Antiseptic compositions having both rapid and residual persistent biocidal activity, comprising an iodine complex with a bacteriostat exhibiting synergistic antimicrobial activity and good shelf stability. The compositions find a use as antiseptic skin cleansers, antiseptic solutions for use under plaster casts and dressings, antiseptic lotions for skin disinfection, preoperative skin washers and shower preparations, shampoos, medicated after-shave preparations, tinea preparations, hospital laundry rinsers, nappy (diaper) sanitisers, surface sprays, foot-rot preparations and animal shampoos.
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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DESCRIPTION

ANTISEPTIC COMPOSITIONS

TECHNICAL FIELD

The present invention relates to antiseptic compositions which have both a rapid and residual antimicrobial and antiviral action. More particularly, the invention relates to compositions containing an iodophor which has a rapid action together with one or more agents having a residual antibacterial and/or antiviral action.

The compositions of the invention find use in medical applications such as antiseptic skin cleansers, antiseptic solutions for use under plaster casts and dressings, antiseptic lotions for skin disinfection, e.g. prior to surgery or first aid procedures, preoperative skin wash and shower preparations, shampoos, medicated after-shave preparations, tinea preparatons, hospital laundry rinses, nappy (diaper) sanitisers and surface sprays.

Agricultural/veterinary applications in which the compositions of the invention find use include preparations for treatment and prophylaxis of foot rot and animal shampoos.

It has been surprisingly discovered that some synergism occurs between the iodophor and the residual antibacterial antiviral agent.

BACKGROUND ART

There is continuous demand by surgeons and members of the medical profession for a practical method of handcleansing other than using only soap and water, but which would provide additionally to the cleansing of the skin, rapid disinfection combined with residual protection against immediate re-infection.

A desirable hand and skin cleansing composition would be one which would combine, additionally to the effective cleansing of the skin, rapid disinfection and protection against subsequent re-infection.

Iodine, because of its exceptional biocidal properties has long been a favoured germicidal ingredient for skin cleansing compositions.
The advantages of iodine in combination with iodine carriers resulting in complex formation, having available iodine as active biocidal constituent, over previous iodine preparations having the iodine solubilised by forming the triiodide with an alkali or hydrogen iodide, such as tincture of iodine or Lugol's solution, are well known and as exemplified in US Patent No 3 777 022.

Iodine, in its complex formation, especially in combination with polyvinylpyrrolidone, known as povidone-iodine, has, because of its rapid action and wide microbial spectrum been used as the active germicidal ingredient in various brands of antiseptic skin cleansers for pre-operative scrub-up and general ward use.

Despite the great advantages of these antiseptic hand and skin cleansing products over others, not containing iodine, they suffer from the disadvantage, that once used, they leave the skin with no residual prophylactic protection against re-infection.

Other germicides such as the quaternary ammonium compounds or chlorhexidine salts, although not quite as fast acting as the iodophors, have found wide application in various antiseptic preparations.

Although such other germicides do not possess the wide microbial spectrum of the iodophors, and are not equally active against the various strains of Gram-positive and negative micro-organisms, they do provide a persistant antibacterial effect on the skin after application.

Bacteriostats form a third group of antimicrobial agents which have found wide use in skin and handwashing preparations. They have a high affinity to the skin and confer remanent antibacterial properties, which continue to build up on repeated application, eventually conferring a complete shield on the skin against re-infection. They also reduce the resident bacterial flora of the skin to a minimum, which is not removed by the conventional antibacterial agents mentioned previously.
The importance of combining a fast acting broad spectrum biocide such as the iodine complex lacking persistent action after application with an agent providing residual and continuous anti microbial activity is self evident.

This is true in a wider sense of all applications where rapid disinfection of any surface is required and persistent protection against re-infection is desired, even if only for a limited time.

This is of special importance for medical personnel when an antiseptic hand and skin cleansing preparation combining an iodine complex with a bacteriostat with residual properties allows the immediate disinfection of the skin and additionally provides an antibacterial shield against possible re-infection.

The provision of an antiseptic composition combining even, rapid biocidal action over practically the complete microbiological spectrum, combined with remanent antibacterial effectiveness present therefore an important advance in the technique of hand and skin sanitation and disinfection of surfaces in general.

