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3,272,700
**STABILIZED AQUEOUS SOLUTION OF
 TETRACAINE SALT**

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 Sterling Drug Inc., New York, N.Y., a corporation of
 Delaware
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 1 Claim. (Cl. 167-52)

This application is a continuation-in-part of my co-
 pending application Serial No. 167,955, filed January 22,
 1962, now abandoned.

This invention relates to an improved aqueous solution
 of an acid-addition salt of 2-dimethylaminoethyl 4-n-
 butylaminobenzoate and to a method of maintaining clarity
 in said solution.

2-dimethylaminoethyl 4-n-butylaminobenzoate, also
 known generically as tetracaine, is a well-known commercial
 local anesthetic. It has been sold for almost twenty-five
 years in the form of its hydrochloride in aqueous solution
 in various concentrations adapted for prolonged spinal
 anesthesia, for surface anesthesia for dental practice,
 etc.

Manufacturers of such solutions, while enjoying commercial
 success over the years with these readily acceptable and
 efficacious aqueous preparations have been at the same time
 faced with the persistent problem of how to increase the
 storage life of the solutions. On standing, these tetracaine
 solutions have the disadvantage of yielding small quantities
 of precipitated 4-n-butylaminobenzoic acid, a hydrolysis
 degradation product of tetracaine. The 4-n-butylaminobenzoic
 acid, which is relatively insoluble in aqueous solutions,
 separates as crystals or produces cloudiness in the solution.

I have now found that the precipitation of 4-n-butyl-
 aminobenzoic acid from solutions of tetracaine salts, for
 instance the hydrochloride, is prevented by incorporating
 in the solutions a small quantity of an oxyethylated alkyl-
 phenol-formaldehyde polymer. The resulting solutions, the
 composition aspect of my invention, have increased shelf
 life when stored for long periods at room temperature
 (25° C.) and even at temperatures of 37°, 40° and 50°
 C. or when heated as high as 121° C. for periods of one
 to three hours.

The oxyethylated alkylphenol-formaldehyde polymers
 useful in the compositions of the invention are prepared
 by condensing a mole of an alkylphenol with 0.5-1.0 mole
 of formaldehyde and reacting the product thus obtained
 with 8-60 moles of ethylene oxide, as described in U.S.
 Patent 2,454,541. Particularly useful polymers are the
 oxyethylated p-tertiary-octylphenol-formaldehyde polymers
 produced by condensing approximately equimolar amounts
 of p-tertiary-octylphenol and formaldehyde and then
 reacting the product with 10-20 moles of ethylene oxide.
 A preferred compound of this group is the product containing
 ten ether groups per p-tertiary-octylphenol nucleus which
 is known under the brand names, "Superinone" and
 "Triton WR-1339," chemically as oxyethylated tertiary
 octylphenol formaldehyde polymer or p-isooctylpolyoxy-
 ethylenephenol formaldehyde polymer, and, generically
 as tyloxapol [J. Am. Med. Assoc., 181, 243 (1962)];
 the preparation of a closely similar and equivalently
 useful compound is described in Example 1 of U.S. Patent
 2,454,541, wherein eleven moles of ethylene oxide are
 used.

Aqueous solutions of the invention preferably have about
 0.4 to about 1 percent (weight per volume) of an oxyethylated
 alkylphenol-formaldehyde polymer. Greater quantities of
 the polymer, up to about 10 percent or more, can be used
 but to no particular advantage. Preferred embodiments are
 aqueous solutions containing about 0.1 to 2 percent of 2-dimethylaminoethyl
 4-n-butyl-

aminobenzoate hydrochloride and about 0.4 to 1 percent of
 tyloxapol. A particularly preferred embodiment contains
 1.0 percent of tetracaine hydrochloride and 0.8 percent
 of tyloxapol.

