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(51) Int.Cl.⁶ A61K 7/48

(30) 1997/04/10 (197 14 765.8) DE

(54) **UTILISATION D'ESTERS OLIGOMERES, DE FAIBLE POIDS
MOLECULAIRE, D'ACIDES α -HYDROXYLIQUES
ET/OU D'ACIDES O-HYDROXYLIQUES AROMATIQUES
DANS DES FORMULATIONS COSMETIQUES**

(54) **USE OF LOW MOLECULAR OLIGOMER ESTERS OF α -
HYDROXY ACIDS AND/OR AROMATIC OF O-HYDROXY
ACIDS IN COSMETIC FORMULATIONS**

(57) L'invention concerne l'utilisation d'esters oligomères, de faible poids moléculaire, d'acides α -hydroxyliques et/ou d'acides o-hydroxyliques aromatiques dans des formulations cosmétiques, l'acide α -hydroxylique et/ou l'acide o-hydroxylique aromatique correspondants étant libérés de manière contrôlée par hydrolyse pendant l'utilisation.

(57) The invention relates to the use of low molecular oligomer esters of α -hydroxy acids and/or aromatic o-hydroxy acids in cosmetic formulations, wherein the corresponding α -hydroxy acid and/or aromatic o-hydroxy acid is controllably released by hydrolysis during use.

(57) Abstract

The invention relates to the use of low molecular oligomer esters of α -hydroxy acids and/or aromatic o-hydroxy acids in cosmetic formulations, wherein the corresponding α -hydroxy acid and/or aromatic o-hydroxy acid is controllably released by hydrolysis during use.

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**Use of low molecular weight, oligomeric esters of
 α -hydroxy acids and/or aromatic o-hydroxy acids in
cosmetic formulations**

5 The invention relates to the use of low
molecular weight, oligomeric esters of α -hydroxy acids
and/or aromatic o-hydroxy acids in cosmetic
formulations.

10 In recent years α -hydroxy acids called "AHAs"
for short, have been investigated for their activity to
an increased extent in modern cosmetology and have been
used as an anti-ageing substance. These acids are often
also referred to as fruit acids, a name which indicates
15 their natural origin. Examples of the most important
fruit acids are glycolic acids (from sugar cane),
lactic acid (from sour milk), citric acid (from citrus
fruits), tartaric acid (from wine), malic acid (from
apples) and also pyruvic acid (from papaya fruits).
However, aromatic o-hydroxy acids, such as, for
20 example, salicylic acid, also have the same effects.

 The clinical and therapeutic activity of these
AHAs was first investigated during the 1980s and since
this time they have been used by dermatologists in
concentrations of more than 12% for the treatment of
25 extremely dry skin and chronic eczema. In this
connection, it has now been shown that these acids have
other effects on the skin. During treatment the skin
became smoother, softer, impurities disappeared and the
skin looked more healthy.

30 The AHAs in fact work by softening the
glutinous substance which holds the outer layers of the
epidermis together. This accelerates normal desquama-
tion of the dead skin cells and fine surface lines are
smoothed in the process.

35 Salicylic acid too, which has likewise been
used for a long time for the treatment of acne,
psoriasis, warts or dandruff is of great importance as
a keratolytically and keratoplastically acting

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substance in cosmetics since its use effects mild peeling of the skin.

5 The market is now being flooded by a large number of cosmetic products which comprise such AHAs and also aromatic o-hydroxy acids and are positioned as antiwrinkle cream or antiageing product or as product for regenerating the skin.

10 Another theory for the mode of action of the α -hydroxy acids and aromatic o-hydroxy acids, in addition to the skin peeling already described, consists, however, in the view that the AHAs merely irritate the skin, which leads to a slight swelling of the skin and thus to smoothing. Should this effect actually lie behind the antiageing results, then the
15 use of these free acids and their advantages must be called into serious question, particularly with regard to the long-term effect.

Incorporation of the free acid into the cosmetic carrier has further disadvantages. Firstly,
20 the relatively low pH can lead to considerable incompatibility reactions, secondly the readily water-soluble acids are washed out again shortly after application.

Products which comprise derivatives of these
25 AHAs which initially do not bring about a great drop in pH and from which the AHAs would be released slowly over a relatively long period would be desirable.