Various attempts have been made to combine bacteriostats with iodine in disinfectant solutions. Most of these have been unsuccessful, as due to possible reaction between iodine and the bacteriostat component of the preparation shown by considerable loss of iodine occurring on standing. Such attempts have been described in U.S. Patent No. 3 777 022 and Canadian Patent No. 729 597.

DESCRIPTION OF THE INVENTION

The present invention provides an antiseptic composition comprising at least one iodine complex and at least one residual antibacterial agent together with a pharmaceutically, veterinary, or agriculturally acceptable carrier or diluent therefore.

In the specification and claims, the term iodine complex is a complex of iodine with polyvinylpyrrolidone known also as povidone-iodine, or nonionic surfactants of the general formula

\[
R(CH\_CH\_0)\_H
\]

\[
2 \_ 2 \_ x
\]
where \( R \) represents and alkylphenol, a fatty alcohol or acid residue and \( x \) is 6 to 100, and preferably 7 to 15, or polycondensates of ethylene oxide and propylene oxide of a molecular weight of not less than 1000, preferably between 2500 and 4000. Such complexes have because of their rapid action and wide microbicidal spectrum become the active germicidal ingredient in various brands of antiseptic skin cleansers for pre-operative scrub-up, general medical and household antiseptic preparations, veterinary uses and disinfectant cleansers for the food and allied industries. Iodine complexes with amphoteric surface active agents and quaternary ammonium compounds are also included in the definition.

The preferred complex of iodine and polyvinylpyrrolidone has 10% available iodine and a K-value of 30.

Other suitable iodine complexes include nonylphenoxy- (ethyleneoxy)-iodine, polyethyleneoxypropyleneoxy-iodine and undecyltrimonium-chloride-iodine, as well as the other commercially available products.

Suitable bacteriostats which may be employed in compositions of the invention include halogenated hydroxydiphenyl derivatives or halogenated salicyl and carbanilides.

Examples of these bacteriostats are those of the formula

\[
\begin{align*}
\text{I} \\
\begin{array}{c}
R_7 \\
R_8 \\
R_9 \\
R_1 \\
R_2 \\
R_3 \\
R_4 \\
R_5 \\
R_6 \\
R_7 \\
R_8 \\
R_9 \\
\end{array}
\end{align*}
\]

wherein each of \( R_1 \) to \( R_9 \) may be hydrogen, halogen, lower alkyl, haloloweralkyl, lower alkoxy, allyl, cyano, amino or acetyl and the O-acyl derivatives thereof provided that at least one of \( R_1 \) to \( R_9 \) is halogen:

\[
\begin{align*}
\text{II} \\
\begin{array}{c}
X_7 \\
X_8 \\
X_9 \\
X_{10} \\
X_1 \\
X_2 \\
X_3 \\
X_4 \\
X_5 \\
X_6 \\
\end{array}
\end{align*}
\]
wherein each of $X_1$ to $X_{10}$ may be hydrogen, halogen, haloalkyl, nitro or alkoxy provided that at least one of $X_1$ to $X_9$ is halogen:

![Chemical Structure](image1)

wherein each of $Y_1$ to $Y_9$ is hydrogen or halogen, provided that at least two of $Y_1$ to $Y_9$ are halogen; and

![Chemical Structure](image2)

wherein each of $Z_1$ to $Z_9$ may be hydrogen or halogen provided that there is at least two halogen substituents on each Phenyl ring.

Such compounds are disclosed in Australian Patents Nos. 200 868, 209 986, 236 460, 273 941, 278 661 and 283 658 and in US Patent Nos. 2 250 840, 2 967 885, 3 254 121, 3 057 920 and 3 064 048.

Examples of the preferred bacteriostats include 2,4,4'-trichloro-2'-hydroxydiphenyl ether (triclosan); 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane systematic name (hexachlorophene); 3,5,4'-tribromosalicylanilide (tribromosalan) and 3,4,4'-trichloro- or 3-trifluoromethyl-4,4'-dichloro-carbanilides (triclocarban and cloflucarban). Triclosan is preferred for carrying out the invention.