Another aspect of my invention resides in a method for
 maintaining clarity in an aqueous solution of a pharmaceuti-
 cally-acceptable salt of 2-dimethylaminoethyl 4-n-butyl-
 aminobenzoate which comprises incorporating in said solution
 normally subject to precipitation or cloudiness on storage
 an oxyethylated alkylphenol-formaldehyde polymer in amount
 sufficient to keep the hydrolysis degradation product
 4-n-butylaminobenzoic acid in solution on storage. Preferred
 essential ingredients of said solution and preferred percentages
 thereof are presented hereinabove.

My invention is further illustrated by the following
 specific embodiments without, however, limiting it thereto.
 U.S.P. grade ingredients are used in the following examples.

Example 1

The following aqueous solutions containing 1 percent
 (weight per volume, i.e., 1 g. per 100 ml.) tetracaine hydro-
 chloride containing 0, 0.1, 1.0 and 10 percent tyloxapol were
 prepared:

Ingredient	1A	1B	1C	1D
Tetracaine hydrochloride	1.0	1.0	1.0	1.0
Sodium chloride	0.67	0.67	0.67	0.67
Acetone sodium bisulfite	0.20	0.20	0.20	0.20
Tyloxapol		0.1	1.0	10.0

The solutions were prepared by dissolving the ingredi-
 ents in distilled water and then were poured into 2 ml.
 flint ampuls, sterilized by heating at 220° F. for three
 minutes and stored at 122° F. (50° C.).

The solutions were assayed for free 4-n-butylamino-
 benzoic acid (BABA) initially and after one and eight
 months storage at 50° C. with the following results:

Preparation	BABA, mg./ml.			pH	
	Initial	1 month at 50° C.	8 months at 50° C.	Initial	Final
1A	0.015	0.103	0.129	3.5	3.5, 3.1
1B	0.018	0.119	0.139	3.4	3.15
1C	0.015	0.150	0.378	3.5	3.08
1D	0.019	0.105	0.429	3.4	2.61

None of the ampuls stored for 8 months at 50° C.
 showed any sign of crystallization after being allowed to
 cool and to stand at room temperature overnight. How-
 ever, on refrigerating at 5° C., some amorphous precipi-
 tate separated in the control (1A) and in the 0.1% tyloxap-
 ol solution (1B). No precipitate formed, even after a
 full week in the refrigerator, in the solutions containing
 1% (1C) or 10% (1D) tyloxapol.

It is seen from the above results that 0.1% tyloxapol
 did not prevent the precipitation of BABA in the solu-
 tion containing 0.14 mg. of BABA per ml. and that 1.0%
 tyloxapol did prevent the precipitation of as much as
 0.38 mg. of BABA per ml., the latter representing 3.8%
 decomposition of the tetracaine hydrochloride. It is also
 seen that 10.0% tyloxapol prevented the precipitation of
 0.43 mg. of BABA per ml., which represents only 4.3%
 decomposition of tetracaine hydrochloride.

Example 2

The following solutions of 1 percent tetracaine hydrochloride containing 0, 0.2, 0.4, 0.6 and 0.8 percent tyloxapol were prepared:

Ingredient	2A	2B	2C	2D	2E
Tetracaine hydrochloride, g.....	5.0	5.0	5.0	5.0	5.0
Sodium chloride, g.....	3.35	3.35	3.35	3.35	3.35
Acetone sodium bisulfite, g.....	1.0	1.0	1.0	1.0	1.0
Tyloxapol, g.....	1.0	1.0	2.0	3.0	4.0
Water for injection, ml., q.s. ad.....	500	500	500	500	500

Each of the above solutions was prepared as follows: The acetone sodium bisulfite was dissolved in about 400 ml. of distilled water containing the tyloxapol. The sodium chloride and tetracaine hydrochloride were then dissolved, respectively; and the pH of the solution was checked and adjusted to 4.6. Distilled water was added to give 500 ml. of solution which was filtered through an ultra fine frit glass filter into a sterile system and then filled into 2 ml. flint ampuls under aseptic conditions. The ampuls were heated at 220° F. for three minutes, submitted for chemical assay and some were then stored at 40° C., some in a refrigerator (about 5° C.) and some at room temperature (about 20-25° C.).

