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(54) **Title:** POORLY WATER-SOLUBLE SALTS OF SUNSCREEN AGENTS

(57) **Abstract**

Poorly water-soluble salts of organic acids, their use as sunscreen agents and sunscreen compositions comprising them. The salts are formed between an organic anion which displays ultraviolet absorption over at least a portion of the wavelength range from 290 to 400 nanometres, and a metal cation characterised in that the metal cation is one or a mixture of aluminium, zinc, titanium, tin, iron or lanthanum and the salt has a solubility of less than 2g/litre in water at 20 °C.

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POORLY WATER-SOLUBLE SALTS OF SUNSCREEN AGENTS

This invention relates to sunscreen agents, that is to say compounds capable of absorbing ultra violet radiation with a wavelength in the range from 290 to 400 nanometres. The invention also relates to sunscreen compositions for application to human skin incorporating the sunscreen agents.

In general terms, harmful ultra-violet (UV) rays, particularly those originating from sunlight, which penetrate the upper atmosphere and reach the earth's surface, can be classified into:

i. the energy-rich UV-B rays (290-320nm wavelength) which possess an intense physiopathological activity on the skin; these are absorbed just above the dermis and they are responsible for erythema and skin pigmentation; and

ii. UV-A rays (320-400nm wavelength) which penetrate deeper into the skin (to the dermis and beyond). Their energy is much lower and the photobiological effects they cause are much more long term in nature, for example, they accelerate skin ageing.

Sunscreen compositions should desirably provide protection against both UV-A and UV-B rays, but protection against UV-A rays is particularly desirable, in order to prevent the long term photobiological effects resulting from UV-A radiation.

Many known sunscreen agents are soluble salts of organic acids such as cinnamate, which incorporate an aromatic nucleus or other conjugates system which provides ultraviolet absorption.

We have now found that a number of poorly water-soluble salts of such organic acids have a similar ultraviolet absorption to that of the corresponding soluble salts, but with a broadening of the absorption band which advantageously enhances absorption in the UV-B and/or UV-A region.

Accordingly in a first aspect this invention provides a sunscreen composition for application to human skin comprising a cosmetically acceptable vehicle incorporating a salt formed between an organic anion which displays ultraviolet absorption over at least a portion of the wavelength range from 290 to 400 nanometres, and a metal cation characterised in that the metal cation is one or a mixture of aluminium, zinc, titanium, tin, iron or lanthanum and the salt has a solubility of less than 2g/litre in water at 20°C.

Of these metals, zinc and aluminium are preferred, especially aluminium.

The water solubility of the salts may possibly be less than 1g/litre.

In EP-A-557089 there are disclosed insoluble macromolecular salts which are layered double hydroxides in which metal ions are linked through hydroxy groups. This invention is particularly concerned with poorly soluble salts which are other than these layered double hydroxides of the formula

$$\left[M_m N_n (OH)_{2(m+n)} \right] y^+ \qquad X^{x-}_{y/x} \cdot zH_2O$$

wherein N is one or a mixture of trivalent metal ions, M is one or a mixture of divalent metal ions or is lithium,

if M is divalent y = n and if M is lithium y = (n-m) and X

denotes interlayer anions at least some of which display ultraviolet absorption over at least a portion of the wavelength range from 290 to 400 nanometres.

The poorly soluble salts of this invention will frequently be simple salts of a single metal cation so that individual crystals will contain only a single metal. Mixtures of such salts could be used, so that more than one metal is present, but in different crystals. The salts of this invention may possibly be devoid of bridging hydroxy groups connecting metal atoms.

In another aspect this invention provides use of poorly soluble salts as defined above as sunscreen agents or to prepare sunscreen compositions. A third aspect of the invention is the poorly soluble salts themselves as defined above.

In general it will be desirable that the ultraviolet absorbing anions have a fairly strong absorption in at least a portion of the stated range from 290 to 400 nanometres. This may be specified as a requirement that the acid form or a simple alkali metal or ammonium salt of the anion exhibits absorption with a molar extinction coefficient of at least 2×10^3, preferably 3×10^3, more preferably at least 5×10^3 and yet more preferably at least 8×10^3 over at least a portion of the stated wavelength range from 290 to 400nm.

The poorly soluble salts of this invention may themselves have molar extinction coefficients of the magnitudes given in the previous paragraph, but it is easier to measure absorbance in solution and thus may be more convenient to specify the extinction coefficient of a soluble salt.

Effective ultraviolet absorption may be provided by an absorption band whose maximum is outside the stated range.

For example the p-methoxy cinnamate ion has an absorption maximum at 285 nanometres but the absorption band is broad enough to provide strong absorption over a range from 290 nanometres up to at least around 320 nanometres.

