly involves the addition of chlorine to an excess of sodium hydroxide.

Solutions containing about 15.70-20.93% (w/v) of sodium hypochlorite [equivalent to 15.00-20.00% (w/v) of active chlorine] are thus obtained, also containing a substantially equivalent amount of sodium chloride and an excess of free bases, generally less than 1% (expressed as NaOH), which gives a pH of about 12.5-13.5 and acts as stabilizer.

Throughout the present description and the claims, this type of solution will be referred to as a concentrated solution.

Concentrated sodium hypochlorite solutions have various industrial uses and, when used in unmodified form or suitably diluted, are also used for disinfecting articles. However, the said solutions cannot be used in unmodified form for clinical and/or veterinary disinfection since they are not tolerated by the skin or mucous membranes.

Moreover, its high pH value also prevents the formation of hypochlorous acid.

Hypochlorite disinfectant solutions are therefore prepared by diluting a concentrated solution with added mineral salts which act as buffers to reduce its pH and thus improve its tolerability and bactericidal activity.

- 3 -

In particular, typical disinfectant solutions for topical use are as follows:

- Dakin's solution (*French Pharmacopoeia* 8th edition, p. 1059) containing about 0.5% sodium hypochlorite, the same percentage of sodium chloride, 1.5% sodium bicarbonate and 1 mg/100 ml of potassium permanganate; and
- the skin disinfecting solution described in the *US Pharmacopoeia* (*USP 24*, p. 1535), which contains 0.02-0.032% sodium hypochlorite, 1.02 g/l monobasic sodium phosphate, 17.61 g/l dibasic sodium phosphate and has a pH of between 7.8 and 8.2. Although it is not mentioned by the USP, since this solution is prepared from a concentrated sodium hypochlorite solution, it also contains at least 0.02-0.032% sodium chloride.

However, reducing the pH of these solutions has the drawback of reducing the stability of the sodium hypochlorite and so, depending on their composition, these solutions can only be stored from a minimum of a few days to a maximum of a few months (S.F. Bloomfield, T.J. Sizer, "Pharm. J. (1985), 153-157).

The said disinfectant solutions must therefore be prepared by the user at the time of use or slightly beforehand.

Specifically, even if stored with care, the abovementioned sodium hypochlorite disinfectant solutions obtained by diluting a concentrated solution with added buffers undergo a spontaneous decomposition which produces sodium chlorate, sodium chloride and small amounts of sodium chlorite.

The formation of sodium chlorate and sodium chlorite also has the drawback that these products have toxicological properties (*Drinking Water and Health, Disinfectants and Disinfectant By-products*, volume 7, National Academy Press, Washington, D.C., 1987) which are such that regulations have been drawn up therefor (*Priority list of substances*

- 4 -

that may require regulation under the safe drinking water act; EPA, 1991, (56), 9, 1470-1474, EPA 40 CFR part 9 141, 142 National Primary Drinking Water Regulations: Disinfectant and Disinfection Byproduct, Final Rule, December 16, 1998).

- 5 The only known method for preparing relatively dilute sodium hypochlorite solutions that do not have the drawbacks of the solutions obtained by diluting a concentrated solution with added buffers is that of the electrolysis of sodium chloride solutions in diaphragm-free electrolytic cells so as to allow the products that are gradually formed
10 by the electrolysis to react together. The dilute sodium hypochlorite disinfectant solutions thus obtained contain an excess of sodium chloride and have a pH of between 10 and 10.5.

 These solutions, subsequently diluted without pH correction or with the possible addition of small amounts of pH correctors, are well
15 tolerated by the skin and mucous membranes. In addition, they are stable for at least two years and can therefore be dispensed in pharmacies.

 Typical examples of possible pH correctors are sodium bicarbonate, sodium tetraborate and monobasic and dibasic sodium phosphate
20 mixtures.

 A disinfectant solution of this type has been sold for many years under the brand name AMUCHINATM and has the following composition:

sodium hypochlorite:	1.15% (w/v), equivalent to 1.1% active chlorine;
25 sodium chloride:	18% (w/v);
sodium chlorate:	17-26%, relative to the abovementioned amount of sodium hypochlorite;
pH	10-10.5.

- 5 -

Hereinbelow, the sodium hypochlorite solutions obtained by the electrolysis of sodium chloride in diaphragm-free electrolytic cells will be referred to as "electrolytic solutions".

Despite the abovementioned advantages, electrolytic solutions
5 contain a large excess of sodium chloride and this may be a drawback in certain types of application such as, for example, rendering water fit for consumption.

The sodium chlorate contained arises due to the fact that, besides the spontaneous decomposition, a secondary reaction of anodic
10 oxidation of the hypochlorite is associated with the primary electrolytic reaction, to a certain extent ($6\text{ClO}^- + 3\text{H}_2\text{O} \rightarrow 2\text{ClO}_3^- + 4\text{Cl}^- + 6\text{H}^+ + 3/2\text{O}_2 + 6\text{e}^-$).

However, the main drawback of electrolytic solutions consists of the high costs of the plants required to produce them and of the costs
15 incurred in their management.

