



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)-

(51) International Patent Classification ⁴ : A01N 25/22, 59/00	A1	(11) International Publication Number: WO 87/ 03779 (43) International Publication Date: 2 July 1987 (02.07.87)
(21) International Application Number: PCT/SE86/00576 (22) International Filing Date: 16 December 1986 (16.12.86) (31) Priority Application Number: 8506072-1 (32) Priority Date: 20 December 1985 (20.12.85) (33) Priority Country: SE (71) Applicant (for all designated States except US): BIOGRAM AB [SE/SE]; Box 260, S-201 22 Malmö (SE). (72) Inventors; and (75) Inventors/Applicants (for US only) : EKMAN, Bo, Magnus [SE/SE]; Månstigen 9, S-216 19 Malmö (SE). KJELLBERG, Bengt, Erik, Sigvard [SE/SE]; Jerrestadsvägen 5, S-245 00 Staffanstorps (SE). LARSSON, Kåre, Viktor [SE/SE]; Trollsjövägen 50, S-237 00 Bjärred (SE). LINDAHL, Åke, Rikard [SE/SE]; Ringduvevägen 50, S-274 00 Skurup (SE).		(74) Agents: BURMAN, Tore et al.; Bergling & Sundbergh AB, Box 7645, S-103 94 Stockholm (SE). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report.</i>
(54) Title: STABILIZED HYDROGEN PEROXIDE COMPOSITION, PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF (57) Abstract A stabilized aqueous hydrogen peroxide composition comprising an aqueous dispersion, which based on the total weight of the composition contains 0.1 - 4 percent by weight of hydrogen peroxide and 0.5 - 15 percent by weight of β-crystals of one or more lipids selected among monoglycerides of fatty acids, ascorbic acid, phosphate or lactic acid esters of fatty acids and monoglycerol ethers, said fatty acids and ether chains, respectively being saturated and having 12 - 18 carbon atoms. The composition is manufactured by firstly forming in an aqueous mixture the β-crystals and then adding the hydrogen peroxide, preferably in the form of an aqueous solution thereof. The invention also relates to the use of the composition as a teat immersion composition for milk-producing animals.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland				

A stabilized hydrogen peroxide composition,
process for the preparation thereof and the use
thereof.

TECHNICAL FIELD

5 The present invention is within the field of stabilized
aqueous hydrogen peroxide compositions, i.e. compositions
wherein the strong tendency of decomposition of the hydrogen
peroxide is reduced or inhibited by the presence of a stabil-
10 izing agent. Such stabilized compositions are previously
known per se, but the novel and characteristic in connection
with the present invention is that the stabilizing agent is
present in essentially much more reduced concentrations than
according to the prior art, which gives an aqueous dispersion
15 having a completely different consistency than that of the
prior art products. This in turn opens up possibilities of
completely novel applications in which the antimicrobial ef-
fects of the hydrogen peroxide which are known per se are
utilized. Furthermore, the invention relates to a process for
the preparation of the novel composition as well as to a spe-
20 cial use thereof, viz. as a teat dipping or immersion compo-
sition intended for milkproducing animals.

BACKGROUND OF THE INVENTION

25 It is previously known that hydrogen peroxide can be
stabilized by β -crystals of 1-monolaurin and 1-monomyristin
in an aqueous medium. Thus, e.g. PCT/SE82/00061 discloses a
germicidal aqueous composition wherein hydrogen peroxide has
been stabilized by means of 1-monolaurin or a mixture of 1-
monolaurin and 1-monomyristin. The hypothesis or theory re-
30 ferred to as an explanation of the reaction-inhibiting effect
means that the hydrogen peroxide would be bonded or attached
to the crystal surfaces. Consequently, in order to obtain a
stable system the number of moles of monoglyceride is in par
with or equal to the number of moles of hydrogen peroxide. In
35 practice this means that the composition disclosed in said
PCT publication is of such a consistency that it must be uti-
lized in the form of an ointment.

In connection with the prior art it can also be added that so called β -crystals and the technique by means of which such can be obtained is also previously known, e.g. from the above mentioned PCT publication and from GB 1,174,672. Thus, those β -crystals which are referred to according to the present invention are hydrophilic crystals from polar lipids, i.e. having hydrophilic dominating surfaces, and further details concerning the crystals can be found within the known art, i.e. inter alia from the above-mentioned two references.

