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(54) Titre : CONTENANT ET SYSTEME DE FERMETURE SERVANT A PRESERVER LA STABILITE DES SOLUTIONS D'HYPOCHLORITE DE SODIUM

(54) Title: CONTAINER AND CLOSURE SYSTEM FOR MAINTAINING STABILITY OF SODIUM HYPOCHLORITE SOLUTIONS

(57) Abrégé/Abstract:
The present invention relates to a vial and stopper system for maintaining the stability of sodium hypochlorite solutions. The particular system according to the present invention is capable of maintaining sodium hypochlorite solutions for periods of greater than one year, and have been shown to be effective for periods of nearly two years.

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(54) Title: CONTAINER AND CLOSURE SYSTEM FOR MAINTAINING STABILITY OF SODIUM HYPOCHLORITE SOLUTIONS

(57) Abstract

The present invention relates to a vial and stopper system for maintaining the stability of sodium hypochlorite solutions. The particular system according to the present invention is capable of maintaining sodium hypochlorite solutions for periods of greater than one year, and have been shown to be effective for periods of nearly two years.

CONTAINER AND CLOSURE SYSTEM FOR MAINTAINING STABILITY OF SODIUM HYPOCHLORITE SOLUTIONS

Background

The present invention relates to a system for maintaining stability of sterile sodium hypochlorite solutions. Sodium hypochlorite (NaOCl) is one of the essential ingredients used in the preparation of Tc-99m labelled erythrocytes. For this application, NaOCl is commonly prepared by dilution of reagent grade NaOCl (5.25% W/V), with normal saline to acheive a concentration of 0.1%. It has been observed that NaOCl solutions diluted in this manner are relatively unstable, and as a precaution are prepared as close as possible to the time of use.

Studies have been conducted on the stability of bulk, non-sterile sodium hypochlorite, most notably those of Fabian et al, Stability of Sodium Hypochlorite, Am. J. Hosp. Pharm., 1982, 39:1016-17; and Morris et al, The Stability of Diluted Hypochlorite Solution, Aust. J. Hosp. Pharm., 10(3):1016-117, 1980. These studies indicated that dilute NaOCl solutions were somewhat stable for periods ranging from one to two years. However, the data presented showed wide differences in the degree of stability acheived for NaOCl, without any apparant reason for the differing results.

Many other studies have been carried out in attempts to prepare stable NaOCl solutions by the inclusion of stabilizers or other additives. In every case known, the addition of stabilizers or additives resulted in even more rapid degradation of the NaOCl solution.

Therefore, there remains a need for a reliable and predictable means to maintain the stability of NaOCl solutions over an extended period of time.

Objects Of The Invention

One object of the present invention is to provide a means for preparing sterile solutions of dilute NaOCl and maintaining the stability thereof for periods of at least one year.

It is another object of the present invention to provide a vial and stopper system capable of maintaining the stability of sterile NaOCl solutions for periods of at least one year.

Summary Of The Invention

The objects of the present invention are acheived by providing a system which is capable of maintaining the stability of sterile NaOCl solutions for periods of at least one year. In particular, the present invention provides a system which includes a unique vial and stopper combination, avoids the addition of all chemical additives, and carefully controls pH and exposure to light.

Detailed Description Of The Invention

An initial study was carried out in order to determine the causes for reduction in stability of NaOCl solutions. This study indicated that the stability of NaOCl solutions is effected by the type of container and closure used, concentration, storage temperature and exposure to light.

In particular, solutions containing 0.1% to 5.0% NaOCl in basic normal saline were tested for stability. FIve different concentrations of NaOCl were tested; 0.1%, 0.5%, 1.0%, 2.5%, and 5.0%. Each of the five concentrations was stored in small vials of polypropylene and of glass, at four different storage conditions; 50°C, 25°C in light, 25°C in darkness, and 5°C. The results of this study are shown in the following Tables 1-10.

TABLE 1
5% NaOCL - Glass Vial

CONDITION	DAYS ON STABILITY 1	10	17	28	41
5°C	4.7	4.7	4.7	4.8	-
25°C Light	4.7	4.4	4.7	4.7	3.7
25°C Dark	4.7	4.6	4.4	4.4	4.5
50°C	4.7	3.7	3.7	3.0	-

TABLE 2
5% NaOCL - Plastic Vial

CONDITION	DAYS ON STABILITY 1	11	25	41
5°C	4.8	4.8	4.5	4.6
25°C Light	4.8	4.5	4.0	3.8
25°C Dark	4.8	4.5	4.4	4.4
50°C	4.8	4.2	0.5	0.1

TABLE 3
2.5% NaOCL - Glass Vial

CONDITION	DAYS ON STABILITY 1	10	25	41
5°C	2.35	2.35	2.35	2.25
25°C Light	2.35	2.2	2.1	1.95
25°C Dark	2.35	2.3	2.35	2.35
50°C	2.35	2.5	1.8	1.6

TABLE 4
2.5% NaOCL - Plastic Vial

CONDITION	DAYS ON STABILITY 1	11	27	41
5°C	2.4	2.8	2.3	2.35
25°C Light	2.4	2.55	1.9	1.8
25°C Dark	2.4	2.45	2.3	2.35
50°C	2.4	2.2	1.1	.15

