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<b>(21) International Application Number:</b> PCT/EP97/06071 <b>(22) International Filing Date:</b> 29 October 1997 (29.10.97) <b>(30) Priority Data:</b> P 196 47 692.5      5 November 1996 (05.11.96)      DE <b>(71) Applicant (for all designated States except US):</b> AIR LIQUIDE SANTE DEVELOPPEMENT [FR/FR]; 10, rue Cognacq Jay, F-75007 Paris (FR). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BEHREND, Sabine [DE/DE]; Datumer Chaussee 170, D-25421 Pinneberg (DE). GORONCY-BERMES, Peter [DE/DE]; Egilskamp 20, D-22145 Hamburg (DE). MOHR, Michael [DE/DE]; Kisdorfer Weg 20, D-24568 Kaltenkirchen (DE). PUCH- STEIN, Burghard [DE/DE]; Edwin-Scharff-Ring 60, D-22309 Hamburg (DE). <b>(74) Agent:</b> CONAN, Philippe; L'Air Liquide S.A., 75, quai d'Orsay, F-75321 Paris Cedex 07 (FR).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished          upon receipt of that report.</i>
<b>(54) Title:</b> WASHING DISINFECTANT FOR HYGIENIC AND SURGICAL HAND DISINFECTION  <b>(57) Abstract</b> <p>Composition comprising octenidine dihydrochloride, at least one C<sub>1</sub> to C<sub>8</sub>-alkyl alcohol, at least one surfactant chosen among non-ionic or cationic surfactants, water and optionally at least one <math>\alpha</math>-hydroxycarboxylic acid. The use for the washing disinfection of the skin, such as the washing disinfection of the hands.</p>		

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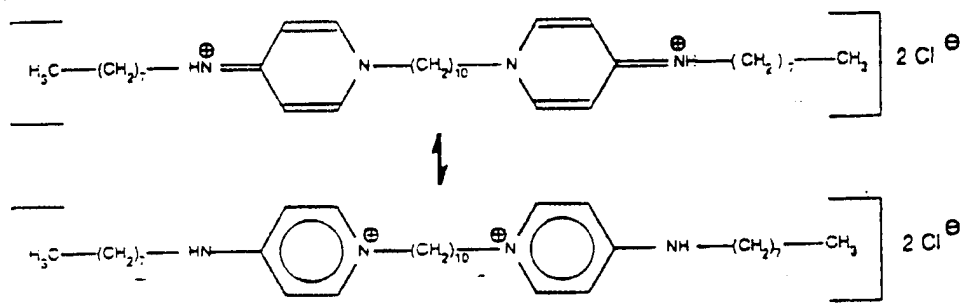
Washing disinfectant for hygienic and surgical hand disinfection

5           The importance of hand disinfection for preventing nosocomial infections in hospitals and medical practices has been undisputed since Semmelweis.

          Particularly in non-German-speaking countries, hand disinfection by washing is still very important, both in the  
10 ward and in the operating theatre. There, it is traditionally clearly preferred to the so-called rub-in method using alcoholic products, since the hands can be simultaneously cleaned and disinfected with the preparations used.

          The preparations for this field of use which are  
15 currently on the market contain, as a rule, chlorhexidine salts in a relatively large amount (4%) as residual active ingredients. The presence of such large amounts of active ingredients and the associated increased extent to which these active ingredients remain on the skin frequently result in skin  
20 intolerances which furthermore can scarcely be reduced by introducing additives. The nonionic surfactants frequently used in these preparations either have poor degradability (e.g. block polymers) or entail the potential danger of nitrosamine formation (e.g. amine oxides). For example, a commercially  
25 successful product is known which contains block polymers and amine oxides as surfactants in addition to the active ingredient chlorhexidine digluconate, which is present in a concentration of 4% by weight. It is also generally known that most members of these classes of surfactants cause the skin to dry out to an  
30 extreme extent and hence lead to poor skin tolerance of the formulations developed therefrom.