SUMMARY OF THE INVENTION

According to the present invention it has turned out that hydrogen peroxide can be stabilized in an aqueous medium in the presence of β -crystals of certain lipids, wherein the amount or proportion of said β -crystals is considerably much lower than according to the prior art, more specifically at least 10 times lower and generally approximately 30 times lower. This means essential advantages as compared to the known ointment base through the fact that in principle the consistency of the obtained composition is a liquid instead of an ointment, and the stabilizing effect which is obtained by the invention is extremely unexpected in view of the previously known hypotheses. Thus, these do not suggest any possibility of stabilizing hydrogen peroxide by means of such a low concentration of β -crystals which is now utilized. The unexpected effect obtained by the invention seems to indicate, the invention however not being limited to said theory, that surfaces of the β -crystals bind or inactivate some of the intermediates in the decomposition of hydrogen peroxide. Such a theory might explain why autocatalysis does not take place and why that low proportions of crystals can stabilize hydrogen peroxide. Through the fact that the autocatalysed decomposition of hydrogen peroxide is inhibited, the hydrogen peroxide can for instance be made compatible with several normally oxidation sensitive substances, such as e.g. polymers of a biological origin, surface active substances and others. A specially interesting use of the composition, which

will also be disclosed more in detail below, is also the test immersion composition referred to above.

More specifically the stabilized aqueous hydrogen peroxide composition according to the invention is characterized in that it comprises an aqueous dispersion which, based on the total weight of the composition, contains 0.1 - 4 percent by weight of hydrogen peroxide, and 0.5 - 15, preferably 0.5 - 10, percent by weight of β -crystals of one or more lipids chosen among monoglycerides from fatty acids, ascorbic acid, phosphate or lactic acid esters from fatty acids and monoglycerol ethers, said fatty acids and ether chains being saturated and having 12-18 carbon atoms.

The composition referred to above in connection with the composition claimed is based on those ingredients which are essential and interesting to the invention. Of course the hydrogen peroxide composition claimed can, however, also contain other additives which do not interfere with the stabilization of the hydrogen peroxide which is accomplished according to the invention and which are previously known per se in connection with hydrogen peroxide compositions and/or in those applications for which the composition claimed is intended or suited. However, there is no need to disclose these more in detail herein.

Thus, the concentration of hydrogen peroxide in the composition is generally within the range of 0.1 - 4 percent by weight, the specific use in each single case being decisive of the exact amounts of hydrogen peroxide to be used. This is within what can be easily determined by a person skilled in the art based on the prior art. However, an especially preferable concentration range for certain interesting applications according to the invention is 0.1 - 2 percent by weight and in many cases 0.2 - 1 percent by weight, which percentages are also based on the total composition claimed as defined above.

As concerns the proportion of β -crystals it is chosen within the above-mentioned range of 0.5 - 15, especially 0.5 - 10, percent by weight dependent on the stability which is

desired for the hydrogen peroxide composition in each single case. Thus, in this connection stability is not any unambiguous and well-defined term but in principle it may mean each and every minor improvement of the resistance against decomposition as compared to an aqueous composition which is completely free from any stabilizing agent. However, for many uses stability means that the concentration of hydrogen peroxide is not changed with more than $\pm 5\%$ for a period of approximately 1 year. According to the invention it has been shown that in many cases such an effect can be obtained within the concentration range of 1-5 percent by weight, which is, thus, preferable in many cases, and an especially interesting range in certain cases can be 1-3 percent by weight.

With reference to the theory and the practice in connection with the preparation of the hydrophilic β -crystals which are used in the composition according to the invention reference is made to the above-mentioned prior art. However, the group of substances which is referred to in connection with the invention is the above-mentioned group. The monoglyceride used may be an 1- or 2-monoglyceride or an equilibrium mixture that is obtained in the manufacture according to a molecular distillation with about 90% of 1-mono- and 10% of 2-monoglyceride, preferable compounds within said group, e.g. 1-compounds, being monolaurin, monomyristin, monopalmitin and monostearin or a mixture of two or more of these. Especially preferable are monolaurin or a mixture of monolaurin and monomyristin, wherein the proportion of monolaurin is at least 10 percent by weight.