The object of the present invention was then to bring the AHAs customary in cosmetics into a form which
30 is insoluble in water and primarily does not lead to a massive drop in the pH and from which the effective AHAs are released over a relatively long period.

It has now been found that α -hydroxy acids and/or aromatic o-hydroxy acids can be esterified to be
35 water-insoluble, oligomeric products which can then hydrolyse in the presence of water and release the monomeric AHAs.

The invention thus provides the use of low molecular weight, oligomeric esters of α -hydroxy acids

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and/or aromatic o-hydroxy acids in cosmetic formulations, the corresponding α -hydroxy acid and/or aromatic o-hydroxy acid being controllably released by hydrolysis during use.

5 In principle, such polymers and oligomers are known. For example, it is known that highly polymeric esters of selected lower hydroxy acids, and in particular of lactic acid, are well tolerated by the body and are used in operative techniques, for example,
10 as body-compatible and body-absorbable thread material, which is degraded over a period of weeks or months and flushed out of the body.

Oligomeric esters, in particular of lactic acid and/or of glycolic acid which have an average degree of
15 oligomerization of up to 100 are disclosed in DE 36 20 685. The latter describes the use in these esters as absorbable carriers and/or film formers in compositions for covering human or animal skin.

However, the use of such oligomers in cosmetic
20 preparations for the purpose of releasing free hydroxy acids is not described anywhere.

The oligomers according to the invention are characterized by an average degree of oligomerization of the chosen acid up to about 30 and preferably up to
25 about 10.

Polyester oligomers from hydroxycarboxylic acids can in principle be prepared directly by polycondensation of the hydroxycarboxylic acids or hydroxycarboxylic acid mixtures, but it is useful for the
30 specific setting of the degree of oligomerization to add, in a known manner, coreactants for the regulation of the degree of oligomerization, where mono- or polyhydric alcohols or organic acids may primarily be suitable here. The two ester-forming groups of the
35 monomers or of the oligomers, i.e. the hydroxyl group on the one hand and the carboxyl group on the other hand, in fact generally suggest themselves as reactive sites.

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In particular, in preferred embodiments alcohols having up to 4, in particular having up to 3, hydroxyl groups are suitable, it being possible here for monohydric alcohols on the one hand to have particular importance, and on the other hand di- and, in particular trihydric alcohols can adopt a key position. In the last-mentioned case, the alcohol is in particular glycerol, which leads to extremely varied products by reaction with the AHA oligomers. Examples of other suitable alcohols are: ethylene glycol, propylene glycol, 1,3-butylene glycol, trimethylolpropane, low molecular weight polyethylene glycols, polypropylene glycol, 1,5-pentanediol or alternatively more highly hydric alcohols.

In the field of the co-use of carboxylic acids, on the one hand physiologically tolerable carboxylic acids, in this case in particular monocarboxylic acids, may be of interest, but also polyfunctional carboxylic acids, for example di- or tricarboxylic acids.

The oligomeric hydroxycarboxylic acids or their derivatives are prepared in a manner known per se. Of course, in all cases - i.e. both in the case of the α -hydroxycarboxylic acids and in the case of the co-reactants - not only the respective free reactive components of the type mentioned, but also those derivatives may be employed which form the desired polyester oligomers in a manner known per se under the conditions of the esterification or transesterification. The esters of the hydroxy acids, for example, are thus suitable, furthermore also the easy-to-handle dimerization products, for example, of lactic acid and/or glycolic acid, i.e. the lactide and/or the glycolide, can be used.

The polycondensation reaction is in this case customarily carried out by heating the starting materials to a temperature above the melting point, preferably in the presence of a catalyst, in particular of an esterification catalyst, under anhydrous conditions in an inert-gas atmosphere. The amount and type

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of the catalyst used determine the process temperature and the duration of the reaction. Since the conversion of the reactions is normally almost 100%, the composition of the final products can be easily
5 controlled by the addition of the reactants. Polycondensation reactions of this type are well known to the person skilled in the art. A detailed listing of a very wide variety of reaction conditions is therefore not necessary here.

10 The invention also provides low molecular weight oligomers comprising α -hydroxy acids and/or aromatic o-hydroxy acids, prepared by reaction of the monomeric α -hydroxy acids and/or aromatic o-hydroxy acids or reactive derivatives thereof with mono- or
15 polyhydric alcohols or organic acids, for use in cosmetic formulations, the corresponding α -hydroxy acid and/or aromatic o-hydroxy acid being controllably released from these oligomers by hydrolysis during use.