TABLE 5
1% NaOCL - Glass Vial

CONDITION	DAYS ON STABILITY 1	10	25	42
5°C	.94	.93	.92	.93
25°C Light	.94	.85	.78	.72
25°C Dark	.94	.90	.92	.92
50°C	.94	.88	.78	.64

TABLE 6
1% NaOCL - Plastic Vial

CONDITION	DAYS ON STABILITY 1	11	27	45
5°C	.94	.96	.88	.92
25°C Light	.94	.91	.76	.72
25°C Dark	.94	.91	.88	.92
50°C	.94	.89	.80	.60

TABLE 7
0.5% NaOCL - Glass Vial

CONDITION	DAYS ON STABILITY 1	10	20	42
5°C	.48	.47	.47	.49
25°C Light	.48	.47	.43	.40
25°C Dark	.48	.48	.45	-
50°C	.48	.48	.45	.42

TABLE 8
0.5% NaOCL - Plastic Vial

CONDITION	DAYS ON STABILITY 1	11	27	44
5°C	.48	.48	.47	.45
25°C Light	.48	.44	.43	.39
25°C Dark	.48	.47	.47	.47
50°C	.48	.46	.43	.42

TABLE 9
0.1% NaOCL - Glass Vial

CONDITION	DAYS ON STABILITY 1	11	20	45
5°C	.096	.091	.091	-
25°C Light	.096	.092	.084	-
25°C Dark	.096	.088	.093	-
50°C	.096	.085	.084	.066

TABLE 10
0.1% NaOCL - Plastic Vial

CONDITION	DAYS ON STABILITY 1	11	27	45
5°C	.096	.094	.094	.090
25°C Light	.096	.086	.084	.070
25°C Dark	.096	.093	.090	.086
50°C	.096	0.88	.086	0.72

As the above tables show, the solutions were generally less stable at higher temperatures and under light, as was expected. However, it was discovered that solutions having higher starting concentrations generally degraded much more rapidly under heat than those at lower starting concentrations. Also, in the 5% and 2.5% NaOCl solutions, degradation was faster in plastic than in glass, and in both cases, the NaOCl was essentially gone after six weeks at 50°C when

stored in the plastic vials, while decomposition was slower in the glass vials. This suggests that polypropylene may have an effect on NaOCl stability. Collectively, this preliminary six week stability evaluation indicated that maintaining NaOCl for periods up to one year was not likely.

Following the initial study described above, a screening program was initiated to identify a preferred container and closure system which would be useful for maintaining sterile NaOCl at acceptable concentration levels for a period of at least one year when stored at room temperature.

In particular, a study was carried out to identify a pharmaceutically acceptable container and closure system which would preserve 0.1% NaOCl solutions at a potency of 0.08% or more for a period of at least one year when stored at room temperature.

NaOCl is well known to be sensitive to light, pH, and a variety of cations which may catalyze decomposition, storage temperature, and concentration. Depending on the environment NaOCl will normally decompose by one of three alternate pathways.

1) At low pH, the primary pathway of decomposition is by liberation of chlorine.
2) Oxygen is liberated from NaOCl in the presence of a variety of organic and inorganic catalysts, particularly Ca, Ni, and Cu.
3) NaOCl may undergo slow, concentration dependent, auto-decomposition when stored at high pH and protected from light.

Based on this known chemistry, it is postulated that an optimum storage environment for NaOCl would be a light protected, high pH environment using a container and closure system that would not contribute chemicals which would promote decompostion.

The container and closure identification study carried out was set up as a matrix experiment to compare the effectiveness of USP Type I glass vials and polypropylene plastic vials, importance of pH, and a variety of elastomeric closures. A solution of 0.1% NaOCl was prepared by diluting NaOCl with water for injection, resulting in an unadjusted pH of 11.3. This pH 11.3, 0.1% NaOCl solution was dispensed into six different container and closure combinations. (Series A). Both 2 and 3 mL vials were used, and each vial was filled to its nominal volume,

i.e. 2 mL in 2 mL vials and 3 mL in 3 mL vials. Sodium hydroxide was added to the remaining bulk solution to adjust the pH to 12.0 and four additional container and closure combinations were dispensed. (Series B). Two other series of dispensed vials were also prepared. THe first such series was a mixture of NaOCl with ACD (series C), while the second such series was a mixture of NaOCL with EDTA (Series D). Both Series C and D showed such rapid and complete decomposition of NaOCl, that zero values were obtained as an initial test point, thus confirming the sensitivity of NaOCl to chemical additives. Study of Series C and D was then discontinued. A summary of the dispensed vials are listed in Table 11.