          The cationic octenidine dihydrochloride has been used to date as an antimicrobial active ingredient in various products and is considered to be very thoroughly described.



For example, octenidine dihydrochloride has proved useful for years in skin and mucous membrane preparations.

However, the use of octenidine dihydrochloride in washing preparations has been prevented to date by the fact that it has not been possible to develop an acceptably skin-friendly product suitable for hygienic and surgical hand disinfection. In particular, the surfactants used in tests have either had an adverse effect on the efficacy of the octenidine or reduce the skin-friendliness to an unacceptable level.

It is therefore the object of the invention to provide a washing hand disinfectant for hygienic and surgical hand disinfection based on octenidine, which disinfectant is substantially more skin-tolerated than the known chlorhexidine formulations and at the same time has a good antimicrobial action comparable with that of the known formulations.

This object is achieved by a composition comprising octenidine dihydrochloride at least one C<sub>1</sub> to C<sub>8</sub>-alkyl alcohol, at least one surfactant chosen among non-ionic or cationic surfactants, water and optionally at least one  $\alpha$ -hydroxy-carboxylic acid

The solution preferably comprises

- a) 0.1 to 4 % by weight of octenidine dihydrochloride,
- b) 5 to 35 % by weight of C<sub>1</sub>- to C<sub>8</sub>-alkyl alcohol,
- c) 0.5 to 45 % by weight of nonionic or cationic surfactant or a mixture thereof and
- d) 0 to 5 % by weight of  $\alpha$ -hydroxycarboxylic acid.

The amounts stated in the description are based in each case on the pure components.

By the choice of the residual active ingredient octenidine dihydrochloride, which has substantially better efficacy than chlorhexidine salts, the active ingredient concentration used in the formulation can be considerably

reduced. Furthermore, the skin intolerance occurring in the case of residual active ingredients owing to the possible, considerably lower concentration of the active ingredient is likewise greatly reduced. With the use of octenidine dihydrochloride, the active ingredient concentration can be reduced, for example, by a factor of 10 or more. Octenidine dihydrochloride is extremely suitable for the desired field of use and has in particular a long-term action in surgical hand disinfection.

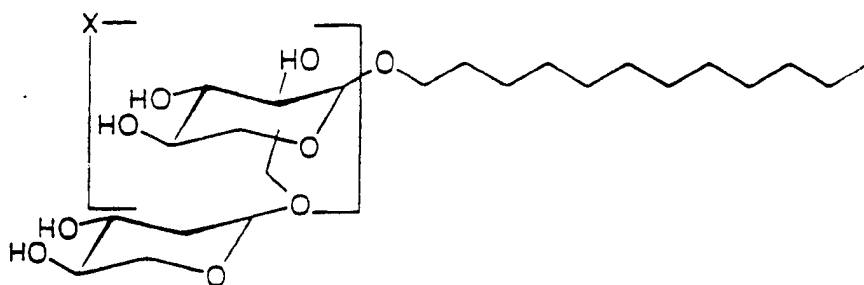
The good action of the octenidine dihydrochloride is possible, and is supported, by the additional and simultaneous use of C<sub>1</sub>- to C<sub>5</sub>-alkyl alcohols and nonionic and/or cationic surfactants which do not have the disadvantages of the abovementioned surfactants (poor degradability, nitrosamine formation) and/or do not adversely affect the efficacy of the active ingredients.

Ethanol, isopropanol or n-propanol or a mixture thereof is preferred as the C<sub>1</sub>- to C<sub>3</sub>-alkyl alcohol, preferably C<sub>1</sub>- to C<sub>6</sub>-alkyl alcohol and in particular C<sub>1</sub>- to C<sub>4</sub>-alkyl alcohol.

Nonionic surfactants preferred according to the invention are alkyl polyglycosides (APG), and cationic surfactants preferred according to the invention are quaternary betaines.