The results of the initial assay are summarized as follows:

Ingredient	2A	2B	2C	2D	2E
Tetracaine HCl, mg./ml.....	9.5	9.7	9.7	9.7	9.6
Tyloxapol, mg./ml.....	2.35	4.6	5.50	7.30	
BABA, mg./ml.....	0.022	0.024	0.025	0.024	0.025
pH.....	3.35	3.00	2.95	2.90	2.90

The solution stored at 40° C. were assayed for BABA after three and six months with the following results:

Solution	3 mo. at 40° C.		6 mo. at 40° C.	
	BABA, mg./ml.	pH	BABA, mg./ml.	pH
2A.....	0.098	3.05	0.103	3.05
2B.....	0.159	2.95	0.202	2.95
2C.....	0.167	3.00	0.253	2.95
2D.....	0.171	3.00	0.283	2.90
2E.....	0.171	3.05	0.292	2.88

After storage for six months at 40° C., solutions 2C, 2D and 2E remained clear and solutions 2A and 2B yielded crystals when chilled for six hours in an ice bath. Thus, it is seen that 0.2% tyloxapol did not prevent the precipitation of BABA in the solution containing 0.20 mg. of BABA per ml. and 0.4%, 0.6% and 0.8% tyloxapol did prevent the precipitation of as much as 0.25 mg., 0.28 mg. and 0.29 mg., respectively, of BABA per ml.

Example 3

The following solutions of 1 percent tetracaine hydrochloride containing 0, 0.2, 0.4, 0.6 and 0.8 percent tyloxapol were prepared as in Example 2 but adding a lactic acid-sodium lactate buffer:

Ingredient	3A	3B	3C	3D	3E
Tetracaine HCl, g.....	2.5	2.5	2.5	2.5	2.5
Sodium chloride, g.....	0.925	0.925	0.925	0.925	0.925
Acetone sodium bisulfite, g.....	0.5	0.5	0.5	0.5	0.5
Tyloxapol, g.....	0.5	0.5	1.0	1.5	2.0
Sodium lactate (60%), ml.....	1.5	1.5	1.5	1.5	1.5
Lactic acid (85%), ml.....	0.075	0.975	0.075	0.075	0.075
Water for injection, q.s. ad, ml.....	250	250	250	250	250
Adjusted pH.....	3.98	4.05	4.03	4.05	4.03

The pH was adjusted to the above values using lactic acid. The solutions were filled into sterile 2 ml. flint ampuls, heated at 220° F. for three minutes and stored

at 40° C. after submitting some of the ampuls for initial chemical assay.

The results of the initial assay follow:

Ingredient	3A	3B	3C	3D	3E
Tetracaine HCl, mg./ml.....	9.69	9.69	9.57	9.67	9.73
Tyloxapol, mg./ml.....	2.33	4.40	6.40	8.50	
BABA, mg./ml.....	0.034	0.033	0.033	0.027	0.027
pH.....	3.9	3.9	3.85	3.70	3.70

The solutions stored at 40° C. were assayed for BABA after three and six months with the following results:

Solution	3 mo. at 40° C.		6 mo. at 40° C.		12 mo. at 40° C.	
	BABA, mg./ml.	pH	BABA, mg./ml.	pH	BABA, mg./ml.	pH
3A.....	0.11	3.80	0.10	3.75	0.09	3.68
3B.....	0.11	3.80	0.19	3.80	0.21	3.69
3C.....	0.11	3.80	0.19	3.80	0.31	3.81
3D.....	0.11	3.75	0.20	3.70	0.32	3.60
3E.....	0.11	3.70	0.30	3.65	0.34	3.58

After storage for six months at 40° C., solutions 3B, 3C, 3D and 3E remained clear and solution 3A yielded crystals when chilled for two hours in an ice bath. After storage for twelve months at 40 C., solutions 3C, 3D and 3E remained clear and solutions 3A and 3B yielded crystals when chilled for five hours in an ice bath.