TABLE 11

Group	pH	Container	Closure
I-A	11.3	2 mL Type I Glass	West 541 Red/ Teflon™
II-A	11.3	2 mL Type I Glass	West 1888 Gray/ Teflon™
III-A	11.3	2 mL Type I Glass	Faultless 1534 Red
IV-A	11.3	2 mL Type I Glass	Tompkins H0852
V-A	11.3	2 mL Type I Glass	D77E/A13R
VI-A	11.3	3 mL Type I Glass	Tompkins H0852A2
I-B	12.0	3 mL P/P Plastic	West 541 Red/ Teflon™
II-B	12.0	2 mL Type I Glass	West 541 Red/ Teflon™
III-B	12.0	2 mL Type I Glass	West 1888 Gray/Teflon™
IV-B	12.0	3 mL P/P Plastic	West 1888 Gray/Teflon™

All of the dispensed vials were stored in a dark cabinet at room temperature. The vials were stored on their sides to assure direct contact of the NaOCl with the closure. At periodic intervals, sample vials form each group were titrated for NaOCl concentration, using the USP XXI method of assay without modification, except for the much smaller volumes of NaOCl solution necessitated by the relatively small 2 and 3 mL vials. Triplicate samples (S-1, S-2, and S-3) of NaOCl were removed using a Hamilton syringe and trasferred to a clean dry test tube. A granule of KI was added to the tube followed immediately with 0.2-0.3 mL of 6N acetic acid. Volumetric N/10 sodium thiosulfate was used to titrate the sample until a slight yellow color was observed. A starch indicator was added and titration continued to a colorless end point.

Concentration of NaOCl was calculated as follows:

$$\%NaOCL = \frac{N \text{ sodium thiosulfate} \times mL \text{ sodium thiosulfate} \times 37.22}{\text{volume of sample (mL)} \times 10}$$

The results of this identification study are shown in the following Tables 12-21. Assay of particular sample groups was discontinued when it became obvious that all samples in the group had lost their potency. Sample groups which continued to show good assay values were studied for nearly two years (695 days).

TABLE 12

Sample	I-A
pH	11.3
Container	USP Type I Glass Wheaton Serum Bottle 2 mL
Closure	W541/T West Co Natural Rubber, Sulfur Cured, Teflon™ Faced

AGE (Days)	ML TITRANT			% SOD	% ORIG
	S-1	S-2	S-3	HYPO	STRENGTH
0	0.0348	0.0348	0.0349	0.0926	100.00
12	0.0347	0.0348	0.0348	0.0924	99.81
28	0.0349	0.0348	0.0349	0.0927	100.10
41	0.0350	0.0340	0.0340	0.0912	98.56
70	0.0339	0.0329	0.0329	0.0883	95.41
112	0.0328	0.0328	0.0328	0.0872	94.16
168	0.0298	0.0298	0.0298	0.0792	85.55
234	0.0248	0.0248	0.0248	0.0659	71.20
293	0.0273	0.0271	0.0273	0.0724	78.18
362	0.0233	0.0222	0.0234	0.0610	65.93
455	0.0217	0.0217	0.0217	0.0577	62.31
578	0.0019	0.0020	0.0021	0.0053	5.74
695	0.0008	0.0024	0.0136	0.0149	16.08

TABLE 13

Sample II-A
pH 11.3
Container USP Type I Glass Wheaton Serum Bottle 2 mL
Closure W1888/T West Co Halo-butyl Isoprene Blend, Teflon™ Coated

AGE (Days)	ML TITRANT			% SOD HYPO	% ORIG STRENGTH
	S-1	S-2	S-3		
0	0.0349	0.0349	0.0348	0.0927	100.00
12	0.0348	0.0347	0.0348	0.0924	99.71
28	0.0348	0.0348	0.0349	0.0926	99.90
41	0.0350	0.0350	0.0350	0.0930	100.38
70	0.0349	0.0349	0.0349	0.0927	100.10
112	0.0348	0.0348	0.0348	0.0925	99.81
168	0.0348	0.0338	0.0344	0.0912	98.47
234	0.0348	0.0348	0.0348	0.0925	99.81
293	0.0344	0.0343	0.0345	0.0914	98.66
362	0.0339	0.0340	0.0339	0.0902	97.32
455	0.0338	0.0337	0.0337	0.0896	96.75
578	0.0336	0.0336	0.0332	0.0889	95.98
695	0.0329	0.0322	0.0330	0.0869	93.79

TABLE 14

Sample III-A
pH 11.3
Container USP Type I Glass Wheaton Serum Bottle 2 mL
Closure F1534R

AGE (Days)	ML TITRANT			% SOD HYPO	% ORIG STRENGTH
	S-1	S-2	S-3		
0	0.0349	0.0349	0.0349	0.0926	100.00
12	0.0348	0.0349	0.0348	0.0926	99.95
28	0.0309	0.0318	0.0309	0.0829	89.53
41	0.0280	0.0280	0.0280	0.0744	80.34
70	0.0208	0.0208	0.0208	0.0553	59.68
112	0.0158	0.0158	0.0158	0.0420	45.34
168	0.0068	0.0058	0.0058	0.0163	17.60
234	0.0018	0.0018	0.0018	0.0048	5.16
293	0.0004	0.0002	0.0003	0.0007	0.79
362	0.0000	0.0000	0.0000	0.0000	0.00
578	0.0007	0.0003	0.0002	0.0010	1.06

TABLE 15

Sample IV-A
pH 11.3
Container USP Type I Glass Wheaton Serum Bottle 2 mL
Closure T 13-506 H0852 Butadiene Acrylonitrile Synthetic Rubber Tompkins