The alkyl polyglycoside is preferably a C<sub>5</sub>- to C<sub>20</sub>-alkylpolyglucoside, in particular a C<sub>8</sub>- to C<sub>16</sub>-alkylpolyglucoside, a cocoylpolyglucoside, a laurylpolyglucoside, a decylpolyglucoside or a mixture thereof being preferred.

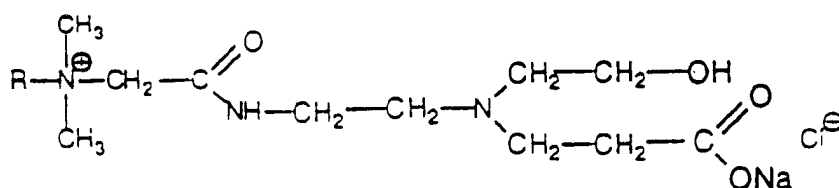
The idealized structure of the alkyl polyglycosides is as follows:



The C-chain length is 8-16 C atoms in the case of the cocoylpolyglucoside, 12-16 C atoms in the case of the

laurylpolyglucoside and likewise 8-16 C atoms in the case of the decylpolyglucoside. Examples of mixtures of alkylpolyglucoside which can also be included in the compositions of the present application are described in the patent applications published under Number EP 0 553 241, WO 9513863, FR 2 734 496.

The quaternary betaine according to the invention is preferably the N-[N' (N' '-2-hydroxyethyl-N' '-carboxyethylaminoethyl)acetamido]-N,N-dimethyl-N-cocoylammonium betaine of the formula :



R = Cocoyl

However, the group R may in general be an alkyl group having 8 to 22, in particular 12 to 18, carbon atoms.

If an  $\alpha$ -hydroxycarboxylic acid is used, the  $\alpha$ -hydroxycarboxylic acid used according to the invention is lactic acid or mandelic acid, mandelic acid being preferred. The  $\alpha$ -hydroxycarboxylic acid can also serve as a skin protection component and/or for adjusting the pH to, preferably, 2 to 7, in particular 3 to 6 and preferably about 5.

It is surprising that the good efficacy of the octenidine dihydrochloride is not influenced by the addition of the surfactants according to the invention, as has been shown to be the case, for example, as a result of the addition of ampholytic surfactants, such as cocamidopropyl betaine.

Table 1 below shows a comparison of the efficacy, in the surgical hand disinfection test according to the CEN Guideline, of this cocamidopropyl betaine-containing octenidine dihydrochloride formulation with a product which is obtainable on the market and contains chlorhexidine digluconate as the active ingredient in a concentration of 4% by weight and block polymer and amine oxide as surfactant (RF values):

**Table 1**

Chlorhexidine digluconate	Octenidine dihydrochloride
formulation + block polymer	formulation + cocamido-
+ amine oxide	propyl betaine

3 min RF = 0.99

3 min RF = 0.61

3 h RF = 0.66

3 h RF = 0.01

Furthermore, it is surprising that the skin intolerances which are known to occur with the use of nonionic surfactants do not arise. This is particularly striking in the case of the preferably used alkyl polyglycosides, the skin intolerance in the case of the APGs being greater than in the case of the quaternary betaines and the degradability in the case of the APGs being greater than in the case of the quaternary betaines and this in turn being greater than in the case of the block polymers.

Further auxiliaries may be added to the composition according to the invention, for example skin protection agents, such as allantoin in an amount of, preferably, 0.1 to 0.3% by weight, so-called refatting agents, such as polyol fatty acid esters or lauryl alcohol with 2 moles of ethylene oxide in an amount of, preferably, 0.5 to 5% by weight, conditioners, such as polyquaternary ammonium compounds in an amount of, preferably, 0.5 to 5% by weight, thickeners, such as hydroxyethylcellulose or derivatives thereof in an amount of, preferably, 0.5 to 2.0% by weight, colorants in an amount of, preferably, 0.001 to 0.1% by weight or perfumes in an amount of, preferably, 0.05 to 1.0% by weight. The stated amounts are based on the total mixture.