In addition, the electrolytic method cannot be used to produce relatively concentrated solutions [$>3\%$ (w/v)] since this would initiate secondary electrolytic reactions which would lead to a reduction in the yield and, above all, to the production of excessively high levels of
20 sodium chlorate, thus harming the quality of the solutions.

Therefore, notwithstanding the many attempts made over more than a century, an inexpensive method for preparing a sodium hypochlorite disinfectant solution that is stable for at least two years, does not contain an excess of sodium chloride, has high bactericidal activity and
25 is well tolerated by the skin and mucous membranes has still not been found.

Hitherto, these objectives have been considered as mutually incompatible since, as already seen, an alkaline pH ensures the stability but has a harmful effect on the tolerability by the skin and

- 6 -

mucous membranes and reduces the bactericidal power. On the other hand, at neutral pH, the bactericidal power is high, but stability is low.

French patent 2 593 704 describes a stabilized and dilute 0.5% sodium hypochlorite solution in which the stabilization is achieved by adding an amount of monosodium phosphate which is sufficient to lower the pH to a value of 9.6-10. According to the said document, the abovementioned disinfectant solution is well tolerated by the skin but has a stability of only six months.

Now, it has been found, surprisingly, that the dilution of a concentrated sodium hypochlorite solution and the addition of dilute hydrochloric acid until the pH is 10.1-10.7 makes this solution well tolerated by the skin and mucous membranes without reducing its stability, without forming appreciable amounts of sodium chlorate and without the addition of other ionic solutes.

Typically, a sodium hypochlorite disinfectant solution thus obtained has the following characteristics:

sodium hypochlorite: 0.021-5.76% (w/v), equivalent to 0.020-5.50%

(w/v) of active chlorine;

sodium chlorate: 1.7% relative to the abovementioned amount of sodium hypochlorite;

water: qs 100 ml

pH 10.1-10.7

This solution is novel since it differs from the other known hypochlorite disinfectant solutions, obtained by diluting a concentrated solution with added buffers, in terms of the pH value and the absence of buffers. In addition, it differs from electrolytic solutions in terms of the levels of sodium chlorate.

In a first aspect thereof, the present invention therefore relates to a sodium hypochlorite disinfectant solution, characterized in that it has a pH of between 10.1 and 10.7 and comprises from 0.021 to 5.76% (w/v)

- 7 -

of sodium hypochlorite and, relative to the said amount of sodium hypochlorite, not more than 2% of sodium chlorate.

Preferably, the amount of sodium hypochlorite included in the disinfectant solution of the present invention ranges from 0.52% to
5 2.09% (w/v), equivalent to 0.50-2.00% of active chlorine.

Advantageously, the pH of the disinfectant solution of the present invention is between 10.1 and 10.5.

Typically, the disinfectant solution of the present invention which comprises from 0.021 to 5.76% (w/v) of sodium hypochlorite, also
10 comprises from 0.015 to 4% (w/v) of sodium chloride.

The disinfectant solution of the present invention may be readily made isotonic by adding a suitable amount of sodium chloride.

In addition, a suitable amount of a colorant that is compatible with the components of the solution may also be added to the disinfectant
15 solution of the present invention. A typical example of a suitable colorant is potassium permanganate.

The addition of dilute hydrochloric acid to pH 10.1-10.7 is sufficient to obtain a hypochlorite disinfectant solution that has all the advantages that will be listed hereinbelow. However, after the pH has
20 been partially corrected with dilute hydrochloric acid, for example to 11, a small amount of another compound capable of correcting the pH, for example from 11 to 10.5, may be added. Typical examples of such compounds are: sodium tetraborate, sodium bicarbonate, sodium carbonate, sodium monohydrogen phosphate, sodium dihydrogen
25 phosphate and the like.

In a second aspect thereof, the present invention relates to a process for preparing a sodium hypochlorite disinfectant solution, in which the said process comprises the dilution of a concentrated sodium hypochlorite solution, characterized in that the pH of this solution is

- 8 -

brought to a value of between 10.1 and 10.7 by adding dilute hydrochloric acid.

Typically, before being subjected to the process of the present invention, the concentrated solution comprises from 15.70 to 20.93% (w/v) of sodium hypochlorite and its pH is about 13.

Preferably, the concentration of hydrochloric acid in the dilute solution used in the process of the present invention ranges from 0.01 to 1 mol/litre and preferably 0.1-1 mol/litre.

The sodium hypochlorite disinfectant solution according to the present invention has the following advantages;

- it is economical since it is readily and quickly prepared by means of very simple apparatus;
- it is well tolerated like Dakin's solution and the other analogous solutions described in the pharmacopoeias and like the electrolytic solutions;
- it is stable like electrolytic solutions and is therefore suitable for sale in pharmacies as a ready-to-use solution;
- it is readily adaptable to various requirements in terms of concentrations and addition of other solutes;
- It has high bactericidal efficacy; and
- it contains very small amounts of sodium chlorate.

The examples which follow serve to illustrate the invention without, however, limiting it.

