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Film-shaped preparations with improved chemical stability containing active substances and method for the production thereof

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(54) Title: FILM-SHAPED PREPARATIONS WITH IMPROVED CHEMICAL STABILITY CONTAINING ACTIVE SUBSTANCES AND METHOD FOR THE PRODUCTION THEREOF

(54) Bezeichnung: WIRKSTOFFHALTIGE FILMFÖRMIGE ZUBEREITUNGEN MIT VERBESSERTER CHEMISCHER STABILITÄT, UND VERFAHREN ZU DEREN HERSTELLUNG

(57) Abstract: The invention relates to a film-shaped preparation containing active ingredients for application in the oral cavity or for transmucosal application. The invention is characterised in that the preparation has a peroxide-number which is at the most 40.

(57) Zusammenfassung: Eine filmförmige wirkstoffhaltige Zubereitung zur Applikation in der Mundhöhle oder zur transmukosalen Applikation, ist dadurch gekennzeichnet, dass die Zubereitung eine Peroxid-Zahl aufweist, die höchstens 40 beträgt.

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Dated this 17th day of November 2004

Ina Langen

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Active substance-containing film-like preparations having improved chemical stability, and processes for their preparation

The invention relates to active substance-containing film-like preparations which can be used for application in the oral cavity and for transmucosal administration of active substances and which are characterized by an improved chemical stability.
The invention further relates to methods of manufacture by which active substance-containing films of the type mentioned can be obtained.

Active substance-containing films typically have a matrix which contains one or more polymers as base substances. In this polymer matrix there is contained at least one active substance, e.g. a medicinal agent, in dissolved or dispersed form. Frequently, various further auxiliaries or additives are added to the matrix, for example in order to adjust various physical or pharmaceutical parameters. Film-shaped preparations of this kind are capable of releasing the active substances contained therein at the site of application, e.g. in the oral cavity, so that they can be absorbed by the body.

Many pharmaceutical substances are chemically unstable and can break down into degradation products, for instance due to extended storage. This degradation reaction causes a decrease of the initially present amount of active substance, and the degradation products formed can be toxicologically risky. As a consequence of this degradative reaction, the stability of the pharmaceutical products is diminished. Responsible for this degradation reaction are on the one hand certain physical parameters (e.g. temperature, action

of light), but also the chemical composition of the pharmaceutical composition.

Degradation reactions to be mentioned here are, above all, oxidative reactions; these occur with particular intensity when active oxygen is present, e.g. in the presence of peroxides. These reactions are autoxidation processes, which take place as chain reactions. Such auto-oxidation reactions and the underlying reaction mechanisms are basically known to those skilled in the art. With film-shaped preparations, in particular, one has to reckon with unwanted oxidative processes as the said preparations have a relatively large surface which may be exposed to the attack of atmospheric oxygen.

To suppress such degradation reactions, these administration forms are usually produced and packed under absence of oxygen, e.g. in a nitrogen atmosphere, or one employs antioxidants.
It has, however, turned out that despite these precautionary measures there occurs a more or less strong decrease in the active substance content when film-like active substance-containing preparations are stored over an extended period, especially if oxidation-sensitive active substances are concerned.

The task underlying the present invention was therefore to indicate film-like active substance-containing preparations of the type mentioned in the introductory portion of claim 1 which possess improved active substance stability. The task was further to indicate processes that enable the production of such preparations.

Surprisingly, this task is solved by means of preparations and processes of manufacture according to the present claims.

According to the invention, in the film-like preparations mentioned the active substance stability can be improved by adjusting the peroxide number of the preparation during manufacture to a value of maximally 40, preferably to not more than 15, and especially to not more than 5.

The peroxide number is a measure for the content of peroxides; it indicates the amount of milli-equivalents of active oxygen per kg of a substance. Due to the restriction of the peroxide number to a maximum value of 40, preferably 15, and especially 5, the inventive film-like preparations are substantially free from active oxygen.

The term "active oxygen" means oxygen which has an oxidation state greater than -2. The term in particular comprises molecular oxygen as well as peroxides of the general structure R-O-O-R', wherein R and R' are H atoms, or R is an alkyl residue and R' an H atom, or R and R' are alkyl residues, and R and R' may be either identical or differ from each other.