For example, the following basic formulations A to C may be used as washing hand disinfectant:

#### Formulation A

10	% by weight of	1-propanol
8	% by weight of	2-propanol
30	0.3 % by weight of	octenidine dihydrochloride
1	% by weight of	mandelic acid and
10	% by weight of	cocoylpolyglucose
	Remainder	water

**Formulation B**

	10	% by weight of	1-propanol
	8	% by weight of	2-propanol
5	0.3	% by weight of	octenidine dihydrochloride
	1	% by weight of	mandelic acid
	10	% by weight of	N-[N' (N' '-2-hydroxyethyl-N' '-
			carboxyethylaminoethyl)acetamido]-N,N-
			dimethyl-N-cocoylammonium betaine
10	Remainder		water

**Formulation C**

	10	% by weight of	1-propanol
	8	% by weight of	2-propanol
15	0.3	% by weight of	octenidine dihydrochloride
	1	% by weight of	mandelic acid
	10	% by weight of	laurylpolyglucoside
	Remainder		water

20           The washing hand disinfectants according to the invention are prepared by initially introducing the alkyl alcohols and dissolving octenidine dihydrochloride therein. The surfactant and the mandelic acid are then added with stirring and, if desired, stirring is continued until a clear solution is

25   obtained. The pH is adjusted to  $5.0 \pm 0.2$  with a base, such as NaOH, or an acid, such as mandelic acid.

          The efficacy of these hand disinfectants according to the invention was tested analogously to the new CEN method in comparison with the abovementioned product obtainable on the

30   market (containing chlorhexidine gluconate as active ingredient) and by a standard British method of Babb et al. (J. Hosp. Infec. (1991) 18 Supp. B, 41 - 49).

**Surgical hand disinfection with washing preparations according to a modified CEN Guideline**

35           (The modification consisted in the use of the chlorhexidine competitor product as reference solution instead of 60% strength by volume 1-propanol solution.)

40   1.   Requirements



The average reduction in the microbial hand flora by treatment of the hands with the test solution for surgical hand washing may not be significantly smaller than the germ count reduction which is achieved using the reference solution (Hibiscrub<sup>®</sup>, Zeneca). The time of use is 3 minutes. The immediate effect and the long-term effect after 3 hours are then determined.

The reduction factors are determined from the differences between the preliminary and subsequent values, usually expressed by the logarithm to the base ten:  
 $\log RF = \log \text{preliminary value} - \log \text{subsequent value}$

## 2. Test subjects

20 test subjects with healthy skin and short fingernails are required for the test.

## 3. Determination of the preliminary values

10 ml of potash soap (20% w/v) are placed in the moistened hands which must be washed according to a specific procedure. In the latter, the following washing steps are performed, each of these steps comprising 5 back-and-forth movements and optionally the hands being changed. First, the palms of the hands are rubbed together. The palm of one hand is then rubbed against the back of the other hand. Next, the palms of the hands are again rubbed together, this time the fingers of the two hands being clasped together. The backs of the fingers of one hand are then rubbed against the palm of the other hand, the fingers of the two hands hooking into one another.

Furthermore, the thumb of one hand is gripped by the other hand and, by means of rotary movements, rubbed against the palm of the hand forming the fist. Finally, the bent fingers of one hand are moved back and forth in a rotating manner in the palm of the other hand. After 30 seconds, the hands are rinsed off and dried. The preliminary values are then determined by massaging the fingertips.

## 4. Use of the reference solution

5 ml of Hibiscrub<sup>®</sup> are placed in the moistened hands which are washed according to the above scheme. After 1.5 minutes, a further 5 ml of the reference solution are pipetted onto the hands and rubbed for a further 1.5 minutes.

Thereafter, the hands are rinsed off for 15 seconds and dried with paper hand towels for the determination of the subsequent

values. One hand of the test subjects serves for determining the immediate value (3 minutes) and the other for determining the long-term action (3 hours) after wearing a glove.