EXAMPLE 1

Solution 1

750 ml of distilled water were added to 58.97 ml of a solution, containing 19.5% (w/v) of sodium hypochlorite, 18% (w/v) of sodium chloride and less than 10 ppm of sodium chlorate, and having a pH of 13.

1N HCl was then added until the pH was 10.5.

- 9 -

Finally, distilled water was added to make 1000 ml.

The solution thus obtained contained 1.15% (w/v) of sodium hypochlorite [equivalent to 1.1% (w/v) of active chlorine] and 1.06% (w/v) of sodium chloride.

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EXAMPLES 2-3

Solutions 2 and 3

To check the effect of the pH correctors, the process was performed exactly as described in Example 1, except that the pH of the starting solution was first brought to 11 with 1N HCl and then to 10.5 with sodium tetraborate (Solution 2) or sodium bicarbonate (Solution 3).

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EXAMPLE 4

Solution 4

To check the effect of the sodium chloride, the process was performed exactly as described in Example 1, except that the content of sodium chloride was then raised to 18% (w/v).

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TEST 1

Stability

The stability of Solutions 1-4 was studied for 75 days in an environment having a temperature of 40°C and a relative humidity of 75% and for 63 days at ambient temperature (about 24°C).

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The study was performed in comparison with an electrolytic solution (Comparative Solution) of pH 10.3 and containing 1.15% (w/v) of sodium hypochlorite (equivalent to 1.1% of active chlorine), 18% sodium chloride and, relative to the abovementioned amount of sodium hypochlorite, about 26% (w/v) of sodium chlorate.

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The results are illustrated in Tables I and II below.

-10-

Table I
(T=40°C; R.H.=75%)

Solution No.	PH		Sodium hypochlorite		Chlorates (ppm)	
	initial	75 days	initial	75 days	initial	75 days
1	10.5	10.1	1.15	0.98	162	1046
2	10.5	10.1	1.15	0.90	134	1413
3	10.5	10.2	1.15	0.93	146	1272
4	10.5	9.8	1.15	0.85	157	1548
Comparative	10.3	9.6	1.15	0.80	2640	4128

Table II
(Ambient temperature)

Solution No.	PH		Sodium hypochlorite		Chlorates (ppm)	
	initial	63 days	initial	63 days	initial	63 days
1	10.5	10.3	1.15	1.14	162	251
2	10.5	10.4	1.15	1.15	134	281
3	10.5	10.4	1.15	1.14	146	272
4	10.5	10.4	1.15	1.15	157	295
Comparative	10.3	10.2	1.15	1.11	2640	2950

- 5 These data prove that the disinfectant solution of the present invention behaves like the comparative electrolytic solution which, as is known, is stable for at least 2 years. Thus, it may reasonably be deduced that the solution of the invention will also be stable for at least two years.

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TEST 2

Bactericidal activity

The bactericidal activity of the disinfectant solution of Example 1 was compared with that of the electrolytic solution mentioned in the preceding Test 1, according to standard UNI EN 1040.

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Strains of *Staphylococcus aureus* ATCC 6538 and *Pseudomonas aeruginosa* ATCC 15442 were subjected, for 5 minutes at 20°C, to

-11-

solutions containing five different concentrations of sodium hypochlorite, respectively: 28.75 ppm, 57.5 ppm, 115 ppm, 230 ppm and 460 ppm, obtained by diluting the solutions under investigation.

- The interpretation of the results according to standard UNI EN 1040
- 5 showed that both the solutions induce a logarithmic reduction $>10^5$ in the bacterial vitality.

In conclusion, the two solutions under investigation showed themselves to have the same bactericidal activity at the same concentrations.

-12-

CLAIMS

1. A sodium hypochlorite disinfectant solution having a pH of between 10.1 and 10.7 and comprising from 0.021 to 5.76% (w/v) of sodium hypochlorite, characterized in that it is buffers-free and contains,
5 relative to the said amount of sodium hypochlorite, not more than 2% of sodium chlorate.
2. A solution according to Claim 1, characterized in that it comprises from 0.52% to 2.09% (w/v) of sodium hypochlorite.
3. A solution according to Claim 1 or 2, characterized in that its pH is
10 between 10.1 and 10.5.
4. A solution according to any one of Claims 1 to 3, characterized in that it also comprises from 0.015 to 4% (w/v) of sodium chloride.
5. A solution according to any one of Claims 1 to 4, characterized in that it comprises an amount of sodium chloride that is sufficient to
15 make it isotonic.
6. A solution according to any one of Claims 1 to 5, characterized in that it also comprises a colorant.
7. A process for preparing a sodium hypochlorite disinfectant solution, comprising the dilution of a concentrated sodium hypochlorite
20 solution, characterized in that the pH of this solution is brought to a value of between 10.1 and 10.7 by adding dilute hydrochloric acid.
8. Process according to Claim 7, characterized in that the said concentrated solution has a pH of 13 and comprises from 15.70 to 20.93% (w/v) of sodium hypochlorite.
- 25 9. Process according to Claim 7 or 8, characterized in that the said dilute hydrochloric acid solution comprises 0.01-1 mol/litre and preferably 0.1-1 mol/litre of hydrochloric acid.