It has been shown that an acceptable storage stability lasting for months, can only be achieved if the relative amount of the active oxygen does not exceed the value of 2%-wt. For example, an active substance-containing film-like preparation ("wafer") may contain 200 mg of an active substance with a molecular weight of 250 dalton, which correspond to 0.8 mMol of active substance. In this case, the portion of active oxygen must not exceed 2% of that value, i.e. a content of 0.016 mMol of active oxygen must not be exceeded. This value corresponds to a peroxide number of ca. 30. The above wafer may be, for instance, a suckable wafer having a weight per area of 500 g/m² and an active substance load of 40% and having a surface dimension of 10 cm².

In the case of thinner, quickly releasing wafers with a lower active substance load there results a correspondingly lower upper limit for the content of active oxygen. If the above-mentioned active substance (molecular weight 250 dalton) is contained in an amount of 14 mg in a wafer, this corresponds to 0.056 mMol of active substance, consequently the content of active oxygen must not exceed the value of 0.001 mMol (corresponding to 2%). This is equivalent to a peroxide number of approx. 14. The mentioned wafer may, for example, have a weight per area of 70 g/m² and an active substance load of 20%-wt., the dead weight of a single system (wafer) being 70 mg.

There are several known methods of determining the peroxide number.
(A) The most widely used is that of reacting a defined amount of the substance to be tested in a chloroform-glacial acetic acid solution having an excess of iodide ions and subsequent retitration of the iodide formed using sodium sulfate.
(B) Less frequently used and restricted to aqueous solution is the method of reacting the substance to be tested with titanium(IV) ions and photometric determination of the peroxocomplex forming.
(C) A particularly simple method is that of a semi-quantitative peroxide test using commercially available test strips.

The invention is based on the finding that the raw materials or formulation constituents used in the production of the film-like preparations, in their initial state frequently contain relatively high concentrations of hydroperoxides and peroxides. This is frequently true of polymers, solvents and certain additives (e.g. permeation enhancers). Favoured by the presence of atmospheric oxygen and heavy metal impurities there occur radical chain reac-

tions in the course of which certain bonds in the active substance molecules are attacked, e.g. C-H bonds in benzyl or allyl position, tertiary C-H bonds, and C-H bonds in the vicinity of ether oxygen atoms. Active substance molecules which contain such molecules are particularly prejudiced by peroxide attacks.

By means of the proposed reduction of the peroxide number in the preparation, the active substance instability caused by the radical chain reaction can be suppressed much more effectively than is possible with the known measures - addition of antioxidants, nitrogen atmosphere. The reason for this is presumably that the addition of antioxidants or stabilisers remains without effect in those cases where already the raw materials used, that is, the components of the formulation contain relatively high concentrations of peroxides or hydroperoxide radicals.

In principle, the peroxide number of the film-like preparations produced can be determined according to the above-described methods (A) or (B). On the other hand, it can possibly prove difficult to dissolve a sufficient amount of the film-like preparation to be tested in a not-too-large amount of the above-mentioned solvent.

For simplification, the preferred way to proceed is to determine the peroxide content of each formulation component of the film-like composition individually (for example according to one of the above-indicated methods), and subsequently to calculate the peroxide number of the composition, the peroxide numbers of the individual formulation components being weighted according to their percentage in the composition and finally added together; this sum constitutes the total peroxide number of the composition. When calculating the total peroxide number, the peroxide content

of the solvents used in the production must also be taken into consideration.

The calculation of the total peroxide number is illustrated by the following calculation example:
A film-like composition consists of three formulation components X, Y and Z, wherein the portion of X is 70%-wt., the portion of Y is 20%-wt., and the portion of Z is 10%-wt. For component X a peroxide number of 10 was determined, in the cases of Y and Z, the peroxide number is 15 and 30, respectively.
The total peroxide number is calculated as follows:
(10 x 70/100) + (15 x 20/100) + (30 x 10/100) =
= 7 + 3 + 3 = 13

As can be seen, the peroxide numbers of the individual components are weighted with a factor that corresponds to their percentage in the composition.

To further improve the stability of the active substances contained in the film-like compositions it is provided, according to a preferred embodiment, that the composition contain at least one antioxidant. Substances taken into consideration are, in particular, antioxidants from the group comprising ascorbic acid, ascorbyl palmitate, sodium sulfite, sodium disulfite, sodium metabisulfite, thioglycerol, thioglycol acid, tocopherols (vitamin E), tocopherol acetate, vitamin A, propyl gallate, octyl gallate, butylhydroxyanisol and butylhydroxytoluene. Apart from these, there are also many antioxidants used in the food industry which are suitable. The concentration of these substances preferably is 0.001 to 5%-wt., especially preferred 0.01 to 3%-wt., each related to the film-like composition.