#### 5. Use of the test solution

5 This procedure is carried out according to the above method for the reference solution.

The test results obtained using the compositions according to the invention are summarized in Table 2 below.

10 **Table 2**

4% of chlorhexidine digluconate + block polymer + amine oxide	0.3% of octenidine dihydrochloride + quaternary betaine	0.3% of octenidine dihydrochloride + APG
3 min 3 h	3 min 3 h	3 min 3 h
0.88 0.53	0.80 0.82	
0.88 0.53		0.92 0.75

#### **Standard British method according to Babb et al.**

##### 1. Determination of the preliminary values

15 The hands are washed, rinsed off and dried according to the scheme already described. Thereafter, a glove (Regent Biogel) is placed over each hand and filled with 50 ml of wash solution. After the gloves have been filled, the hands are massaged for 1 minute. To determine the germ count, at least 3  
20 ml of the wash solution are taken by means of a pipette.

##### 2. Use of the reference and test solutions

Reference and test solutions are used as follows:

- Wash hands for 30 seconds with potash soap
- Rinse off for 15 seconds
- 25 • Pipette 5 ml of solution into the hands and rub
- Brush each hand, including fingernails, for 15 seconds
- Wash hands and lower arm for 15 seconds
- Rinse off for 15 seconds
- Pipette 5 ml of solution into the hands and wash for 2 minutes  
30 according to the scheme already described
- Rinse off for 15 seconds
- Dry hands with paper hand towels

One hand of the test subjects serves for determining the immediate value (3 minutes) and the other for determining the

long-term action (3 hours) after wearing a glove. Germ recovery for determining the subsequent values is carried out as for the calculation of the preliminary values with the aid of gloves which are placed over the hands and filled with 50 ml of wash solution. After the hands have been massaged (1 minute), at least 3 ml are taken and are used for determining the germ count.

The test results obtained are summarized in Table 3 below.

Table 3

<u>4% chlorhexidine digluconate</u>		<u>0.3% octenidine dihydro-</u>	
<u>+ block polymer + amide oxide</u>		<u>chloride + APG</u>	
2 min 45 sec	3 h	2 min 45 sec	3 h
0.91	1.16	0.78	1.21

The efficacies of the preparations compared are approximately the same. However, the preparations according to the invention are better in terms of their skin tolerance.

## Claims

1. Composition comprising octenidine dihydrochloride, at  
5 least one C<sub>1</sub> to C<sub>8</sub>-alkyl alcohol, at least one surfactant chosen  
among non-ionic or cationic surfactants, water and optionally at  
least one  $\alpha$ -hydroxycarboxylic acid.
2. Composition according to Claim 1, characterized in that  
it comprises :
- 10 a) 0.1 to 4% by weight of octenidine dihydrochloride,  
b) 5 to 35% by weight of C<sub>1</sub>- to C<sub>8</sub>-alkyl alcohol,  
c) 0.5 to 45% by weight of nonionic or cationic surfactant or a  
mixture thereof and  
d) 0 to 5% by weight of  $\alpha$ -hydroxycarboxylic acid.
- 15 3. Composition according to Claims 1 or 2, characterized in  
that it comprises :
- a) 0.1 to 2% by weight of octenidine dihydrochloride,  
b) 10 to 30% by weight of C<sub>1</sub>- to C<sub>8</sub>-alkyl alcohol,  
c) 0.5 to 20% by weight of nonionic or cationic surfactant or a  
20 mixture thereof and  
d) 0.1 to 2% by weight of  $\alpha$ -hydroxycarboxylic acid.
4. Composition according to Claims 1, 2 or 3 characterized  
in that it comprises :
- a) 0.1 to 0.5% by weight of octenidine dihydrochloride,  
25 b) 10 to 20% by weight of C<sub>1</sub>- to C<sub>8</sub>-alkyl alcohol,  
c) 5 to 15% by weight of nonionic or cationic surfactant or a  
mixture thereof and  
d) 0.5 to 1.5% by weight of  $\alpha$ -hydroxycarboxylic acid.
5. Composition according to any of Claims 1 to 4,  
30 characterized in that the C<sub>1</sub> to C<sub>8</sub>-alkyl alcohol is a C<sub>1</sub> to C<sub>6</sub>-  
alkyl alcohol.
6. Composition according to claim 5, wherein the C<sub>1</sub> to C<sub>6</sub>-  
alkylalcohol is a C<sub>1</sub> to C<sub>4</sub>-alkyl alcohol, such as éthanol,  
propanol or isopropanol or a mixture thereof.
- 35 7. Composition according to any of claims 1 to 6 wherein  
the non-ionic surfactant is a C<sub>8</sub>- to C<sub>20</sub>-alkylpolyglucoside or a  
mixture thereof, in particular a C<sub>8</sub>- to C<sub>16</sub>-alkylpolyglucoside or  
a mixture thereof and preferably a cocoylpolyglucoside, a  
laurylpolyglucoside, a decylpolyglucoside or a mixture thereof.