The decomposition of hydrogen peroxide is catalyzed also by metal ions, such as e.g. Fe and Cu. These metal ions may be present in the water which is used in the manufacture or may be dissolved from metal parts of the equipment. However, according to the present invention it has been shown that combinations between a complex forming agent and β -crystals of the type referred to above are advantageous for the stability of hydrogen peroxide in the presence of metal ions. More specifically the effect of said combination or mixture

is much greater than the sum of the effects of the separate ingredients, i.e. a synergistic effect is obtained.

Therefore, a preferable composition according to the invention is a composition which contains a metal ion complex forming agent in an amount that enhances the stability of the hydrogen peroxide in the presence of said metal ion.

The type of complex forming agent is selected in accordance with previously known principles, i.e. in dependency of what metal ion(s) is (are) present within the system. However, as examples of especially interesting complex forming agents there can be mentioned EDTA (ethylene diamine tetraacetic acid), citric acid, ascorbic acid and different phosphonic acids.

Nor is it possible to say anything general about the proportion of the complex forming agent in the composition claimed. Thus, it is dependent on the proportion of metal ions present in the system, which means that the proportion of the complex forming agent is chosen by a person skilled in the art from case to case. Generally, however, the proportions of the above-mentioned specific complex forming agents are preferably the following:

	EDTA	< 0.1 percent by weight
	citric acid	< 2 " " "
	ascorbic acid	< 2 " " "
25	phosphonic acid	< 2 " " "

these percentages being based on the weight of the total composition.

The stabilized hydrogen peroxide composition can be manufactured by first forming β -crystals of the above-mentioned lipids in a manner known per se, e.g. as is disclosed in the references referred to in the opening part of the specification, and then adding the hydrogen peroxide in the desired amount to the formation of the dispersion according to the invention.

However, an especially preferable process according to the invention is a process wherein the lipid is mixed with at least part of the water to be present in the final composi-

tion, preferably to a lipid concentration of 15 - 30 percent by weight, a temperature is imparted to the mixture which is above the so called transition or conversion temperature of the lipid, which temperature is defined as the lowest temperature at which a particle of the lipid in contact with an excess of water absorbs water and is converted to cylindrical or spherical particles with a marked birefringence, the mixture is maintained above said temperature while stirring until said conversion has taken place, the mixture is cooled with continued stirring to room temperature or the desired temperature so as to form β -crystals, and hydrogen peroxide is added in an amount of 0.1 - 4 percent by weight of the total weight of the final composition, the hydrogen peroxide preferably being added as a solution in the remainder of the water to be used for the composition.

Thus, as should be clear from the above-mentioned, the mixture of lipid and water is preferably prepared in part only of the total water to be present in the composition, the remainder thereof being added together with the hydrogen peroxide. If further additives are to be present in the composition, such as for instance the above-mentioned complex forming agents, these are also preferably added in the form of an aqueous solution, i.e. instead of being mixed directly into a final preparation from β -lipid crystals and water.

To obtain the best possible result the mixture is preferably kept in the process according to the invention, at a temperature which is 5-15°C, e.g. 10°C, above the conversion temperature until equilibrium has been reached.

Then the temperature of the equilibrium mixture is slowly lowered to the desired temperature, which is generally room temperature, a rapid stirring preferably being maintained to prevent the separation of a homogeneous aqueous phase within the mixture. However, the stirring rate should preferably not be so high as to cause any foaming effect. The temperature is preferably lowered at a rate of 0.5 - 5°C per minute until crystallisation has taken place, whereupon the cooling rate is not critical.

As concerns application areas of the hydrogen peroxide composition according to the invention, it should be noted that some uses are disclosed in the working examples below. Moreover, the composition claimed can of course be utilized in such connections where hydrogen peroxide compositions have previously been used. However, an especially interesting use of the invention is represented by the use of the composition as a teat immersion composition for milk-producing animals, which use will be disclosed more in detail below.

Teat immersion is today utilized in order to improve the hygienic quality of milk and to prevent the development of udder inflammations, so called mastitis. The primary contents of those agents which are available to day is iodine or chlorohexidine. Iodine has several disadvantages, such as e.g. tissue changes within the teat, influence upon the milk and a doubtful effect. Chlorohexidine imparts taste effects to the milk and after having been used for some time it may cause a resistancy development. Hydrogen peroxide, i.e. the active ingredient of the composition according to the invention, does not show any of the disadvantages referred to. Moreover, the novel light-flowing consistency of the composition claimed is the characteristic which in practice enables the use of a hydrogen peroxide composition in this context, i.e. that the treatment can be accomplished by a simple dipping or immersion of the teats into a solution having a good flowability.

