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| <p>(21) International Application Number: PCT/GB99/04122</p> <p>(22) International Filing Date: 8 December 1999 (08.12.99)</p> <p>(30) Priority Data: 09/207,309 8 December 1998 (08.12.98) US</p> <p>(71) Applicant (for all designated States except US): BLOCK DRUG COMPANY, INC. [US/US]; 257 Cornelison Avenue, Jersey City, NJ 07302-3198 (US).</p> <p>(71) Applicant (for SD only): WHALLEY, Kevin [GB/GB]; 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): GASMAN, Robert, C. [US/US]; 16 Springbrook Road West, Montville, NJ 07045 (US). WONG, Eddie [US/US]; 24 Pitney Avenue, New Providence, NJ 07974 (US). AHN, Hyung-Kook [KR/US]; 28 Scenic Drive, Dayton, NJ 08810 (US).</p> <p>(74) Agent: ABLEWHITE, Alan, James; Marks & Clerk, 57-60 Lincoln's Inn Fields, London WC2A 3LS (GB).</p> | <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p> | |
| <p>(54) Title: DENTURE ADHESIVE</p> | | |
| <p>(57) Abstract</p> <p>A denture adhesive comprising a copolymer salt at least partially cross-linked by amide linkages through lysine, histidine, arginine, derivatives or family members of lysine, histidine or arginine and mixtures thereof.</p> | | |

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DENTURE ADHESIVE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to denture adhesives and to processes for making and using denture adhesives.

2. Description of Related Art

Dentures are substitutes for missing teeth and serve as a replacement for all or some of the teeth found in the oral cavity. Despite diligent efforts by dental professionals and designers of dental prostheses, dentures do not always fit perfectly. Over time, even well-fitting dentures can become ill-fitting due to natural shrinkage and changes in the gum or mucous tissues. Therefore, adherent creams, liquids or powders are often used to secure or temporarily fix dentures within the mouth.

There are a number of desirable attributes of such a denture adhesive composition. The denture adhesive should develop a high degree of tack upon contact with saliva so that the dentures can be held in place as soon as they are seated in the mouth. It is also highly desirable that the saliva hydrated adhesive be spread over the denture-mucosa interface in order to seal the denture in place effectively. The mucilage should possess sufficient cohesive strength to withstand the stresses of mastication, which may rupture the seal and thus dislodge the denture. The denture adhesive must also exhibit sufficient resistance to degradation under the extreme environmental changes that can occur in the oral cavity during such common actions as drinking hot or cold beverages. Of course, the adhesive must also be releasable so that the

denture wearer may remove the dentures for cleaning and maintenance. Denture adhesives are generally sold as a cream, liner or strip, liquid or powder, and many examples are well known in the art.

A major factor in selecting one denture adhesive over another in the marketplace, however, remains the holding performance of a denture adhesive. Thus, workers in the field have been constantly seeking better holding performance.

Early denture adhesives contained finely ground particles of natural gums that expanded when wet to become a viscous gel, which acted as a cushion and an adherent between a denture plate and gum tissue. These denture adhesives, however, have been largely supplanted by polymeric denture adhesives in recent years.

A popular current choice for a polymeric denture adhesive comprises a methyl vinyl ether/maleic anhydride copolymer known as "Gantrez®." This polymer is combined with a number of other ingredients to form the final denture adhesive.

Polymers, of course, have been known for many years and have been used for many different purposes. Depending on the monomer or monomers selected, a polymer may have a vast array of properties and be useful for a number of different purposes. Once the basic constituents of the polymer or copolymer have been selected, any number of modifications may be made to affect various properties of the final polymer or copolymer. The chain length of the polymer may be regulated to be short or long, and, in the case of copolymers of two or more chemically distinct monomers, the order of the monomers may be regulated to form a block copolymer or an alternating copolymer or anything in between.