The film-like compositions according to the invention are provided with a polymer matrix which can be mono-layered or

multi-layered. In any case, at least one layer contains active substance. The polymer matrix contains at least one polymer, or a polymer mixture, as base substance(s). The polymer portion preferably amounts to 10 to 95%-wt., especially preferred 25-85%-wt., in each case relative to the complete film-like composition.
The thickness of the inventive active substance-containing films is preferably in the range of from 0.01 to 5 mm, especially preferred in the range of from 0.05 to 1 mm.

For making the polymer matrix, the following polymers are particularly preferred: cellulose ether, especially ethyl cellulose, propyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, mixtures of cellulose ethers, as well as cellulose acetate, polyvinyl alcohols, polyvinyl acetate, polyvinyl pyrrolidone, polyethylene oxide polymers, polyurethane, polyacrylic acid, polyacrylates, polymethacrylates, alginates, pectins, gelatine, starch and natural rubbers.

A further preferred embodiment of the invention provides that the matrix contain one or more polymer(s), selected from the group of the hydrophile, water-soluble polymers or polymers degradable in aqueous media. In this way it is possible to control the active substance release from the preparation by way of the solubility or the degradability in aqueous media, e.g. in body fluids. The films can, for instance, be formulated as quickly or as slowly releasing systems.

As hydrophilic, water-soluble polymers or polymers degradable in aqueous media, the following are, in particular, to be taken into consideration: cellulose derivatives, especially hydroxypropylmethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose and methyl cellulose, as well as polyvinyl alcohol, polyvinyl acetate, polyvinyl pyrroli-

done, polyacrylates, water-soluble polysaccharides, especially pullulan, xanthan, alginates, dextranes and pectins, proteins, preferably gel-forming proteins, especially gelatine.

It is further provided, according to another preferred embodiment, that at least one layer or at least one surface of the preparation have mucoadhesive properties.

The mucoadhesive properties are determined essentially by the type of the matrix-forming polymer(s) as well as by the relative portions of these polymers in the preparation. As matrix-forming polymers which may be components of a mucoadhesive formulation according to the invention, the following polymers are preferably taken into consideration - without excluding any other suitable raw materials: polyvinyl alcohols (e.g. Mowiol®); cellulose derivatives such as hydroxpropylmethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose (e.g. Walocel), methyl cellulose, hydroxyethyl cellulose and hydroxypropylethyl cellulose; starch and starch derivatives; gelatine (various types); polyvinylpyrrolidone; gum arabic; pullulan, acrylates.

As active substances contained in the inventive preparations basically all pharmaceutical active substances are taken into consideration, as well as any other active substances which are suitable for intervening in physiological processes in humans or animals.
The inventive preparations are especially suited for administering active substances that due to their chemical structure are sensitive to an increased extent to oxidative degradation reactions. Among these are first of all those active substances which possess one of the following partial structures:

- secondary or tertiary amino groups
- C=C double bonds, conjugated double bonds
- C-H groups in allyl position
- benzylic C-H groups
- tertiary C-H groups
- sulfide groups, thioether groups or sulfoxide groups.

Examples for such active substances are: steroids such as 17-beta-estradiol, heterocyclic compounds such as dihydropyridine (e.g. calcium antagonists of the dihydropyridine type), nicotine, (-)-5,6,7,8,-tetrahydro-6-[propyl[2-(2-thienyl)-ethyl]amino]-1-naphthol, aromatic compounds, especially substituted aromatic compounds (e.g. adrenaline, salicylic acid and salicylic acid derivatives, phenothiazine); oxidation-sensitive biopolymers, proteins, oxidation-sensitive substances such as amine, hydroxylamine, alcohols and aldehydes.

To achieve certain effects or to modulate the chemical or physical properties, it can be of advantage if the film-like preparations contain one or more additives selected from the groups of softeners, dyes and pigments, degradation promoters, wetting agents, absorption- or permeation-enhancing substances, pH regulators, fillers, flavouring and aromatic substances and sweeteners. Pharmaceutically acceptable substances are known to those skilled in the art. These additives may preferably be present in a total concentration of up to 50%-wt, especially at a total concentration of from 1.0 to 15%-wt.