AGE (Days)	ML TITRANT S-1	S-2	S-3	% SOD HYPO	% ORIG STRENGTH
0	0.0349	0.0349	0.0349	0.0926	100.00
12	0.0338	0.0338	0.0338	0.0898	96.99
28	0.0328	0.0328	0.0329	0.0873	94.21
41	0.0320	0.0320	0.0320	0.0850	91.82
70	0.0289	0.0288	0.0288	0.0766	82.74
112	0.0258	0.0258	0.0258	0.0686	74.03
168	0.0188	0.0178	0.0188	0.0491	52.99
234	0.0158	0.0158	0.0158	0.0420	45.34
293	0.0005	0.0008	0.0007	0.0016	1.76
362	0.0016	0.0016	0.0016	0.0040	4.28
578	0.0008	0.0008	0.0008	0.0020	2.11

TABLE 16

Sample V-A
pH 11.3
Container USP Type I Glass Wheaton Serum Bottle 2 mL
Closure D77E/A13R

AGE (Days)	ML TITRANT S-1	S-2	S-3	% SOD HYPO	% ORIG STRENGTH
0	0.0349	0.0349	0.0349	0.0926	100.00
12	0.0308	0.0309	0.0308	0.0819	88.47
28	0.0089	0.0088	0.0089	0.0236	25.44
41	0.0260	0.0260	0.0260	0.0691	74.61
70	0.0010	0.0010	0.0010	0.0027	2.87
112	0.0008	0.0010	0.0010	0.0025	2.68
168	0.0000	0.0000	0.0000	0.0000	0.00
234	0.0000	0.0000	0.0000	0.0000	0.00
293	0.0000	0.0000	0.0000	0.0000	0.00
362	0.0000	0.0000	0.0000	0.0000	0.00
578	0.0000	0.0000	0.0000	0.0000	0.00

TABLE 17

Sample VI-A
pH 11.3
Container USP Type I Glass Vial, 3 mL
Closure T 13-70 H0852A2 Tompkins Butadiene Acrylonitrile Synthetic Rubber

AGE (Days)	ML TITRANT S-1	S-2	S-3	% SOD HYPO	% ORIG STRENGTH
0	0.0349	0.0349	0.0349	0.0926	100.00
12	0.0327	0.0328	0.0328	0.0871	94.02
28	0.0308	0.0308	0.0309	0.0819	88.47
41	0.0280	0.0280	0.0280	0.0744	80.34
70	0.0268	0.0268	0.0268	0.0712	76.90
112	0.0248	0.0248	0.0248	0.0659	71.16
168	0.0108	0.0109	0.0109	0.0289	31.18
234	0.0038	0.0038	0.0038	0.0101	10.90
293	0.0028	0.0023	0.0024	0.0061	6.60
362	0.0000	0.0000	0.0000	0.0000	0.00
578	0.0000	0.0000	0.0000	0.0000	0.00

TABLE 18

Sample I-B
pH 12.0
Container Wheaton Plastic 3cc Serum Vial natural P/P (K213) B21707
Closure W541/T West Co Natural Rubber, Sulfur Cured, Teflon™ Faced

AGE (Days)	ML TITRANT			% SOD HYPO	% ORIG STRENGTH
	S-1	S-2	S-3		
0	0.0337	0.0336	0.0328	0.0887	100.00
12	0.0348	0.0348	0.0348	0.0925	104.30
28	0.0349	0.0349	0.0349	0.0927	104.60
41	0.0340	0.0340	0.0340	0.0904	101.90
70	0.0333	0.0333	0.0333	0.0885	99.86
112	0.0328	0.0328	0.0328	0.0872	98.30
168	0.0328	0.0328	0.0328	0.0872	98.30
234	0.0268	0.0268	0.0268	0.0712	80.32
293	0.0225	0.0222	0.0219	0.0590	66.53
362	0.0158	0.0153	0.0157	0.0415	46.75
455	0.0277	0.0278	0.0275	0.0735	82.92
578	0.0028	0.0026	0.0024	0.0069	7.79
695	0.0000	0.0030	0.0057	0.0077	8.69

TABLE 19

Sample II-B
pH 12.0
Container USP Type I Glass Wheaton Serum Bottle 2 mL
Closure W541/T West Co Natural Rubber, Sulfur Cured, Teflon™ Faced

AGE (Days)	ML TITRANT			% SOD HYPO	% ORIG STRENGTH
	S-1	S-2	S-3		
0	0.0349	0.0348	0.0349	0.0927	100.00
12	0.0348	0.0348	0.0348	0.0925	99.81
28	0.0349	0.0349	0.0348	0.0927	100.00
41	0.0340	0.0340	0.0350	0.0912	98.47
70	0.0348	0.0338	0.0338	0.0907	97.90
112	0.0311	0.0318	0.0308	0.0830	89.58
168	0.0298	0.0298	0.0299	0.0793	85.56
234	0.0248	0.0248	0.0248	0.0659	71.13
293	0.0109	0.0112	0.0112	0.0295	31.84
362	0.0217	0.0221	0.0226	0.0588	63.48
455	0.0059	0.0056	0.0054	0.0150	16.16
578	0.0088	0.0089	0.0089	0.0236	25.43
695	0.0000	0.0070	0.0058	0.0113	12.24

TABLE 20

Sample	III-B
pH	12.0
Container	USP Type I Glass Wheaton Serum Bottle 2 mL
Closure	W1888G/T West Co Halo-butyl Isoprene Blend, Teflon™ Coated