Once the structure of the polymer or copolymer has been defined, the properties of the polymer or copolymer may still be modified significantly by various chemical or physical methods. One method of modifying the properties of a polymer or copolymer is to modify

various ligands that may be present on the polymer chain. For example, with a MVE/MA copolymer, the anhydride group may be hydrolyzed to the corresponding dicarboxylic acid. The carboxylic acid, in turn, may be fully or partially neutralized to form a salt or the carboxylic acid may be fully or partially esterified with various groups. The modification of the carboxylic acid leads to a change in the properties of the copolymer. The copolymer may be plasticized or otherwise modified by the addition of a cation or covalently bound ligand.

These ionic or covalent bonds may lead to crosslinking of the copolymer chains. If a salt is formed with a divalent cation, the cation may form an ionic "cross-link" between two copolymer chains. Such a cross-link may be very easily dissociated in the presence of water. If a compound contains two or more groups capable of forming an ester with a carboxylic acid ligand, then covalent cross-links may be formed between adjacent copolymer chains. These covalent cross-links may have more or less resistance to hydrolysis depending on the ligand chosen.

Polymers and copolymers of anhydrides, including maleic anhydride, have been known for a long time and have been used for many purposes. U.S. Patent No. 2,313,565 is directed to a copolymer of an acid anhydride with a vinyl ether monomer. Anhydride copolymers have also been used as carriers for sustained release pharmaceuticals, at least where the pharmaceutical could be used as an amine salt. In U.S. Patent No. 3,121,043, the anhydride is lightly cross-linked with the pharmaceutical salt, and the active pharmaceutical is released over time as the amine link is hydrolyzed.

Anhydride copolymers may also be used in hair spray or cosmetics; as thickening agents; and as anti-static agents for flammable liquids. U.S. Patent No. 5,753,215 discloses MVE/MA copolymers monoesterified with butanol and neutralized by diamines or polyvalent metal salts. The diamines include lysine, arginine and cystine, and the polyvalent metal salts include bromides, chlorides, nitrates, acetates, carbonates and sulphates of calcium, zinc, magnesium, barium, aluminum and zirconium. Anhydride copolymers have been used to

support biological molecules in U.S. Patent No. 5,760,166. Anhydride copolymers have also been used to precipitate proteins from aqueous media in U.S. Patent Nos. 5,534,597 and 5,294,681. A gel-forming system useful in wound dressings contains a mixture of polymers as discussed in U.S. Patent No. 5,578,661. Another gel is discussed in U.S. Patent No. 5,521,256. Sodium hydroxide is added to a crosslinked MVE/MA copolymer, thereby forming a gel solution.

Denture adhesives are not the only adhesive materials that contain anhydride copolymers. U.S. Patent No. 5,298,56, is directed to an adhesive useful in recycling of corrugated paper. Another adhesive, used to help bond polymers such as ethylene or vinyl alcohol copolymers to polyolefins and polyamides, is discussed in U.S. Patent No. 5,115,033. An anhydride polymer is part of an electrically conductive gel composition for use in establishing a low resistance contact between an electrode and a biological body in U.S. Patent No. 5,178,143. While this gel is not, strictly speaking, an adhesive, it is made from a crosslinked, neutralized copolymer of maleic anhydride and vinyl ether.

One problem with denture adhesive copolymers, particularly MVE/MA copolymers, is that covalent cross-linking is not an attractive approach to fine-tuning the desired properties of the denture adhesive. Covalent cross-linking can reduce the affinity of the copolymer for water, which can have an adverse effect on the properties of the copolymer for some important applications. Cross-linking agents have been tried with denture adhesives, including propylene glycol and glycerin in U.S. Patent No. 5,696,181. U.S. Patent No. 5,066,709 is directed to a bioadhesive composition comprising a MVE/MA copolymer monofunctional lactam side groups.

One formulating a denture adhesive must consider organoleptic properties in addition to the functional aspects of a cross-linking agent. A certain amount of a cross-linking agent can be expected to hydrolyze in an aqueous environment such as the oral cavity, especially if the covalent cross-link is accomplished through an ester linkage. Thus, the cross-linking agent

itself must be nontoxic at a minimum and should also not provide an unpleasant taste, texture or other sensation to the user.