As softeners, there are, for example, those from the group of hydrocarbons, alcohols (especially higher alcohols such as dodecanol, undecanol, octanol), triglycerides, multivalent alcohols, carboxylic acids, derivatives of carboxylic acids, ethers, esters (e.g. diethyl phthalate, n-butyl

adipate, citric acid esters) and amines which are taken into consideration.

To improve the physical properties, the active substance matrix may contain fillers, for example titanium dioxide, zinc oxide, chalk, active charcoal, finely dispersed silicon dioxide or corn starch.

As absorption or permeation accelerators (enhancers) those substances are especially suited which are selected from the group comprising the following substances and classes of substances: saturated or unsaturated fatty acids, fatty acid esters, especially esters with methanol, ethanol or isopropanol (e.g. oleic acid ethyl ester, oleic acid methyl ester, lauric acid methyl ester, lauric acid ethyl ester, adipic acid methyl ester, adipic acid ethyl ester), strait-chain or branched fatty alcohols or the esters thereof, especially esters with acetic acid or lactic acid (e.g. ethyl oleate, ethyl laurate, ethyl palmitate, ethyl lactate, propyl lactate, propyl palmitate, propyl laurate, propyl oleate), multivalent aliphatic alcohols or polyethylene glycols, sorbitan fatty acid esters and their derivatives obtainable by way of ethoxylation, fatty alcohol ethoxylates, polyoxyethylene fatty acid esters; lauric acid diethanolamide, oleic acid diethanolamide, coconut fatty acid diethanolamide, D-alpha-tocopherol, lauric acid hexyl ester, 2-octyl dodecanol, dexpanthenol, isopropylidene glycerol, transcutol (= diethylene glycol monoethyl ether), DEET (= N,N-diethyl-m-toluene amide), solketal, ethanol, 1,2-propanediol or other short-chain alcohols (e.g. alcohols with up to 6 C atoms), as well as menthol and other essential oils or components of essential oils. To optimize the active substance flow, it is also possible to use two or more enhancers in combination.

The inventive preparations are advantageously suitable for transmucosal administration of drugs, for example via the oral mucosa, but also to other mucosal surfaces of the body. Because of the mucoadhesive properties of the active agent-containing film layer, it is possible for a controlled active substance release to take place over a prolonged period of time. The film-like preparations can preferably be used for releasing active substances or other substances, e.g. flavouring or aromatic substances, in the oral cavity.
The inventive preparations can in addition be used as oral administration forms which enable the release and/or absorption of pharmaceutical active substances in the gastrointestinal tract. In the case of suckable film-like preparations, for example, the active substance-containing solution or suspension being formed during the action of sucking can be swallowed and subsequently absorbed in the gastrointestinal tract. As suckable active substance-containing systems, relatively thick films are preferred, preferably of a thickness of up to 5 mm, especially from 0.5 to 5 mm.
The invention does, however, also comprise oral film-like administration forms which are intended for swallowing and where the active substance release substantially begins to take place only upon entering the gastrointestinal tract. This also includes such film-like active substance-containing systems which after oral administration initially disintegrate in the oral cavity into fragments, which are then swallowed.

The present invention further relates to processes of manufacture through which film-like preparations of the aforementioned kind can be obtained.
According to the invention, the manufacture takes place in such a manner that in a first step the peroxide number of each and every one of the formulation components intended

for making the preparation according to recipe (including the solvents used) is determined.
Subsequently, in a further step, the formulation components are selected in such a manner that the sum of the peroxide numbers of the individual formulation components amounts to 40 at the most, with the peroxide number of each one of the formulation component being weighted according to the percentage of that component in the preparation.

From the formulation components thus selected, a solution, dispersion or melt is prepared which contains the active substance(s) to be released.
This solution, dispersion or melt is coated by knife coating, roll coating, spraying and extrusion methods onto an inert support, and dried or allowed to cool, which results in the formation of a film layer.

If during the determination of the peroxide numbers of the individual components it turns out that the peroxide content is too high, it is possible to either select a substitute substance for that component (e.g. a raw material from another manufacturer) which possibly has a lower peroxide number, or to subject the formulation component concerned to a treatment suitable for reducing the peroxide content. To this end, a treatment with reducing agents is taken into consideration, for example with an inorganic sulfite or hydrogen sulfite, preferably with sodium sulfite or sodium hydrogen sulfite, in each case in aqueous solution (e.g. 5 to 30%-wt). For this treatment, the above-mentioned aqueous solution of the reductive agent is added to the formulation component concerned in an alcoholic solution, preferably in methanolic or ethanolic solution. Through this treatment the peroxides present are readily destroyed in a quick reaction.
Depending on the dissolving properties of the component to be treated, the latter may also be dissolved in an aqueous

solution, or in an alcohol-water mixture. If the formulation component or auxiliary substance is a liquid (e.g. a solvent) the treatment can be carried out in such a manner that an aqueous solution of the reducing agent (e.g. sodium sulfite) is added directly to the liquid.