Example 4

The following solution containing 0.15 percent tetracaine hydrochloride and 0.8 percent of tyloxapol was prepared:

Ingredient:	Mg./ml.
Tetracaine HCl	1.5
Sodium chloride	8.6
Calcium chloride·2H ₂ O	0.33
Potassium chloride	0.30
Tyloxapol	8.0

The anesthetic and the three inorganic chlorides were dissolved in most of the distilled water, the tyloxapol added and dissolved, the pH adjusted to 5.2 by addition of 0.1 N sodium hydroxide solution, and the remaining water added. The solution was filtered through an ultra fine frit glass filter into a sterile system and then filled into 100 ml. glass stoppered flint vials. The vials were heated at 220° F. for thirty minutes and stored at 37° C. for twelve months. Assays initially and after six and twelve months are summarized as follows:

Ingredient	Initial, mg./ml.	6 mo./37° C., mg./ml.	12 mo./37° C., mg./ml.
Tetracaine.....	1.48	1.46	1.32
Tyloxapol.....	8.0	7.6	6.6
BABA.....	0.015	0.034	0.056
pH.....	5.5	4.2	4.45

The solution after twelve months at 37° C. was clear and colorless.

Example 5

Following the procedure described in Example 2, the following solution containing 1.0 percent tetracaine hydrochloride and 0.80 percent of tyloxapol was prepared:

Ingredient:	Quantity
Tetracaine HCl	50.00
Tyloxapol	40.00
Sodium chloride	33.50
Acetone sodium bisulfite	10.00
Water for injection, q.s. ad	5000

Results of the initial assay and assays after storage at 37° C. for twelve months and at room temperature (25° C.) for twenty-three months are given as follows:

Ingredient	Initial	12 mo., 37° C.	23 mo., 25° C.
Tetracaine HCl, mg./ml.---	9.64	9.22	9.38
Tyloxapal, mg./ml.-----	7.94	8.4	8.42
BABA, mg./ml.-----	-----	0.31	0.23
pH-----	3.70	3.50	3.68

The two stored solutions were clear and colorless after the storage periods. Also, the same solution was stored for thirty-four months at 25° C., was next heated at 250° F. for twenty minutes, and, on assay, was found to contain only 0.26 mg./ml. of BABA and to have a pH of 3.70.

As noted below, this embodiment gave good results when tested clinically.

Example 6

For comparative heat stability studies, the following solutions of 1 percent tetracaine hydrochloride containing 0 and 0.8 percent tyloxapal were prepared, the former solution (6A) being a presently commercial preparation and the latter (6B) being a preferred embodiment of my invention.

Ingredient	6A	6B
Tetracaine HCl, g.-----	1.00	1.00
Tyloxapal, g.-----	-----	0.80
Sodium chloride, g.-----	0.67	0.67
Acetone sodium bisulfite, g.-----	0.20	0.20
Water for injection, ml., q.s. ad-----	100.00	100.00

These solutions were prepared following the procedure described in Example 2 and in addition to heating some of the ampulled solution at 220° F. for three minutes, as in Example 2, some of the solution was assayed with no heating and some assayed after heating for different times indicated below. My solution with tyloxapal assayed as follows:

Solution 6B	Not Heated	220° F., 3 min.	121° C., 15 min.	121° C., 30 min.	121° C., 45 min.	121° C., 60 min.
Tetracaine HCl, mg./ml.---	9.9	9.8	9.8	9.7	9.8	9.7
Tyloxapal, mg./ml.-----	8.2	8.2	8.2	8.2	8.2	8.2
BABA, mg./ml.-----	0.012	0.014	0.029	0.042	0.053	0.069
pH-----	3.35	3.15	3.15	3.15	3.15	3.15

The commercial preparation with no tyloxapal assayed as follows:

Solution 6A	Not Heated	220° F., 3 min.	121° C., 15 min.	121° C., 30 min.	121° C., 45 min.	121° C., 60 min.
Tetracaine HCl, mg./ml.---	9.7	9.8	9.9	9.8	9.7	*9.7
BABA-----	0.010	0.013	0.032	0.044	0.059	0.072
pH-----	3.40	3.70	3.70	3.60	3.60	3.50

* Crystal formation when chilled in refrigerator (about 4° C.).