The inventors have found by raising the molecular weight of the copolymer in the denture adhesive with a cross-linked polymer or polymer salt, the denture adhesive of the present invention has improved holding performance over currently marketed denture adhesives without adversely affecting the organoleptic qualities. We also found that the amide linkages between the cross-linking compound and the copolymer of the present invention appear to hydrolyze relatively slowly, allowing for improved hold over a long period of time.

SUMMARY OF THE INVENTION

The invention provides A denture adhesive comprising a safe and effective amount of a cross-linked partial copolymer salt, wherein the copolymer salt is at least partially cross-linked by amide linkages through a cross-linking agent selected from the group consisting of lysine, histidine, arginine, derivatives or family members of lysine, histidine or arginine and mixtures thereof.

The invention further provides a method of making a copolymer salt comprising the steps of cross-linking an alkyl vinyl ether/polymerizable anhydride copolymer with lysine, histidine, arginine, derivatives or family members of lysine, histidine or arginine and mixtures thereof; at least partially hydrolyzing the anhydride to form the acid and neutralizing the acid to form a salt thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Polymer - Copolymer. A denture adhesive in accordance with the invention begins with the polymer or copolymer to be used. Polymers or copolymers containing acid anhydride groups are capable of forming cross-links with lysine, histidine, arginine, derivatives or family

members of lysine, histidine or arginine and mixtures thereof and are within the scope of the invention to the extent that such polymers or copolymers are useful as ingredients in denture adhesives.

A preferred embodiment of the invention uses a copolymer of an acid anhydride. A more preferred embodiment of the invention uses a copolymer of an alkyl vinyl ether with an unsaturated acid anhydride, and a highly preferred embodiment of the invention uses a methyl vinyl ether/maleic anhydride copolymer. Ethylene / maleic anhydride copolymers, vinyl pyrrolidone / maleic anhydride copolymers, isobutylene / maleic anhydride copolymers, vinyl acetate / maleic anhydride copolymers, alkylacrylate / maleic anhydride copolymers, vinyl ether / citraconic anhydride copolymers, vinyl ether / itaconic anhydride copolymers and many other 1:1 alternating copolymers of an unsaturated acid anhydride and another vinyl monomer may also be used in the invention.

Of the many methyl vinyl ether/maleic acid or anhydride copolymers that may be used, copolymers manufactured under the name "Gantrez®" are preferred. Preferred Gantrez polymers include the Gantrez AN series of the anhydride form of the polymer, commercially available from International Specialty Products of Wayne, New Jersey, U.S.A.

Preferably, the polymer has a specific viscosity of at least about 1.0 and preferably from about 2.5 to about 6.0. Specific viscosity is measured as a solution of 1g of copolymer in 100 ml of methyl-ethyl ketone (MEK) at 25°C. Higher and lower specific viscosities are within the scope of the invention, but lower than 2.5 specific viscosity polymers are not preferred because these polymers can have poor cohesive properties in denture adhesive formulations.

Partial salts of the copolymers must be used, including mixed partial salts of different cations. Preferred cations include, but are not limited to, calcium, magnesium, strontium,

ferrous iron, sodium, potassium, zirconium oxy, zinc, and other non-toxic cations. Preferably, the acid groups are not entirely cross-linked and neutralized.

A 1% solution of the copolymer in deionized water should have a pH of from about 4 to about 8, preferably from about 4.5 to about 7.5, and most preferably from about 5 to about 7.

Cross-linking Agent. The cross-linking agent of the invention includes the naturally occurring amino acids lysine, histidine, arginine, derivatives or family members of lysine, histidine or arginine and mixtures thereof. The preferred amino acid, lysine (2,6 diaminohexanoic acid), is an amino acid having the structure:
 $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$. Derivatives, including, but not limited to, acid salts thereof and substituted amines capable of forming cross-links with the acid anhydride groups on the MVE/MA copolymer may be within the scope of the invention as may nontoxic diamino acids with a shorter or longer chain length, side chains or ligands and derivatives thereof.