The use of sodium sulfite or sodium hydrogen sulfite is especially advantageous since these substances are pharmaceutically acceptable auxiliaries so that later separation is not necessary.
If precipitation of reaction products occurs, the latter can be separated by centrifugation, sedimentation or filtration.

Following this treatment, the materials are practically free of peroxides and can be employed without hesitation even where the load was previously substantial. An additional improvement of the stability can be attained by using antioxidants, which suppress, or slow down, the formation of new peroxides during the storage of the systems.

The invention and its advantageous properties will be illustrated by means of the following examples.

Film-like preparations were prepared according to the following recipes:

Example 1:
Ethanol/water

Nicotine	15%
HPMC	79.998%
Menthol	5%
Ascorbylpalmitate	0.002%

Example 2:
Ethanol/water

Nicotine	15%
HPMC	79.99%
Menthol	5%
Sodium disulfite	0.01%

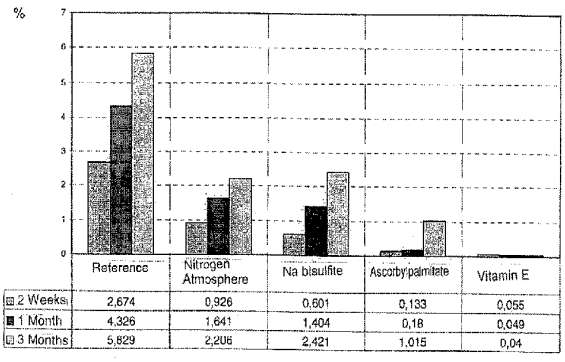
Example 3:
Ethanol/water

Nicotine	15%
HPMC	79.95%
Menthol	5%
Vitamin E	0.05%

Comparative Example:
Like Example 1, but without ascorbylpalmitate.

Film-like preparations of the compositions indicated in the examples were subjected to a stability test. In this test, the films were stored at 40°C and a relative air humidity of 75%, and the reduction in the active agent content caused by oxidative processes was determined at certain time intervals (2 weeks, 1 month, 3 months). The results are shown in Fig. 1; the percentage values indicate the content of degradation products, relative to the content of active substance (agent).

Fig. 1



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CLAIMS

1. Film-like, active substance-containing preparations for application in the oral cavity or for transmucosal application, characterized in that the preparation has a peroxide number which is adjusted during manufacture to a maximum value of 40.

2. Preparation according to claim 1, characterized in that it has a peroxide number which is adjusted during manufacture to a maximum value of 15.

3. Preparation according to claim 1, characterized in that it has a peroxide number which is adjusted during manufacture to a maximum value of 5.

4. Preparation according to any one of claims 1 to 3, characterized in that it is substantially free of active oxygen, the term "active oxygen" referring to molecular oxygen as well as to oxygen-containing compounds wherein oxygen has an oxidation state higher than -2.

5. Preparation according to any one of the preceding claims, characterized in that the peroxides comprises the general structure R-O-O-R', wherein R and R' are selected from a group consisting of alkyl residues and hydrogen, and wherein R and R' are the same or different.

6. Preparation according to any one of the preceding claims, characterized in that it contains at least one antioxidant.

7. Preparation according to claim 6, characterized in that the antioxidant is selected from a group comprising ascorbic

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acid, ascorbylpalmitate, sodium sulfite, sodium disulfite, sodium metabisulfite, tocopherols (vitamin E), tocopherol acetate, thioglycerol, thioglycol acid, vitamin A, propyl gallate, octyl gallate, butylhydroxyanisol and butylhydroxytoluene.

8. Preparation according to claims 6 or claim 7, characterized in that the concentration of the antioxidant(s) is 0.001 to 5%-wt.

9. Preparation according to claim 8, characterized in that the concentration of the antioxidant(s) is 0.01 to 3%-wt.

10. Preparation according to any one of the preceding claims, characterized in that it has a mono-layered or multi-layered polymer matrix, with at least one layer having an active substance content.