It will often be the case that absorption in the range 290 to 400 nanometres will be provided by an absorption band with a maximum in the range 260 to 360 nanometres.

Preferably the anions do not have strong absorption in the visible band from 400 to 700 nanometres, especially in the part of it from 450 nanometres upwards, notably from 450 or 500 to 650 nanometres. The extinction coefficient for absorption in such ranges may preferably be no greater than 5×10^2 throughout the ranges concerned.

The molar extinction coefficient of a substance is usually measured in solution and is then given by the formula

$$\epsilon = \frac{1}{cl} \log_{10} \frac{I_o}{I}$$

where I is the intensity of radiation transmitted through the sample,

I_o is the intensity of radiation transmitted through a reference sample consisting of the same solvent but without the substance under test,

c is molar concentration in moles/litre, and

l is the path length through the solution, in centimetres.

The anions which absorb ultraviolet radiation may suitably be one or more of the following:

para amino benzimidazole-5-sulphonate

3-imidazol-4-yl acrylate
salicylate
p-methoxy cinnamate
2 ethyl hexyl-2-cyano-3,3 diphenyl acrylate
3,3,5 trimethylcyclohexyl-2-acetamido benzoate
p-aminobenzoate
cinnamate
3,4-dimethoxy phenyl glyoxylate
α-(2-oxoborn-3-ylidene)-p-xylene-2-sulphonate
α-(2-oxoborn-3-ylidene)toluene-4-sulphonate
α-cyano-4-methoxy cinnamate
2-phenyl benzimidazole-5-sulphonate
2-hydroxy-4-methoxy benzophenone-5-sulphonate
2,2'-dihydroxy-4,4'-dimethoxy benzophenone-3,3'-disulphonate.

These anions, when in the free state, are known to display absorption in the wave length range from 290 to 400 nanometres. All of them are regarded as acceptable materials to serve as sunscreen agents.

Particularly preferred anions are:

cinnamate
4-methoxycinnamate
salicylate
p-aminobenzoate.

The poorly soluble salts can readily be prepared by precipitation from an aqueous solution of the corresponding alkali metal or ammonium salt, and then separated by filtration.

The sunscreen compositions of this invention include a cosmetically acceptable vehicle. The poorly soluble salts of this invention can be suspended as a dispersion in the vehicle.

Preparation may simply consist of adding the poorly soluble salt to the vehicle, and then mixing to form a suspension. Preferably the vehicle is aqueous. For use the composition is rubbed onto skin and the water then evaporates, along with any volatile organic compounds included in the vehicle. This leaves the poorly soluble salt as a deposit on the skin.

The aqueous vehicle may be an oil-in-water emulsion with the poorly soluble salt suspended in that emulsion.

It is envisaged that a sunscreen composition according to this invention will contain from 0.05 to 50% by weight of the poorly soluble salt, more preferably from 0.1 to 30% by weight, yet more preferably 2 to 20% by weight. The amount which is incorporated will affect the amount of ultraviolet absorption achieved, of course. Therefore amounts towards the upper end of the range would be used for sunscreen compositions intended to give a high degree of protection against ultraviolet radiation.

Other materials may be included in sunscreen compositions according to this invention. It is within the scope of this invention to incorporate an additional sunscreen agent. Possibilities include nonionic organic sunscreen agents, inorganic sunscreen agents such as finely divided titanium dioxide and particles of organic polymers.

Other materials which may possibly be included in a sunscreen composition include thickening agents, emollient oils, humectants and fluids to enhance lubricity, notably silicone oils. Minor constituents which may be present include perfume and preservatives.

EXAMPLES

Example 1:
Preparation of a sparingly soluble cinnamate salt of aluminium.

1.47g cinnamic acid and 0.4g sodium hydroxide were dissolved in 38ml of water. 2.66g of anhydrous aluminium chloride were dissolved in 7.5ml of water. The two solutions were then combined yielding a white precipitate. The solid product was filtered off, washed with cold water and then oven dried at 90°C.

X-ray powder diffraction pattern of the product showed major peaks at 12.1A, 6.1A, 5.2A and 3.9A which are characteristic of this material.

Scanning electron microscope imaging showed the product to be composed of 0.1μm diameter crystals.

Thermal and chemical analysis yielded the following chemical data

% Al	=	7.27%
% cinnamate	=	89.8%

The UV spectrum of a suspension containing 25mg/l of the product in water showed a broad adsorption band centred at 272nm and with a tail extending to at least 440nm. The absorbance at 360nm was 8.9% of the absorbance at 272nm, whereas for sodium cinnamate the absorbance at 360nm is less than 0.2% of the absorbance at 272nm.