AGE (Days)	ML TITRANT S-1	S-2	S-3	% SOD HYPO	% ORIG STRENGTH
0	0.0350	0.0349	0.0349	0.0928	100.00
12	0.0347	0.0348	0.0348	0.0924	99.52
28	0.0348	0.0348	0.0348	0.0925	99.62
41	0.0349	0.0349	0.0348	0.0927	99.81
70	0.0349	0.0340	0.0349	0.0919	99.05
112	0.0339	0.0340	0.0338	0.0901	97.04
168	0.0348	0.0348	0.0348	0.0925	99.62
234	0.0348	0.0348	0.0348	0.0925	99.62
293	0.0339	0.0339	0.0340	0.0902	97.14
362	0.0334	0.0333	0.0338	0.0890	95.90
455	0.0333	0.0334	0.0334	0.0887	95.52
578	0.0323	0.0331	0.0330	0.0872	93.89
695	0.0332	0.0334	0.0330	0.0882	95.04

TABLE 21

Sample	IV-B
pH	12.0
Container	Wheaton Plastic 3 cc Serum Vial Natural P/P (K213) B31707
Closure	W1888G/T West Co Halo-butyl Isoprene Blend Teflon™ Coated

AGE (Days)	ML TITRANT S-1	S-2	S-3	% SOD HYPO	% ORIG STRENGTH
0	0.0348	0.0348	0.0348	0.0925	100.00
12	0.0348	0.0348	0.0348	0.0925	100.00
28	0.0348	0.0348	0.0349	0.0926	100.10
41	0.0348	0.0340	0.0340	0.0911	98.47
70	0.0348	0.0339	0.0339	0.0909	98.28
112	0.0328	0.0328	0.0329	0.0873	94.35
168	0.0328	0.0328	0.0328	0.0872	94.25
234	0.0328	0.0328	0.0328	0.0872	94.25
293	0.0288	0.0287	0.0279	0.0757	81.80
362	0.0316	0.0313	0.0310	0.0832	89.94
455	0.0300	0.0298	0.0301	0.0796	86.11
578	0.0299	0.0298	0.0300	0.0795	85.92
695	0.0295	0.0281	0.0280	0.0758	81.99

This identification study showed remarkable differences in the ability of the various container and closure systems to preserve chemical potency of NaOCl. In particular, systems having elastomeric closures which were not coated with Teflon™, exhibited a pronounced decrease in NaOCl concentration during the first month of the study. In contrast, both Teflon™ coated stopper types (West 541 red/Teflon™ and West 1888 gray/Teflon™) preserved the NaOCl for at least three months. After three months, only the 1888 gray/Teflon™ coated stopper continued to be effective.

In addition, the results clearly show that USP type I glass vials were more effective at preserving the chemical potency of NaOCl than polypropylene plastic vials.

In a further test, three separate lots of 0.1% NaOCl solutions were dispensed in syringes and tested for stability using the following criteria set forth in Table 22.

TABLE 22

TEST	LIMITS	NO. OF SAMPLES	TEST INTERVAL
Appearance	Clear, colorless solution essentially free of visible particulate matter	1	Each time
pH	11.0 - 13.0	1	Each time
Sodium Hypochorite	0.08 - 0.11 % w/v	3	Each time
Physical Appearance	Absence of cracks, peeling, leaking, deformity (each component. Free of deformity on plunger sealing rib. Rubber tip cap in position. Check for change in transparency, and interaction between syringe and plunger.	3	Each time
Vapor Transmission	Report loss or gain	2	Each time

The syringes used in this study were Hypak 2 1/4 mL colorless USP Type I glass, siliconized syringes. These syringes included closures consisting of a syringe tip of west 890 gray butyl, a threaded plunger (West 1883 gray butyl Teflon™ faced), and a BD plunger rod. Vapor transmission tests were carried out according to the following protocol.

Test two syringes at each test interval.

Technique: Weigh the same syringe at each test interval on a balance having 0.001 G of readability and calculate the weight loss or gain with respect to initial weight.

The prepared syringes were stored under several different conditions, listed below.

A. 25°C, 500-1000 foot candles of light (fc)
B. Controlled Room Temperature (CRT)
C. 37°C at 80% relative humidity (RH)
D. 50°C
E. 5°C
F. Freeze/Thaw stress test conditions

Tests were carried ont on the different storage groups according to the schedule shown in Table 23.

TABLE 23

	STORAGE CONDITIONS				
Test Interval	25° C 500-1000 fc	CRT	37° C 80% RH	50° C	5° C
Initial	X	X	X	X	X
1 Week	X	X			
1 Month	X	X	X	X	
2 Month	X	X	X	X	
3 Month	X	X	X	X	
6 Month	X	X			X
12 Month	X				X
18 Month	X				
24 Month	X				

Results of the above tests are presented in the following Tables 24-26, each table representing one of the three lots of solutions prepared.