It is preferred that the compositions of the invention contain a greater amount by weight of available iodine than of bacteriostat.

It is preferred that the iodine complexes are present in the compositions of the invention so as to provide from 0.01 to 5.0% w/v especially 0.35 to 2.0% w/v available iodine. It is preferred that the compositions contain 0.01 to 3.0% w/v, especially 0.5 to 2.0% w/v of the bacteriostats.
It is further preferred that if one or more surfactants should be part of the composition according to the invention, one at least should be a nonionic surface agent.

Antiseptic compositions of the invention remain stable at temperatures below 25°C over considerable time of up to two years in the absence of light.

The combined biocidal activity of the available iodine and the bacteriostat is greater against certain bacteria than could be expected from the values of the biocidal strength of the separate iodine or bacteriostat components added together.

The cumulative effect of the iodine complex and bacteriostat is shown by minimum inhibitory tests in vitro by serial dilutions using Difco AOAC medium and illustrated by the following table:

<table>
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<th>Triclosan 1.0% w/v in a detergent solution</th>
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<tr>
<td>E.coli 6.4 x 10⁹</td>
</tr>
<tr>
<td>Staph.aureus 6.3 x 10⁹</td>
</tr>
<tr>
<td>P.valgaris 6.0 x 10⁹</td>
</tr>
<tr>
<td>Ps.aeruginosa</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Povidone-Iodine 0.75% av.iodine in same detergent solution</th>
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</thead>
<tbody>
<tr>
<td>E.coli 6.4 x 10⁷</td>
</tr>
<tr>
<td>Staph.aureus 6.3 x 10⁹</td>
</tr>
<tr>
<td>P. Vulgaris 6.0 x 10⁹</td>
</tr>
<tr>
<td>Pr.aeruginosa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Povidone-Iodine 0.5% and Triclosan 1.0% w/v in same</th>
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</thead>
<tbody>
<tr>
<td>E.coli 6.4 x 10⁹</td>
</tr>
<tr>
<td>Staph.aureus 6.3 x 10⁹</td>
</tr>
<tr>
<td>Ps.vulgaris 6.0 x 10⁹</td>
</tr>
<tr>
<td>PS.aeruginosa 6.0 x 10⁹</td>
</tr>
</tbody>
</table>

+ = bacterial growth
- = no growth
Where surface active agents are used to supply the necessary detergency in compositions where detergency is needed, they must not only be saturated compounds but also be stable in solution having a pH less than 6 to avoid separating from solution on prolonged standing. Hand cleansers of the invention retain satisfying foaming properties at the pH of the composition. Although the pH of the composition can range for practical reason between 2 to 6, it is preferable to select a pH between 4 to 5 for skin cleansers and antiseptics and around 2 for surface disinfectant cleansers.

Suitable surface active agents are nonionics such as the nonylphenolpolyethoxy condensates, the alkali, ammonium and triethanolamine salts of phenoxy-or alkylxypolyoxyethylene sulfonates, or polycondensates with ethylene oxide and propylene oxide, used on their own, or mixtures thereof.

It is advantageous to use, in conjunction with the surfactants, foaming agents such as the fatty acid diethanolamides or an alkylidimethylamine oxide such as a lauryldimethylamine oxide, lauryldiethanolamide being preferred.

The bacteriostat is suitably added in a common solvent such as ethanol, isopropanol or propylene glycol or directly, provided the composition has sufficient solubilising power to keep the bacteriostat in solution.

According to the various compositions and their different applications, various ingredients will have to be added to give the composition additional desired properties. Care has to be taken in the choice of such ingredients to assure that they will be compatible with the iodine complex and not affect its stability.

If desired, glycerine or other emollients commonly used in hand and skin cleansing preparations can be added, provided they are compatible with the iodine complex and bacteriostat used in the composition.
MODES FOR CARRYING OUT THE INVENTION

The following examples illustrate preferred embodiments of the present invention. They should not be construed as limiting the claims hereto. The ingredients are combined by standard cold mixing processes.