The amount of cross-linking in the copolymer needs to be controlled. Excess cross-linking can make a batch of copolymer unsuitable for use. Preferably, the percent substitution of lysine in the polymer is less than about 5% and more than about 0.005%. More preferably, the percent substitution is more than about 0.01% and less than about 1% and most preferably the percent substitution is about 0.05% to 0.5%.

Optional hydrophilic polymer. The copolymer salt may be combined with a hydrophilic polymer to enhance the ability of the denture adhesive to form a swellable, tacky and viscous adhesive material upon contact with saliva in the oral cavity.

The preferred hydrophilic polymers are selected from the group comprising sodium carboxymethyl cellulose, sodium alginate, polyoxyethylene oxide, karaya gum, hydroxyethyl cellulose, locust bean gum, xanthan gum, carrageenan, methyl cellulose and mixtures thereof.

The hydrophilic polymer may comprise from about 10 to about 60% by weight of the final denture adhesive, preferably from about 15% to about 55% by weight and most preferably from about 20% to about 50% by weight.

Other components. The cross-linked polymer salt of the invention may be incorporated into the denture adhesive composition in an effective amount as the sole adhesive component or in combination with other water soluble polymers and excipients as is known in the art such as fillers, lubricants, flavors, coloring agents, preservatives and the like. Mineral oil, vegetable oil, petrolatum, preservatives, such as the alkyl parabens, fumed silica and mint flavor are examples of common excipients used in known commercial denture adhesive compositions. The amounts employed will be varied depending on the particular copolymer salt used and the cross-linking agent, the degree of cross-linking, the ratio of the inorganic cations to the organic cross-linker, the amount of the hydrophilic polymer and the other constituents of the adhesive compositions. In general, the crosslinked copolymer salt comprises from about 10% to about 70% by weight of the adhesive compositions, and preferably from about 20% to about 60%. The suitable hydrophilic polymers include both natural and synthetic gums, preferably sodium carboxymethyl cellulose, polyethylene oxide and sodium alginate.

Preparation. To make the cross-linked copolymer in accordance with the invention, the copolymer and the cross-linking agent are dispersed in water at room temperature (about 10% solids content) and mixed to form the cross-linked polymer. The preferred cross-linking agent lysine is very reactive with the anhydride groups in the polymer, and the anhydride groups react with the amino groups in the lysine in preference to hydrolysis in water. Without being limited by theory, we speculate that the amino group immediately adjacent to the carboxyl group in lysine is reacting with the anhydride via a mechanism known as the Dakin-West reaction. In this reaction, an acid anhydride, $(R=CO)_2O$ reacts with an alpha amino acid, $R-CH(NH_2)-COOH$, to acylate the amine group and form a cross-link through the alpha amino group and the alpha carboxyl group, $R=-CO-CHR-NH-CO-R=$, and CO_2 . This bond is a is a

true covalent bond and is not vulnerable to hydrolysis when the denture adhesive is placed in an aqueous environment in the mouth. The other amino group may then react with an anhydride group in another polymer chain to form a cross-linked polymer system.

A partial salt is then formed by full or partial hydrolysis of the remaining anhydride groups and partial neutralization of the resulting acid. The solution or dispersion is then dried to form a film or a flake of the desired copolymer.

The dried copolymer partial salt is milled to a suitable particle size material and may then be combined with other ingredients to form a denture adhesive.

EXAMPLES To demonstrate that a copolymer of methyl vinyl ether and maleic anhydride could have its performance improved by increasing its molecular weight using an alpha amine carboxylic acid cross-linking agent, the following non-limiting examples were carried out.

Examples 1-9 A lysine-poly methylvinyl ether/maleic acid was prepared by adding 99.62 g of a methylvinyl ether/maleic anhydride copolymer (GANTREZ AN 169) to 1250 ml. of vigorously mixed deionized water. 0.38 g of L-Lysine monohydrate was added to the mix, and the resulting mixture was held at room temperature for 30 minutes with continuous mixing.