Example 2:
Preparation of a sparingly soluble salicylate salt of aluminium.

20.8g sodium salicylate were dissolved in 100ml of water. 34.6g of anhydrous aluminium chloride was dissolved in 100ml of water. The two solutions were then combined yielding a white precipitate. The solid product was filtered off, washed with cold water and then oven dried at 90°C.

X-ray powder diffraction pattern of the product showed major peaks at 9.9A, 5.16A, 3.52A, and 3.22A which are characteristic of this material.

Scanning electron microscope imaging showed the product to be composed of small lath shaped crystals of dimension 2 x 0.2 x 0.05μm.

Thermal and chemical analysis yielded the following chemical data

% Al	=	6.98%
% salicylate	=	82.7%

The uv spectrum of a suspension containing 25mg/l of the product in water showed a broad adsorption band centred at 302nm and with a tail extending to at least 340nm. The absorbance at 315nm was 24% of the absorbance at 302nm, whereas for sodium salicylate the absorbance at 315nm is less than 2.8% of the absorbance at 315nm.

Example 3:

Preparation of a sparingly soluble 4-methoxycinnamate salt of zinc.

75.6g 4-methoxycinnamic acid and 17.0g sodium hydroxide were dissolved in 1.6 litres of water. 115.8g of anhydrous zinc chloride were dissolved in 100ml of water. The two solutions were combined yielding a white precipitate. The solid product was filtered off, washed with cold water and then oven dried at 90°C.

The X-ray diffraction pattern of the product showed major peaks at 19.6A, 9.8A, and 6.5A which are characteristic of this material.

Thermal and chemical analysis yielded the following chemical data

% Zn	=	15.7%
% 4-methoxycinnamate	=	84.3%

The UV powder reflectance spectra showed a broad absorption band extending from below 250nm to about 340nm and with a tail extending to about 380nm.

Example 4:

The following formulations were prepared.

	WT.%	INGREDIENT
Phase A	75.9%	Water
Phase B:	5%	Sunscreen*
	10%	Finsolv
	1%	Brij 72
	4%	Brij 721
Phase C:	1%	Xanthan Gum
	3%	Propylene glycol
Phase D:	0.1%	Glydant plus

* The sunscreens used were:

i) the cinnamate salt of aluminium (Example 1).

ii) the salicylate salt of aluminium (Example 2).

iii) the 4-methoxycinnamate salt of zinc (Example 3).

The process for formulation was

Heat Phase B to 80°C and homogenise. Heat Phase A to 80°C and then slowly add Phase B while stirring. Add in Phase C and then cool to 40°C and add Phase D.

CLAIMS

1. A sunscreen composition for application to human skin comprising a cosmetically acceptable vehicle containing a salt formed between an organic anion which absorbs ultraviolet radiation over at least part of the range from 290 to 400 nanometres, and a metal cation, characterised in that the metal cation is one or more of aluminium, zinc, titanium, tin, iron or lanthanum and the salt has a solubility of less than 2g/litre in water at 20°C.

2. A sunscreen composition according to claim 1 wherein the metal cation is aluminium, zinc or a mixture thereof.

3. A sunscreen composition according to any one of the preceding claims wherein the organic anion is one or more of

para amino benzimidazole-5-sulphonate
3-imidazol-4-yl acrylate
salicylate
p-methoxy cinnamate
2 ethyl hexyl-2-cyano-3,3 diphenyl acrylate
3,3,5 trimethylcyclohexyl-2-acetamido benzoate
p-aminobenzoate
cinnamate
3,4-dimethoxy phenyl glyoxylate
α-(2-oxoborn-3-ylidene)-p-xylene-2-sulphonate
α-(2-oxoborn-3-ylidene)toluene-4-sulphonate
α-cyano-4-methoxy cinnamate
2-phenyl benzimidazole-5-sulphonate
2-hydroxy-4-methoxy benzophenone-5-sulphonate
2,2'-dihydroxy-4,4'-dimethoxy benzophenone-3,3'-disulphonate.

4. A sunscreen composition according to claim 3 wherein the organic anion is one or more of

cinnamate
4-methoxycinnamate
salicylate
p-aminobenzoate.

5. A salt of a metal cation which is one or more of aluminium, zinc, titanium, tin, iron or lanthanum and an organic anion which absorbs ultraviolet radiation over at least part of the range from 290 to 400 nanometres, which salt has a solubility of less than 2g/litre in water at 20°C.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/42 A61K7/44 C07C57/44 C07C59/68 C07C65/10
C07C229/60

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 6 A61K

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

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 10, no. 17 (C-324) & JP,A,60 174 710 (KANEBO KK) 9 September 1985 see abstract ---	1-5
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