From the above results, it is noted that the presence of tyloxapal did not induce the hydrolysis of the tetracaine, the BABA concentrations being about the same for the two solutions when treated the same. However, the preparation with no tyloxapal (6A) showed crystal formation when heated at 121° C. for sixty minutes and then stored in a refrigerator (about 4° C.) for a few days. In contrast, my solution (6B) even when heated at 121° C. for as long as three hours and then stored in a refrigerator for a few days showed no crystal formation.

by standard procedures and the presence of the tyloxapal in the solutions was found not to have any significant change on the local anesthetic activity, toxicity, or irritancy when compared with corresponding solutions without the tyloxapal. For example, the average duration of urethral anesthesia in rabbits was 137±9.0 minutes for 1.0 percent tetracaine hydrochloride alone and 161±19.3 minutes for 1.0 percent tetracaine hydrochloride with 1.0 percent tyloxapal; these data show that the addition of tyloxapal had slight if any effect on duration of anesthesia by tetracaine hydrochloride alone. Similarly, no significant change in local anesthetic activity occurred when 1 percent tyloxapal was added to a 0.25 or 0.50 percent tetracaine hydrochloride solution when tested by the intradermal wheal test in guinea pigs.

The acute oral toxicity in mice of tetracaine hydrochloride plus a 2 percent aqueous solution of tyloxapal was not significantly different from that of tetracaine hydrochloride in distilled water without tyloxapal. When a 25 percent aqueous solution of tyloxapal alone was studied for toxic effects in mice, no deaths occurred with oral doses as high as 10,000 mg./kg., i.e., LD₅₀ >10,000 mg./kg.

The acute intravenous LD₅₀ determinations in mice carried out with 1.0 percent tetracaine hydrochloride alone, with 1.0 percent tetracaine hydrochloride containing 1.0 percent tyloxapal, and with 0.25 percent tetracaine hydrochloride containing 1.0 percent tyloxapal were respectively: 6.7±0.7, 6.3±0.6 and 6.2±0.6 mg./kg. in terms of tetracaine hydrochloride. Thus, the addition of tyloxapal to tetracaine hydrochloride, in the concentrations studied, had no significant effect on the acute intravenous LD₅₀ for tetracaine hydrochloride in mice. When a 25 percent concentration of tyloxapal alone was studied intravenously for toxic effects in mice, the LD₅₀ was >10,000 mg./kg.

The solution embodiment of my invention described above in Example 5 (also as Examples 2E and 6B) has been studied clinically by leading anesthetists accustomed to doing spinal anesthetics. These investigators tested the solution in 420 patients ranging in age from 13 to 89 and found it to be safe and effective for its intended purpose. They obtained good results with 384 patients, fair results with 31 patients, and poor results with only 5 patients; side effects were mild and were observed in

only a small number of patients, e.g., mild hypotension (7), nausea (4), vomiting (11) and headache (1).

Other aqueous local anesthetic solutions can be prepared in accordance with the foregoing description by using, in addition to the essential ingredients of tetracaine hydrochloride and oxyethylated alkylphenol-formaldehyde polymer, other anesthetics, preservatives, buffering agents, etc., provided they are mutually compatible with the essential ingredients of the solution.

I claim:

A stabilized aqueous solution of a pharmaceutically-acceptable acid-addition salt of 2-dimethylaminoethyl 4-n-butylaminobenzoate having as the stabilizing agent tyloxapal.

tween about 0.4 to about 1.0 percent tyloxapol per 0.1 to 2 percent of said benzoate.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,272,700

September 13, 1967

Irwin S. Shupe

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, line 30, for "quantties" read -- quantities --;
column 3, line 69, fourth Table, third column, line 6, for
"0.975" read -- 0.075 --; columns 5 and 6, fourth Table,
seventh column, line 1, for "a9.7" read -- 9.7 --; same column
line 2, for "0.072" read -- a0.072 --.

Signed and sealed this 5th day of September 1967.

(SEAL)

Attest:

ERNEST W. SWIDER

Attesting Officer

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Commissioner of Patents