The mixture was then heated to 85-90°C and held at that temperature for 2 hours with continuous mixing. The resulting solution was discharged into trays (while maintaining batch temperature and mixing speed) and dried in an 85°C oven. The resulting copolymer was a 0.36% substituted Lysine GANTREZ Acid.

The same method was used with different amounts of lysine to form the different DS Lysine-GANTREZ Acid copolymers shown in Table 1. A Comparative example of a copolymer that had not been cross-linked was also prepared (0% Lysine). The viscosity of the

dry lysine-GANTREZ Acid was measured by milling the dry copolymer and then preparing a 0.25 weight percent solution of the copolymer in deionized water. The viscosity of the solution was measured using a Cannon-Fenske Viscometer at 25°C. These results are shown in Table 1.

Table 1 -- Viscosity Measurements

| Example | Material Tested | Specific Viscosity (η_{sp}) |
|-----------|-----------------|------------------------------------|
| Compare 1 | 0.00% Lysine | 4.06 |
| 2 | 0.03% Lysine | 4.21 |
| 3 | 0.06% Lysine | 3.63 |
| 4 | 0.09% Lysine | 4.12 |
| 5 | 0.12% Lysine | 3.96 |
| 6 | 0.24% Lysine | 4.15 |
| 7 | 0.30% Lysine | 4.36 |
| 8 | 0.36% Lysine | 5.09 |
| 9 | 0.48% Lysine | 6.66 |

The increase in solution viscosity with increasing amounts of lysine shows that the molecular weight of the copolymer increases with the addition of lysine. After the addition of 0.24 percent substituted lysine, polymer molecular weight started to increase. Starting with the 0.6 percent substituted lysine GANTREZ acid (results not shown in Table 1), the molecular weight increased to a point where it was difficult to measure the viscosity.

Examples 10-17 A partial calcium salt of poly methylvinyl ether/ maleic acid was prepared by adding 74.87 g GANTREZ AN 169 to 1250 ml. of vigorously mixed deionized water. Then L-Lysine monohydrate 0.24 g was added to the mixture, and the resulting mixture was held at room temperature for 30 minutes with continuous mixing to form a slurry solution. 24.89 g of calcium hydroxide was added to the slurry solution and the mixture was heated to 85-90°C. The temperature was maintained at 85-90°C for 2 hours with continuous mixing. The solution of the partial salt was discharged into trays (while maintaining batch temperature and mixing speed), and the solution was heated in an 85°C oven until dry.

The salt was milled and used to make a denture adhesive cream formula. This salt is 0.3 Lysine-70 Ca GANTREZ Salt. Using different amounts of lysine and metal oxides,

different percentages of substitution of Lysine-GANTREZ Salts were prepared and used to make denture adhesive creams by combining 30% of the salt (by weight) with 24% by weight carboxymethyl cellulose, 18% by weight mineral oil and 28% by weight petrolatum. A comparative example of a denture adhesive cream was made without lysine.

The shear strength of the denture adhesive creams were measured and the results are shown in Table 2. The shear strength was measured with an Instron Model 1122. Denture adhesive creams made with lysine cross-linked GANTREZ copolymer partial Ca salts show improved performance.

Table 2 -- Shear Strength

| Example | Material Tested | Shear Strength (g/in ²) |
|------------|------------------|-------------------------------------|
| Compare 10 | 0.0% lysine; 65% | 590 |
| 11 | 0.3% lysine; 65% | 787 |
| 12 | 0.5% lysine; 65% | 689 |
| 13 | 0.7% lysine; 65% | 708 |
| 14 | 0.0% lysine; 70% | 673 |
| 15 | 0.3% lysine; 70% | 877 |
| 16 | 0.5% lysine; 70% | 696 |
| 17 | 0.7% lysine; 70% | 795 |

Examples 18-19 A 0.5 percent substitution lysine, 40 percent substitution Zinc, 20 percent substitution Magnesium, and 10 percent substitution Sodium methylvinyl ether maleic acid copolymer salt was prepared by adding 75.93 g of GANTREZ AN 169 to 1,000 ml. of vigorously mixed deionized water. Then 0.40 g L-Lysine monohydrate was added to the mixture, and the resulting mixture was held at room temperature for 30 minutes with continuous mixing.