The novel teat immersion composition according to the invention has turned out to possess the following positive properties: a general antimicrobial effect without any resistancy development, no influence on the milk and a plasticising effect on the teats.

The invention will now be further disclosed by the examples below, which relate to some preferable embodiments of the invention and which are not considered to be limiting upon the scope of the invention in any other respect than what can be gathered from the claims. In connection with the examples it should be noted that the percentages referred to

relate to percentages by weight unless otherwise stated.

EXAMPLE 1

This example relates to the preparation of a composition according to the invention wherein the antibacterial effect of hydrogen peroxide can be utilized, e.g. in the form of a hand-desinfectant, which composition is as follows:

	Hydrogen peroxide	0.5 %
	Laurin monoglyceride	0.35 %
10	Myristin monoglyceride	0.01 %
	Tenside *	30 %
	Water, up to	100.0 %

* In this case tenside means a surface active substance suitable for the cleaning of skin.

The preparation is manufactured in accordance with the method which is disclosed in PCT/SE82/00061 referred to above. This means that 0.35 parts of laurin monoglyceride and 1.05 parts of myristine monoglyceride are admixed with 3.6 parts of water and are heated to 70°C. After 15 minutes at said temperature the temperature is lowered while stirring at 0.5 - 5°C per minute to 25°C. Then 0.5 parts of hydrogen peroxide in 64.5 parts of water and 30 parts of tenside are added.

EXAMPLE 2

This example relates to the manufacture of a stable hydrogen peroxide preparation having a high content of iron. The composition of the preparation is as follows:

	Hydrogen peroxide	2.0 %
30	Laurin monoglyceride	0.3 %
	Myristin monoglyceride	0.9 %
	EDTA	0.05 %
	Water, up to	100.0 %

The preparation is manufactured as is disclosed in Example 1 with the addition of EDTA in connection with the addition of hydrogen peroxide.

After being stored for 9 months and having an iron con-

tent of 1.5 ppm the hydrogen peroxide content of the above-mentioned preparation has not been changed, while a preparation containing merely EDTA, hydrogen peroxide, water and iron (in the form of FeSO_4) in the proportions referred to above contains less than 0.8 % of hydrogen peroxide after two days. After a storage period of 9 months a preparation consisting of the above-mentioned monoglycerides and hydrogen peroxide and water and iron in the proportions referred to above contains 1.8 % of hydrogen peroxide.

EXAMPLE 3

In the way disclosed in Example 1 a composition as is disclosed below is manufactured:

Hydrogen peroxide	0.5 %
Xanthan rubber	0.5 %
Laurin monoglyceride	0.35 %
Myristin monoglyceride	1.05 %
Water, up to	100.0 %

Among other things this Example shows that the hydrogen peroxide according to the invention can be made compatible with thickening agents, such as e.g. polysaccarides. The composition obtained possesses an antimicrobial effect and is useful inter alia as a teat immersion agent.

EXAMPLE 4

In the manner disclosed in Example 1 a composition as the one disclosed below is manufactured:

Hydrogen peroxide	0.2 %
Myristin monoglyceride	1.0 %
Washing-active tenside	25.0 %
Water, up to	100.0 %

The present Example shows an interesting use which is based on the fact that the inhibition of the decomposition of hydrogen peroxide means that preparations containing tensides for washing or cleaning can be preserved with hydrogen peroxide. Without such an inhibition liberated oxygen would oxidize the tenside. The preparation obtained is stable against

microbiological contamination for at least 3 years and does not contain any allergy-causing preservatives. This preparation can also be manufactured in a concentrated form to be diluted to the above-mentioned concentration with the product to be preserved.

EXAMPLE 5

A number of comparative stability tests were made to study how the percentages of β -crystalline monoglycerides influence on the decomposition reaction rate of hydrogen peroxide. The results of said tests are presented in Table 1.