11. Preparation according to claim 10, characterized in that the matrix contains one or more polymer(s) selected from a group comprising cellulose ether as well as cellulose acetate, polyvinyl alcohols, polyvinyl acetate, polyvinyl pyrrolidone, polyethylene oxide polymers, polyurethane, polyacrylic acid, polyacrylates, polymethacrylates, alginates, pectins, gelatine, starch and natural rubbers.

12. Preparation according to claim 11, characterized in that the group comprising cellulose ether comprises ethyl cellulose, propyl cellulose, carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), mixtures of cellulose ethers.

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13. Preparation according to claim 10, characterized in that the matrix contains one or more polymer(s) selected from a group of hydrophile, water-soluble polymers or polymers degradable in aqueous media.

14. Preparation according to claim 13, characterized in that the group of hydrophile, water-soluble polymers or polymers degradable in aqueous media comprises cellulose derivatives, especially hydroxypropylmethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose and methyl cellulose, as well as polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, polyacrylates, water-soluble polysaccharides, pullulan, xanthan, alginates, dextrane and pectins, proteins, preferably gel-forming proteins, especially gelatine.

15. Preparation according to any one of the preceding claims, characterized an that at least one layer or at least one surface of the preparation has mucoadhesive properties.

16. Preparation according to any one of the preceding claims, characterized in that it contains one or more additives selected from a group of plasticizers, dyes and pigments, degradation enhancers, wetting agents, absorption- or permeation-enhancing substances, pH regulators, fillers, flavouring and aromatic substances and sweeteners.

17. Preparation according to any one of the preceding claims, characterized in that it contains at least one active substance which due to its chemical structure is susceptible to attack by peroxide radicals.

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18. A method of medical treatment, comprising a use of a preparation according to claims 1 to 17 for transmucosal administration of medicinal active substances.

19. A method of medical treatment, comprising a use of a preparation according to claims 1 to 17 for application in the oral cavity.

20. A method of medical treatment, comprising a use of a preparation according to claims 1 to 17 as oral administration form for releasing active substances in the gastrointestinal tract.

21. A method of medical treatment, comprising a use of a preparation according to claims 1 to 17 for releasing flavouring or aromatic substances in the oral cavity.

22. Process for the production of a film-like active substance-containing preparation for application in the oral cavity or for transmucosal application, characterized by the following steps:

(a) determining the peroxide number of each and every one of the formulation components provided for making the preparation according to recipe;

(b) selecting the formulation components in such a manner that the sum of the peroxide numbers of the individual formulation components is maximally 40, with the peroxide number of each one of the formulation components being weighted according to the percentage of these components in the preparation;

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(c) preparing a solution, dispersion or melt which contains the selected formulation components as well as the active substance(s) to be released;

(d) coating this solution, dispersion or melt onto an inert support using doctor-knife application, roll application, spraying or extrusion methods, and subsequent drying or cooling, which results in the formation of a film layer.

23. Process according to claim 22, characterized in that the sum of the peroxide number is maximally 15.

24. Process according to claim 23, characterized in that the sum of the peroxide number is maximally 5.

25. Process according to any one of claims 22 to 24, characterized in that, following step (a), at least one formulation component is subjected to a treatment with reducing agent(s) which is/are suitable for reducing the peroxide content.

26. Process according to claim 25, characterized in that the mentioned treatment is carried through in such a manner that an aqueous solution of an inorganic sulfite salt or hydrogen sulfite salt is added to the formulation component in an alcoholic solution.

27. Process according to claim 26, characterized in that the inorganic sulfite salt or hydrogen sulfite salt comprises sodium sulfite or sodium hydrogen sulfite.

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28. Process according to claim 26, characterized in that the alcoholic solution, comprises methanolic or ethanolic solution.

29. Film-like, active substance-containing preparations for application in the oral cavity or for transmucosal application as substantially described hereinbefore.

30. A method of medical treatment as substantially described hereinbefore.

31. Process for the production of a film-like active substance-containing preparation for application in the oral cavity or for transmucosal application as substantially described hereinbefore.

Fig. 1

	Referenz	Stickstoff-Atmosphäre	Na-Bisulfit	Ascorbylpalmitat	Vitamin E
2 Wochen	2,674	0,926	0,601	0,133	0,055
1 Monat	4,326	1,641	1,404	0,18	0,049
3 Monate	5,829	2,206	2,421	1,015	0,04