8. Composition according to any of claims 1 to 7 wherein the cationic surfactant is N-[N' (N' '-2-hydroxyethyl-N' '-carboxyethylaminoethyl)acetamido]-N,N-dimethyl-N-cocoylammonium betaine.

5 9. Composition according to any of claims 1 to 8 wherein the  $\alpha$ -hydroxycarboxylic acid is mandelic acid or lactic acid.

10. Composition according to any of Claims 1 to 9, characterized in that it comprises :

10 % by weight of 1-propanol

10 8 % by weight of 2-propanol

0.3 % by weight of octenidine dihydrochloride

1 % by weight of mandelic acid

10 % by weight of cocoylpolyglucoside.

11. Composition according to any of Claims 1 to 9, characterized in that it comprises :

10 % by weight of 1-propanol

8 % by weight of 2-propanol

0.3 % by weight of octenidine dihydrochloride

0.5 % by weight of lactic acid

20 10 % by weight of cocoylpolyglucoside.

12. Composition according to any of Claims 1 to 9, characterized in that it contains

10 % by weight of 1-propanol

8 % by weight of 2-propanol

25 0.3 % by weight of octenidine dihydrochloride

1 % by weight of mandelic acid

10 % by weight of laurylpolyglucoside.

13. Composition according to any of Claims 1 to 9, characterized in that it comprises :

30 10 % by weight of 1-propanol

8 % by weight of 2-propanol

0.3 % by weight of octenidine dihydrochloride

1 % by weight of mandelic acid

35 10 % by weight of N-[N' (N' '-2-hydroxyethyl-N' '-carboxyethylaminoethyl)acetamido]-N,N-dimethyl-N-cocoylammonium betaine.

14. Composition according to any of Claims 1 to 13, characterized in that the pH is in the range from 3 to 6.

15. Composition according to any of claims 1 to 14 which  
40 further comprises one or more compounds chosen among the skin

protection agents, the refatting agents, the conditioners, the thickeners, the colorants and the perfumes.

16. Process for the preparation of a composition according to any of Claims 1 to 15, characterized in that the alkyl  
5 alcohols are initially introduced, octenidine dihydrochloride is dissolved therein and the surfactant and optionally the  $\alpha$ -hydroxycarboxylic acid are then added with stirring.

17. Process according to Claim 16, characterized in that stirring is continued after mixing with the components until a  
10 clear solution is obtained.

18. Process according to Claim 16 or 17, characterized in that the pH is adjusted by means of NaOH or the  $\alpha$ -hydroxycarboxylic acid.

19. The use of a composition as claimed in any of Claims 1  
15 to 14 as a disinfectant.

20. The use according to claim 19 for the washing disinfection of the skin, such as the washing disinfection of the hands.

21. The use according to claim 19 or 20 for the hygienic and  
20 surgical hand disinfection.