The α -hydroxy acids and o-hydroxy acids used
20 are preferably the compounds listed in the following: glycolic acid and lactic acid, which both occur in the metabolism of the living organism and are processed and excreted by the body, lactic acid being used here in the form of its racemate or alternatively in the form
25 of its optical antipodes or as any desired mixtures of the optical antipodes; α -hydroxybutyric acid, α -hydroxyvaleric acid, citric acid, tartaric acid, malic acid, trimethylene carbonate, ϵ -caprolactone, salicylic acid, m-hydroxybenzoic acid, p-hydroxybenzoic
30 acid, gallic acid, racemic acid, benzilic acid, mandelic acid or alternatively pyruvic acid.

Very particular preference is given in this case to glycolic acid and/or lactic acid or dimerization products thereof.

35 In important embodiments of this invention, homooligomers are used. This means that only a single α -hydroxy acid or one of its reactive derivatives or only a single o-hydroxy acid or one of its reactive

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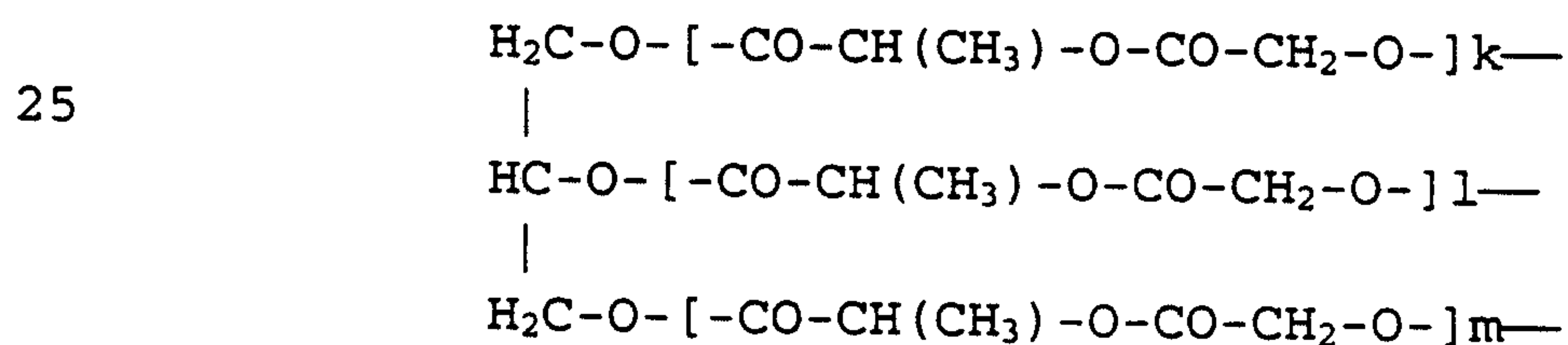
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derivatives, e.g. only lactic acid or only salicylic acid, are used to prepare the oligomeric esters.

In a further, preferred embodiment of this invention, heterooligomers are used. This means that in the polycondensation reaction for the preparation of the oligomeric products two or more different α -hydroxy acids and/or aromatic o-hydroxy acids are used. It is, therefore, also possible to use mixtures of α -hydroxy acids and, for example, salicylic acid as monomers.

Particularly preferred oligomers are synthesized, for example, from the following monomers: glycerol, lactide and glycolide; ethylene glycol, lactic acid and glycolic acid; propylene glycol, lactide and glycolide; glycerol and lactide; glycerol, glycolic acid and hydroxybutyric acid; ethylene glycol and hydroxyvaleric acid; glycerol and ethyl lactate; glycerol, trimethylene carbonate and glycolic acid; ethylene glycol and lactide; ethylene glycol, glycolic acid and ethyl lactate; glycerol, glycolic acid and ϵ -caprolactone.

In this connection, the product of glycerol, lactide and glycolide looks, for example, as follows:



where the sum $k+l+m$ is preferably less than or equal to 12, particularly preferably less than or equal to 6 (based on lactide).

The listing of the preceding compounds is only a small selection of particularly preferred products and should in no case have limiting character.