EXAMPLE 1

ANTISEPTIC SKIN AND HAND CLEANSER

iodine complex * 4.0g
nonionic surfactants ** 5.0g
sodiumlauryl ethoxysulfate *** 20.0g
lauryldimethylamineoxide **** 5.0g
glycerol 1.0g
trichlocarban 2.0g
propanol 5.0mL
phosphoric acid to adjust to pH 4.5
water to make 100.0mL

* (Antarox VRO 20 available from GAF Corp. USA)
** (Antarox CO 730 available from GAF Corp. USA)
*** (Empigen 5Q25 available from Albright & Wilson Inc.)
**** (Empigen OB available from Albright & Wilson Inc.)
EXAMPLE 2
SANITISING CLEANSE

povidone-iodine, containing 10.0% w/v available
iodine 7.5g
sodium salt of sulphonated alkylphenoxy poly
(ethylenecoxy)ethanol * 20.0g
lauryldiethanolamide 2.0g
glycerol 1.0g
triclosan 0.5g
isopropanol 10.0mL
phosphoric acid to adjust to pH 4.5
water to make 100.0mL

* (Fenopan Co., available from GAF Corp. USA)

The bacteriostat is dissolved in the isopropanol prior
to mixing with the other ingredients.

EXAMPLE 3
ANTISEPTIC SOLUTION

povidone-iodine, containing 10.0% w/v available
iodine 10.0g
ethanol isopropanol mixture 2:1 40.0mL
tribromsalan 0.25g
nonionic surfactant 0.50g
phosphate-citrate buffer to adjust to pH 4.5
water to volume 100.00mL

The triclosan is dissolved in the alcohol mixture prior
to mixing.
EXAMPLE 4
ANTISEPTIC TINCTURE

povidone-iodine, containing 10.0% w/v available
iodine 5.0g
lanogel 61* 0.25g
ethanol 70.00mL
triclosan 0.25g
phosphate-citrate buffer to adjust to pH 4.5
Water to volume 100.0mL

* Nonionic lanolin derived surfactant (Amerchol Corp. New Jersey USA)

EXAMPLE 5
PREOPERATIVE SKIN WASH & SHOWER PREPARATION

povidone-iodine, containing 10.0% w/v available
iodine 10.0g
nonionic surfactant 5.0g
sodium laurylthoxysulfate* 30.0g
Coconutdiethanolamide 2.0g
propylene glycol 10.0mL
triclosan 1.0g
phosphoric acid to adjust to pH 4.5
Water to volume 100.0mL

* (Empigen 5Q25 available from Albright & Wilson Inc.)

The PVP-I and the sodium lauryl and coconutdiethanolamide were dissolved in water and triclosan dissolved in the propylene glycol was added slowly with efficient stirring. The pH was adjusted and the composition adjusted to final volume with water.
EXAMPLE 6
MEDICATED AFTER SHAVE

povidone-iodine, containing 10.0% w/v available iodine 0.5g
Glucan E 10* 4.0g
Glucan P 20* 3.0g
ethanol 45.0mL
propylene glycol 10.0mL
triclosan 0.01g
triclocarban 0.01g
glycerin 2.5g
phosphate-citrate buffer to pH 5.5
perfume, colour q.s
water to volume 100.0mL

* [nonionicpropoxylated glucose derivate (Amerchol Corp.
New Jersey, U.S.A.)]

EXAMPLE 7
TINEA TREATMENT

povidone-iodine, containing 10.0% w/v available iodine 10.0g
polyethylene glycol 400 60.0g
polyethylene glycol 4000 25.0g
triclosan 0.5g
water 4.0g

The mixture of the polyethylene glycols was heated to 45°C and the triclosan dissolved with slight stirring followed by the PVP-I. The clear melt was left to cool slowly until a creamy consistency was obtained. The ointment like product is then ready for packing.
EXAMPLE 8
TREAT DIP - for mastitis prophylaxis

iodine complex * 2.5g
glycerin 4.0g
propylenglycol 3.0mL
triclosan 0.5g
phosphate-citric buffer to pH 4.0
water to volume 100.0mL

* (Antarox VRO 20 available from GAF Corp. USA)