A solution of 250 ml of deionized water containing 15.85 g zinc oxide, 3.93 g magnesium oxide and 3.90 g sodium hydroxide was added gradually to the lysine GANTREZ AN slurry and the mixture was heated to 85-90°C and held at that temperature for 2 hours with continuous mixing. The solution of the partial salt was discharged into trays (while

maintaining batch temperature and mixing speed), and the salt was heated at 85°C until dry. The dry salt was milled and used to make a denture adhesive cream formula.

Consumer tests showed that the denture adhesive cream made with the above salt was preferred over a comparative example, a denture adhesive made with a similar salt without lysine.

CLAIMS

1. A denture adhesive comprising a safe and effective amount of a cross-linked partial copolymer salt, wherein the copolymer salt is at least partially cross-linked by amide linkages through a cross-linking agent selected from the group consisting of lysine, histidine, arginine, derivatives or family members of lysine, histidine or arginine and mixtures thereof.
2. A denture adhesive according to claim 1, wherein said adhesive is formulated as a liquid, powder, cream, paste, gel or liner.
3. A denture adhesive according to claim 1 or claim 2, wherein said polymer contains an alkyl vinyl ether and a copolymerizable, unsaturated, alkyl anhydride.
4. A denture adhesive according to any of claims 1 to 3, wherein said polymer is selected from the group consisting of: a) a copolymer comprising an alkyl vinyl ether and a vinyl ether copolymerizable carboxylic acid anhydride.
5. A denture adhesive according to claim 4, wherein the anhydride comprises maleic anhydride.
6. A denture adhesive according to claim 4 or claim 5, wherein said alkylvinyl ether is methylvinyl ether.
7. A denture adhesive according to any of claims 1 to 6, wherein said copolymer salt contains a cation selected from the group consisting of: cations of calcium, magnesium, strontium, sodium, potassium, zirconium oxy, zinc, iron, tin and mixtures thereof.

8. A denture adhesive according to any of claims 1 to 7, wherein the mole percent substitution of said lysine or its derivatives or family members in the polymer is less than about 5% and more than about 0.005%.

9. A method of making a denture adhesive material according to any of claims 1 to 8, comprising the steps of:
 - (a) forming a partially cross-linked copolymer from a copolymer comprising an acid anhydride by reacting the anhydride containing copolymer with lysine, histidine, arginine, derivatives or family members of lysine, histidine or arginine and mixtures thereof;
 - (b) at least partially hydrolyzing at least a portion of the remaining anhydride groups in said partially cross-linked copolymer to form a partial carboxylic acid; and
 - (c) at least partially neutralizing said carboxylic acid groups to form a partial salt of a cross-linked copolymer.

10. A copolymer salt which is at least partially cross-linked by amide linkages through a cross-linking agent selected from the group consisting of lysine, histidine, arginine, derivative or family members of lysine, histidine or arginine or mixtures thereof, wherein said copolymer is a copolymer of a polymerizable ether and a polymerizable acid or anhydride.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04122

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K6/083 C09J135/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | WO 98 43595 A (PROCTER & GAMBLE) 8 October 1998 (1998-10-08) page 2, paragraph 3 - paragraph 4 page 3, line 1 -page 5, line 4 page 5, paragraph 4 page 7, paragraph 4 -page 8, paragraph 1 page 9, paragraph 5 -page 10, paragraph 1 | 1-10 |
| Y | US 5 753 215 A (MONDET JEAN ET AL) 19 May 1998 (1998-05-19) cited in the application column 2, line 20 - line 24 column 4, line 26 - line 31 | 1-10 |
| A | WO 97 10772 A (BLOCK DRUG CO) 27 March 1997 (1997-03-27) page 4, line 30 -page 6, line 24 | 1-6, 10 |
| | -/- | |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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