TABLE 1

Concentration of hydrogen peroxide

Percentage of <u>monoglyceride</u>	Concentration of hydrogen peroxide		
	28 %	1.4 %	0 %
Number of <u>analyses</u>	n=6	n=6	n=7
Time (months)			
0	0.564	0.618	0.531
1		0.601	0.037
2	0.590	0.599	0
3		0.588	
5		0.595	
6	0.544	0.603	
8	0.536	0.595	

As is clear from the above-mentioned results a composition according to the invention, i.e. the one containing 1.4 % of hydrogen peroxide, is comparable to a previously known composition containing 28 % of hydrogen peroxide as concerns the decomposition rate while a composition without any monoglyceride is decomposed at a very high rate. These results are quite unexpected in view of the theories upon which the prior art compositions are based and means great advantages as has already been discussed.

CLAIMS

1. A stabilized aqueous hydrogen peroxide composition, *characterized* in that it comprises an aqueous dispersion which, based on the total weight of the composition, contains
5 0.1 - 4 percent by weight of hydrogen peroxide and 0.5 - 15, preferably 0.5 - 10 percent by weight of β -crystals of one or more lipids selected from monoglycerides of fatty acids, ascorbic acid, phosphate or lactic acid esters of fatty acids and monoglycerol ethers, said fatty acids and ether chains,
10 respectively, being saturated and having 12-18 carbon atoms.

2. A composition according to claim 1, *characterized* in that the monoglyceride is monolaurin, monomyristin, monopalmitin or monostearin or a mixture of two or more of these.

3. A composition according to claim 2, *characterized*
15 in that the monoglyceride is monolaurin or a mixture of monolaurin and monomyristin wherein the proportion of monolaurin is at least 10 percent by weight.

4. A composition according to any one of the preceding claims, *characterized* in that the concentration of hydrogen peroxide is 0.1 - 2 percent by weight, especially 0.2 - 1
20 percent by weight.

5. A composition according to any one of the preceding claims, *characterized* in that the concentration of β -lipid crystals is 1-5 percent by weight, especially 1-3 percent by weight.
25

6. A composition according to any one of the preceding claims, *characterized* in that it contains a metal ion complex-forming agent in a concentration that improves the stability of the hydrogen peroxide in the presence of said
30 metal ion.

7. A composition according to claim 6, *characterized* in that the complex-forming agent is selected among ethylene diamine tetraacetic acid (EDTA), citric acid, ascorbic acid and phosphonic acids, and that the concentrations thereof are

preferably the following:

	EDTA	< 0.1 percent by weight
	citric acid	< 2 " " "
	ascorbic acid	< 2 " " "
5	phosphonic acid	< 2 " " "

based on the weight of the total composition.

8. A process for the preparation of a stabilized aqueous hydrogen peroxide composition as claimed in any one of claims 1-7, *characterized* by mixing the lipid with at least part of the water to be present in the final composition, preferably to a lipid concentration of 15-30 percent by weight, imparting to said mixture a temperature above the so called conversion temperature of the lipid, which temperature is defined as the lowest temperature at which a particle of the lipid in contact with an excess of water absorbs water and is converted to cylindrical or spherical particles having a strong birefringence, maintaining the mixture above said temperature while stirring until conversion has taken place, cooling the mixture with continuous stirring to room temperature or the desired temperature so as to form β -crystals and adding hydrogen peroxide in an amount of 0.1 - 4 percent by weight of the total weight of the final composition, the hydrogen peroxide preferably being added as a solution in the remainder of the water for the composition.

9. A process according to claim 8, *characterized* by keeping the mixture at a temperature that is 5-15°C above said conversion temperature until equilibrium has been reached.

10. A process according to any one of claims 8 and 9, *characterized* by cooling the mixture at a rate of 0.5 - 5°C per minute.

11. Use of a composition as claimed in any one of claims 1-7 as a teat immersion composition for milk-producing animals.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE86/00576

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC 4		
A 01 N 25/22, 59/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched 7		
Classification System	Classification Symbols	
IPC 4 US C1	A 01 N 25/22, 59/00; A 61 K 33/40, 7/48 424:130, 134, 14	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X, Y	WO, A1, 82/03173 (B.T. AF EKENSTAM ET AL) 30 September 1982 & EP, 0073790 CA, 1182043 US, 4557935	1-11
X, Y	GB, A, 1 174 672 (V.K. LARSSON) 17 December 1969 & FR, 1553792 CH, 498627 DE, 1617602 US, 3772446	1-11
* Special categories of cited documents: 10 "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "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) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" 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 "Y" 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. "Δ" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1987-02-11	1987-02-18	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	 Gerd Wranne	