The heterooligomers generally have advantageous properties since they show lower tendency towards crystallization and the onset of clouding associated therewith. In addition, they can be more rapidly

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degraded on account of higher water absorption and hydrolysis rate.

On the other hand, this more rapid hydrolysis rate is responsible for the fact that the corresponding oligomer products are very sensitive to hydrolysis and are unstable in customary hydrous cosmetic preparations. It is therefore necessary to formulate them without water. One advantageous way of solving this problem is the separate formulation of anhydrous AHA oligomers optionally with suitable auxiliaries and a second hydrous component which comprises the auxiliaries customary for cosmetic preparations. The two components are only mixed directly prior to application of the finished cosmetic preparation. This can, preferably, be carried out using mixing systems which are known per se from (medical) technology, such as, for example, systems for mixing bone cements, reactive adhesives or moulding materials. An example which can be mentioned is the double chamber syringe with attached static mixer which is known to a person skilled in the art. In the case of these mixing systems it is also possible to simply adjust and vary the mixing ratio of oligomer phase to aqueous phase. Thus, for example, mixing ratios of from 1:10 to 1:1 are possible. Also suitable are, for example, mixing systems from MIXPAC Systems AG.

The invention thus also provides a cosmetic preparation consisting of a ready-to-use set of two or more separate components, of which one component comprises an anhydrous formulation of oligomer products according to at least one of Claims 1 to 7, optionally with other auxiliaries, and as one other component comprises a water-containing cosmetic formulation, optionally with other auxiliaries and additives customary in such cosmetic preparations.

The advantage of using the described oligomeric products is then that there is primarily no great reduction in pH, which could irritate the skin. However, during hydrolytic attack of the oligomeric

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structure in situ the monomeric AHAs and the aromatic o-hydroxy acids are gradually released, and can then trigger their known advantageous effects on the skin. In addition, it is of course possible for a relatively
5 large amount of these oligomers, which serve as donor for the free acids, to be incorporated, meaning that the effect is considerably better compared with the use of free AHAs.

The components for formulating corresponding
10 cosmetic preparations can be chosen from the large number of known and proven substances. The oligomer esters of α -hydroxy acids and/or aromatic o-hydroxy acids can be readily mixed with customary skincare components and auxiliaries, recourse advantageously
15 being had to an anhydrous preparation.

In the case of the separate formulation, on the one hand an anhydrous formulation of the oligomers possibly with suitable auxiliaries or additives is prepared and on the other hand a cosmetic preparation
20 consisting of the customary skincare components. For example, in the preparation of an O/W cream, the oligomers can be present in the oily phase, the aqueous phase is formulated separately. Or, it is also possible to prepare an oligomer mixture without any additives as
25 one phase, the remaining components customary for a skincare preparation then being present in the second aqueous phase. The two separate phases are then only mixed in each case prior to application.

A number of customary components and additives
30 may be listed below:

Fatty alcohols, fatty acid esters, in particular triglycerides of fatty acids, fatty acids, lanolin, natural or synthetic oils or waxes, emulsifiers such as, for example, Tegacid special,
35 Teginacids, Tego Care (all from Th. Goldschmidt, Essen), Cremophors (BASF, Ludwigshafen), Emulgins (Henkel, Düsseldorf), Hostacerin DGS or alternatively Hostaphat (Hoechst), optionally perfume oils, lower

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alcohols, glycols or polyols and also thickeners such as, for example, silica.

5 The cosmetic preparations according to the invention may comprise the oligomer products in amounts of from about 5 up to nearly 100%, use of the pure oligomer substance also being possible. The preferred content of oligomer esters in the finished product is from 5% to 50%.

10 It is assumed that a person skilled in the art can utilize the above description in the widest sense without further detail. Preferred embodiments are thus merely to be perceived as a descriptive disclosure which is in no way limiting.

15 The complete disclosure of all applications, patents and publications listed above and below are incorporated into this application by reference.

The examples below serve to illustrate the present invention.

20 **Example 1**

4 Mol of L-lactide and 1 mol of glycerol were melted under nitrogen and with stirring in a customary bench apparatus and then heated to 190°C over the course of 1 hour. The reaction was left to proceed at 25 188 - 192°C for 5 h, and the glycerol-oligo-lactide product was drawn off whilst hot. 0.5% of o-phosphoric acid (based on the amount of lactide) had been added as catalyst.