TABLE 24

Date NaOCl Manufactured 26-May Date Stability Study Initiated . 15- June
Container: 2 1/4 mL Syringe, Type I Glass, Siliconized, Code K994
Closure: Tip - 890 Gray Butyl Code K994; Plunger - 1883 Gray Butyl, Teflon™ Faced

Storage Condition	Storage Time (Month)	Appearance	pH	% Sodium Hypochlorite	Physical Appearance	Vapor Transmission (+% or -%)	
	0	Pass	11.7	0.104	Pass	ND	ND
5°C	1	Pass	11.8	0.104	Pass	ND	ND
	2	Pass	11.9	0.103	Pass	ND	ND
	3	Pass	11.8	0.104	Pass	ND	ND
	6	Pass	11.9	0.096	Pass	0.00	0.00
	12	Pass	11.9	0.104	Pass	0.01	0.02
CRT	1	Pass	11.8	0.102	Pass	0.00	-0.01
	2	Pass	11.7	0.102	Pass	-0.01	-0.01
	3	Pass	11.8	0.102	Pass	0.00	0.00
	6	Pass	11.7	0.102	Pass	-0.03	-0.03
	12	Pass	11.8	0.099	Pass	-0.02	-0.02
	18	Pass	11.7	0.094	Pass	-0.04	-0.04
	24	Pass	11.7	0.091	Pass	-0.03	-0.04
37°C, 80%RH	1	Pass	11.7	0.102	Pass	0.02	0.02
	2	Pass	11.6	0.099	Pass	0.01	0.01
	3	Pass	11.6	0.095	Pass	0.02	0.02
50°C	1	Pass	11.6	0.097	Pass	-0.04	-0.04
	2	Pass	11.6	0.094	Pass	-0.08	-0.08
	3	Pass	11.5	0.092	Pass	-0.09	-0.09
25°C 500-1000fc	1/4	Pass	11.9	0.044	Pass	-0.01	-0.01
Freeze/Thaw		Pass	11.9	ND	Pass	ND	ND

ND = test not performed

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TABLE 25

Date NaOCl Manufactured 04-June Date Stability Study Initiated 15-June
Container: 2 1/4 mL Syringe, Type I Glass, Siliconized, Code K994
Closure: Tip - 890 Gray Butyl Code K994; Plunger - 1883 Gray Butyl, Teflon™ Faced

Storage Condition	Storage Time (Month)	Appearance	pH	% Sodium Hypochlorite	Physical Appearance	Vapor Transmission (+% or -%)	
	0	Pass	11.8	0.102	Pass	ND	ND
5°C	2	Pass	11.9	0.102	Pass	ND	ND
	3	Pass	11.9	0.102	Pass	ND	ND
	6	Pass	11.8	0.098	Pass	0.00	0.00
	12	Pass	11.9	0.101	Pass	0.02	0.02
CRT	1	Pass	11.8	0.102	Pass	-0.01	-0.01
	2	Pass	11.7	0.102	Pass	-0.02	-0.01
	3	Pass	11.8	0.102	Pass	-0.01	-0.01
	6	Pass	11.7	0.098	Pass	-0.03	-0.03
	12	Pass	11.8	0.097	Pass	-0.02	-0.02
	18	Pass	11.7	0.097	Pass	-0.05	-0.05
	24	Pass	11.8	0.093	Pass	-0.03	-0.04
37°C, 80%RH	1	Pass	11.8	0.102	Pass	0.02	0.02
	2	Pass	11.6	0.100	Pass	0.01	0.02
	3	Pass	11.7	0.099	Pass	0.02	0.02
50°C	1	Pass	11.7	0.098	Pass	-0.04	-0.04
	2	Pass	11.6	0.093	Pass	-0.07	-0.07
	3	Pass	11.6	0.091	Pass	-0.08	-0.09
25°C 500-1000fc	1/4	Pass	11.8	0.099	Pass	-0.01	-0.01
	1	Pass	11.8	0.081	Pass	-0.02	-0.02
	2	Pass	11.7	0.061	Pass	-0.03	-0.02
Freeze/Thaw		Pass	11.9	ND	Pass	ND	ND

ND = test not performed

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TABLE 26

Date NaOCl Manufactured 03-June Date Stability Study Initiated 15-June
Container: 2 1/4 mL Syringe, Type I Glass, Siliconized, Code K994
Closure: Tip - 890 Gray Butyl Code K994; Plunger - 1883 Gray Butyl, Teflon™ Faced

Storage Condition	Storage Time (Month)	Appearance	pH	% Sodium Hypochlorite	Physical Appearance	Vapor Transmission (+% or -%)	
	0	Pass	11.7	0.103	Pass	ND	ND
5°C	1	Pass	11.6	0.102	Pass	ND	ND
	2	Pass	11.9	0.102	Pass	ND	ND
	3	Pass	11.9	0.101	Pass	ND	ND
	6	Pass	11.8	0.097	Pass	0.00	0.00
	12	Pass	11.9	0.101	Pass	0.01	0.02
CRT	1	Pass	11.8	0.101	Pass	-0.01	-0.01
	2	Pass	11.7	0.102	Pass	-0.02	-0.02
	3	Pass	11.8	0.101	Pass	-0.01	-0.01
	6	Pass	11.7	0.093	Pass	-0.04	-0.04
	12	Pass	11.8	0.097	Pass	-0.03	-0.02
	18	Pass	11.7	0.096	Pass	-0.05	-0.06
	24	Pass	11.7	0.089	Pass	-0.04	-0.04
37°C, 80%RH	1	Pass	11.7	0.099	Pass	0.03	0.03
	2	Pass	11.7	0.100	Pass	0.02	0.02
	3	Pass	11.7	0.096	Pass	0.02	0.03
50°C	1	Pass	11.6	0.099	Pass	-0.04	-0.04
	2	Pass	11.7	0.091	Pass	-0.07	-0.08
	3	Pass	11.6	0.091	Pass	-0.08	-0.10
25°C 500-1000fc	1/4	Pass	11.8	0.095	Pass	-0.01	-0.01
	1	Pass	11.7	0.073	Pass	-0.02	-0.02
Freeze/Thaw		Pass	11.9	ND	Pass	ND	ND

ND = test not performed

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The results of these tests shows a trend for NaOCl concentration to decrease very slowly with time, and for increased storage temperature to increase the rate of decomposition. Exposure to intense light produced rapid and significant NaOCl degradation. The syringes showed no evidence of deterioration or quality loss as a result of the freeze/thaw stress test.