EXAMPLE 9
DOG SHAMPOO

iodine complex * 5.0g
nonionic surfactant 5.0g
sodium lauryl ethoxy sulfate 20.0g
coconutdiethanolamide 2.0g
propylene glycol 5.0g
hexachlorophene 0.5g
phosphoric acid to adjust to pH 4.0
water to volume 100.00mL

* (Antarox VRO 20 available from GAF Corp. USA)

EXAMPLE 10
BATH PREPARATION FOR PRE-OP AND DERMATOLOGICAL CONDITIONS

iodine complex * 10.0g
nonionic surfactant 10.0g
triclosan 1.75g
sodium laurylethoxy sulphate 40.0g
coconutdiethanolamide 5.0g
citric acid to adjust to pH 4.5
water to make 100.00mL

* (Antarox VRO 20 available from GAF Corp. USA)
COMPARATIVE EXAMPLE 1

An aqueous cleansing solution containing 7.5% povidone-iodine (0.94% w/v available iodine) was divided into two parts, whereby to one part thereof was added 2.0% of triclosan.

After standing for two years at ambient temperatures both products showed identical small losses of available iodine, demonstrating that no reaction between the bacteriostat and the iodine had occurred.
1. An antiseptic composition comprising at least one iodine complex and at least one residual antibacterial agent together with a pharmaceutically, veterinary, or agriculturally acceptable carrier or diluent therefore.

2. A composition as defined in claim 1 wherein the iodine complex is a complex between iodine, and polyvinylpyrolidone or a polycondensate of ethyleneoxide with propyleneoxide, alkylphenols, fatty alcohols, fatty acids, quaternary ammonium compounds or amphotericics surface active agent.

3. The composition as defined in claim 2 wherein the iodine complex is povidone-iodine.

4. A composition as defined in claim 1, wherein the bacteriostat is a halogenated hydroxydiphenyl derivative, a halogenated salicylanilide or a halogenated carbanilide.

5. A composition as defined in claim 4, wherein the bacteriostat is 2,4,4'-trichloro-2'-hydroxydiphenyl ether, 2,2'dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane, 3,5,4'-tribromosalicylanilide, 3,4,4'-trichlorocarbanilide, or 3-trifluoromethyl-4,4'-dichlorocarbanilide.

6. A composition as defined in claim 4, wherein the bacteriostat is 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

7. A composition as defined in claim 1, further comprising a saturated surface active agent stable in solution having a pH less than six.

8. A composition as defined in claim 7, wherein the surface active agent is a nonylphenolpolyethoxy condensate or an alkali ammonium or triethanolamine salt of a phenoxy- or alkylxypolyoxyethylene sulfonate or a polycondensate of ethylene oxide and propylene oxide or a mixture of two or more thereof.

9. A composition as defined in claim 7, further comprising a foaming agent.

10. A composition as defined in claim 9 wherein the foaming agent is a fatty acid diethanolamide or alkyldimethylamine oxide.
11. A composition as defined in claim 1, having a pH-value less than 7.
INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 86/00069

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int. Cl. | A01N 59/12,  A61K 33/18, C11D 3/48 |

II. FIELDS SEARCHED

Classification System  

| IPC | A01N 59/12, A61K 33/18, 27/00, 7/50 |
| US Cl. | 424/150 |

Minimum Documentation Searched

* AU : IPC as above; Australian Classification 87.16 |

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>AU,B, 40487/68 (436196) (WEST LABORATORIES, INC.) 28 May 1973 (28.05.73)</td>
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<td>AU,B, 2412/51 (156301) (GENERAL ANILINE &amp; FILM CORPORATION) 3 May 1954 (03.05.54)</td>
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* Special categories of cited documents:  

d"X" document defining the general state of the art which is not considered to be of particular relevance  

d"E" earlier document but published on or after the international filing date  

d"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  

d"O" document referring to an oral disclosure, use, exhibition or other means  

d"P" document published prior to the international filing date but later than the priority date claimed  

"X" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step  

"X" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art  

"X" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search  

20 June 1986 (20.06.86)

Date of Mailing of this International Search Report  

01-07-86, 01 JULY 1986

International Searching Authority  

Australian Patent Office

Signature of designated officer  

R.M.F. BOYS

Form PCT/ISA/210 (second sheet) (January 1985)
ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 86/00069

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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