30 **Example 2**

1 Mol of glycerol, 2 mol of L-lactide and 1 mol of glycolide were heated to 195°C over the course of one hour under nitrogen and with stirring in a customary bench apparatus. The mixture was then left to 35 react for 5 hours, and the glycerol-oligo-lactide coglycolide (1:2:1) was drawn off whilst hot. The catalyst added was o-phosphoric acid, in an amount of 0.5% based on the total amount of lactide and glycolide. The residual content of glycerol was $\leq 2\%$.

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Example 3

1 Mol of glycerol and 3 mol of glycolide were reacted as in Example 2 to give a glycerol-oligo-glycolide. The catalyst added here was an Sn(II) chloride solution in ether (7 ml of a solution of 2.5 g of SnCl₂ in 1000 ml of ether).

Example 4

1 Mol of ethylene glycol and 1.5 mol of DL-lactic acid were heated up to from 150° to 200°C over the course of 6 hours under nitrogen and with stirring in a customary bench apparatus. The system was then cooled to 150°C and carefully evacuated, and conversion was completed at 200°C and 10 torr. After 30 minutes, the product was drawn off at about 150°C whilst hot.

Example A

Preparation of a skincare cream

Phase I:

At 60°C, ethylene glycol oligolactide of the composition 1:1.5 (preparation as in Example 4) and glycerol oligolactide of the composition 1:5 (preparation as in Example 1) in the ratio 40:60 are mixed homogeneously. The mixture is transferred at this temperature to a 10 ml chamber of a 1:1 double-chamber syringe. After cooling, this mixture has a honey-like consistency.

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Phase II:

The aqueous phase comprises:

3.0%	of 1,2-propanediol (Art. No. 107478)	(1)
1.2%	of preservative	(1)
0.25%	of methyl-4-hydroxybenzoate, sodium salt (Art. No. 106756)	(1)
2.0%	of TWEEN 80 (emulsifier)	(1)

5

Polyacrylic acid, sodium salt is added to match the viscosity of phase II to that of phase I at room temperature. Phase II is then introduced into the second chamber of the double-chamber syringe. The
10 double-chamber syringe is closed in the normal manner.

Source of supply:

(1) Merck KGaA, Darmstadt

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Patent Claims

1. Use of low molecular weight, oligomeric esters of α -hydroxy acids and/or aromatic o-hydroxy acids in
5 cosmetic formulations, the corresponding α -hydroxy acid and/or aromatic o-hydroxy acid being controllably released by hydrolysis during use.
2. Use according to Claim 1, characterized in that the low molecular weight oligomers are obtained by
10 reaction of the monomeric α -hydroxy acids and/or aromatic o-hydroxy acids or also reactive derivatives thereof with mono- or polyhydric alcohols or organic acids.
3. Use according to Claim 1 or 2, characterized in
15 that homooligomers are used which are prepared using just one monomeric α -hydroxy acid or aromatic o-hydroxy acid.
4. Use according to Claim 1 or 2, characterized in that heterooligomers are used which are prepared using
20 two or more different monomeric α -hydroxy acids and/or aromatic o-hydroxy acids.
5. Use according to one of Claims 1 to 4, characterized in that preferably oligomeric reaction products of lactic acid, glycolic acid and/or o-salicylic acid
25 or their reactive derivatives are reacted with mono- or polyhydric alcohols or organic acids.
6. Use according to one of Claims 1 to 5, characterized in that oligomers having an average degree of oligomerization up to about 30, preferably up
30 to about 10, are used.
7. Low molecular weight oligomers comprising α -hydroxy acids and/or aromatic o-hydroxy acids, prepared by reaction of monomeric α -hydroxy acids and/or aromatic o-hydroxy acids or reactive derivatives
35 thereof with mono- or polyhydric alcohols or organic acids, for use in cosmetic formulations, the corresponding α -hydroxy acid and/or aromatic o-hydroxy acid being controllably released from these oligomers by hydrolysis during use.

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8. Cosmetic preparation consisting of a ready-to-use set of two or more separate components, of which one component comprises an anhydrous formulation of oligomer products according to at least one of Claims 1 to 7, optionally with other auxiliaries, and as one other component comprises a water-containing cosmetic formulation, optionally with other auxiliaries and additives customary in such cosmetic preparations.

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