From all of the above test data, it is clear that the optimal container and closure system comprises a combination of a Type I glass container with either a West 1888 gray butyl Teflon™ faced stopper or a West 1883 gray butyl Teflon™ faced stopper. In each of these combinations, minimal loss of NaOCl occurred over a period of nearly two years. In particular, when using a glass vial with a West 1888 gray butyl Teflon™ faced stopper, the NaOCl was maintained at about 93.8 % to 95 % of its original strength after 695 days (about 23 months). In similar results, a combination of a glass vial with a 1883 gray butyl Teflon™ faced stopper maintained the NaOCl solution at about 88.3 % of initial concentration after 24 months.

Pharmaceutical preparations intended for parenteral administration must be prepared in sterile form. Ideally, such preparations are filled into their respective containers, and the sealed containers are terminally sterilized using radiation or steam. Alternately, products which are known to be degraded by steam or radiation may be sterilized by filtration, and the sterile product aseptically filled into its intended container

A test to establish whether radiation sterilization would be viable was conducted at several different radiation exposures. It should be noted that accepted radiation sterilization has normally been done at 2.5 megarad, although lower doses may be accepted with proper validation. The results of the radiation sterilization test are shown below in Table 27.

TABLE 27

Radiation Sterilization Test - 0.1% NaOCl Syringes

Rad Dose (MRAD)	Ml Titrant (.1071) S-1	S-2	S-3	% NaOCl	% of Control
0	0.0369	0.0368	0.0368	0.0977	100.0
5	0.0000	0.0000	0.0000	0.0000	0.0
2.5	0.0038	0.0038	0.0028	0.0092	9.4
1.25	0.0158	0.0158	0.0148	0.0411	42.1
1	0.0198	0.0198	0.0198	0.0526	53.9
0.9	0.0228	0.0218	0.0228	0.0597	61.1
0.8	0.0238	0.0238	0.0238	0.0632	64.7
0.7	0.0258	0.0248	0.0248	0.0668	68.4
0.6	0.0268	0.0268	0.0268	0.0712	72.9

As can be seen from the above table, even the lowest exposure of 0.6 megarad resulted in a unacceptable drop in hypochlorite concentration, i.e. 27.1% drop. Therefore, radiation sterilization results in excessive decomposition of the NaOCl and is an unacceptable means of terminal steilization.

Steam sterilization was also tested according to the following procedure. One mL aliquots of NaOCl solution were dispensed into 1 mL USP Type I glass ampules. Thermal stability was tested by exposing the ampules to temperatures of 115°C and 121°C in a Bier vessel for time periods of 15, 25 and 40 minutes. Following thermal exposure, the samples were analyzed quantitatively for NaOCl as compared with a non-thermally treated controls. Concentration of NaOCl was expressed as a percent of the control. The results of these tests are shown in Table 28.

TABLE 28

Thermal Stability Test - NaOCl Solutions

Temp (°C)	Time (min)	% of Control	Rel St Dev	% NaOCl	Volume of Titrant S-1	S-2	S-3	S-4	S-5	S-6
115	0	100	1.34	0.0987	0.0404	0.0399	0.0404	0.0390	0.0390	0.0390
	15	98.7	0.32	0.0974	0.0391	0.0390	0.0392	0.0391	0.0394	0.0392
	25	98.6	0.24	0.0974	0.0932	0.0392	0.0390			
	40	97.6	0.10	0.0963	0.0387	0.0388	0.0387	0.0387	0.0387	0.0387
121	0	100	1.34	0.0987	0.0404	0.0399	0.0404	0.0390	0.0390	0.0390
	15	98.1	0.18	0.0968	0.0390	0.0389	0.0390	0.0389	0.0389	0.0388
	25	96.9	0.56	0.0957	0.0384	0.0386	0.0388	0.0384	0.0381	0.0384
	40	95.6	0.41	0.0943	0.0381	0.0381	0.0380	0.0378	0.0377	0.0378

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A regression analysis of the data shown in Table 28 was carried out with the following results.

	115°C	121°C
Constant	99.8791	99.8643
Std Err of Y Est	0.2666	0.2055
R Squared	0.9518	0.9920
No Of Observations	4.0000	4.0000
Degrees of Freedom	2.0000	2.0000
X Coefficient	-0.0575	-0.1114
St Err of Coefficient	0.0091	0.0070

The R squared values of both groups indicate that the thermal loss of NaOCl is linear, which allowed the following equations to be derived to describe the extent of NaOCl loss during autoclaving (steam sterilization).

For Autoclaving At 115°C

% NaOCl = 99.88 - 0.0575(minutes at 115°C)

For Autoclaving At 121°C

% NaOCl = 99.86 - 0.1114(minutes at 121°C)

As is apparant from the test results and regression analysis, the rate of decomposition at 121°C is almost twice that at 115°C. Autoclaving at 115°C results in an immediate drop in concentration of about 2.5% with a resultant reduction of shelf life of almost 40%. However, stability projections based on the regression analysis estimate a shelf life of 32.3 months before the NaOCl solutions reach an unacceptably low level of 80% of initial potency. Therefore, post-fill steam sterilization of NaOCl at 115°C appears feasible.

As noted previously, NaOCl solutions are sensitive to light, pH and a variety of cations or impurities. It is therefore essential that these factors be controlled carefully to enable long shelf life of prepared NaOCl solutions.

Exposure to light is relatively easy to control. In particular, the prepared NaOCl solutions dispensed to the container and closure system according to the present invention, are stored in opaque, light barrier, trays.

pH of the NaOCl solutions is controlled at the time of solution formulation. An example of NaOCl solution preparation is described below.

EXAMPLE 1: Preparation of NaOCl Solutions

Abreviations Used

NaOCl - sodium hypochlorite
WFI - water for injection
NaOH - sodium hydroxide

Formulation Process

Step 1. Assay NaOCl within one day of use to determine potency.

A. Pipet 10.00 mL NaOCl to a 500.00 mL volumetric flask containing about 400 mL of water for injection (WFI). Dilute to mark and mix. Wrap in opaque material (aluminum foil) to protect from light.

B. Quantitatively transfer triplicate samples for titration. Immediately add an excess of KI granules, acidify with dilute acetic acid and titrate with volumetric sodium thiosulfate solution to a pale yellow. Add starch indicator and continue titrating to a colorless endpoint which persists for at least 15 seconds.

C. Calculate the strength of NaOCl as follows:

$$\% \text{ NaOCl} = \frac{\text{mL thiosulfate X N thiosulfate X 37.22 X 500mL}}{\text{sample volume X 10mL X 10}}$$

D. Calculate the volume of NaOCl needed to prepare 5.00L of 0.1% solution.

mL of NaOCl = (5000mL X 1.0mg/mL)/% NaOCl X 10

Step 2. Solution Preparation.

A. All glassware must be washed thoroughly in WFI and depyrogenated by dry heat.

B. Add about 4.0 L of cool WFI (25°C) tp an accurately calibrated 5.0 L glass vessel. Quantitatively transfer the volume of NaOCl calculated in Step 1.D.

C. Mix and dilute to about 4,900 mL.

D. Check pH and adjust to 11.8 - 12.2 by addition of 1N NaOH. Do not add HCl to lower pH.

E. Dilute to volume and mix.

F. Filter through sterile 0.22 micron membrane filter.

G. Store at controlled room temperature or lower. Protect from light.

Reduction of impurities and cations is accomplished by dispensing the prepared NaOCl solutions to the container and closure system according to the present invention. The following Examples provide information relative to the preparation and dispensing of Hypak™ 2 1/4 mL colorless USP Type I glass siliconized syringes.

EXAMPLE 2: Prparation of Container and Closure System

The components needed are:

A. Syringe - 2 1/4 mL luer tip B-D syringe barrel, siliconized, with 890 gray rubber tips in place.

B. Syringe Tips - B-D ribbed tip cap, 890 gray, non-siliconized.

C. Syringe Plunger - BD703-12 threaded plunger, 1883 gray Teflon™ faced, presiliconized and sterlized.

D. Plunger Rod - BD plunger rod for 2 1/4 mL Hypak™ syringe.

The components above are available in ready-to-use sterile units. The syringe barrels are pre-siliconized with tip caps in place and are packaged sterile in a pharmaceutical system. Threaded plungers are also available in a ready-to-use sterile pharmaceutical system.

Example 3: Dispensing of NaOCL to Container and Closure System

1. Dispense 0.6 mL aliquots into the prepared sterile Hypak™ 2 1/4 B-D syringes.
2. Place the syringes in the Hypak™ stoppering unit and insert the Teflon™ face 1883 gray threaded plungers at a vacuum setting of 27-29" Hg. The plunger should be positioned to a level where less than 5 mm head space is present between the hypochlorite and plunger.
3. Perform visual inspection on filled units. Reject for particulates, mis-positioned plungers, and mis-aligned plunger rib position.

The foregoing has been a description of certain preferred embodiments of the present invention, but is not intended to limit the invention in any way. Rather, many modifications, variations and changes in details may be made within the scope of the present invention.

THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A system comprising a vial which is closed by a stopper and a dilute sodium hypochlorite solution that is contained in the vial, wherein said vial is a glass vial and said stopper is a halo butyl isoprene blend rubber stopper coated by polytetrafluoroethylene.

2. The system according to claim 1 wherein said sodium hypochlorite solution is sterile.

3. The system according to claim 1, wherein the glass of said vial is U.S.P. Type I boro-silicate glass.

4. The system according to claim 1, wherein the concentration of said sodium hypochlorite solution is about 0.1 (W/V) or less.

5. The system according to any one of claims 1, 2, 3 or 4, wherein it is stored in an opaque, light-barrier tray.