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TITLE

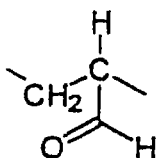
"POLYMERIC COMPOUNDS AND METHODS OF FORMULATING SAME"

FIELD OF THE INVENTION

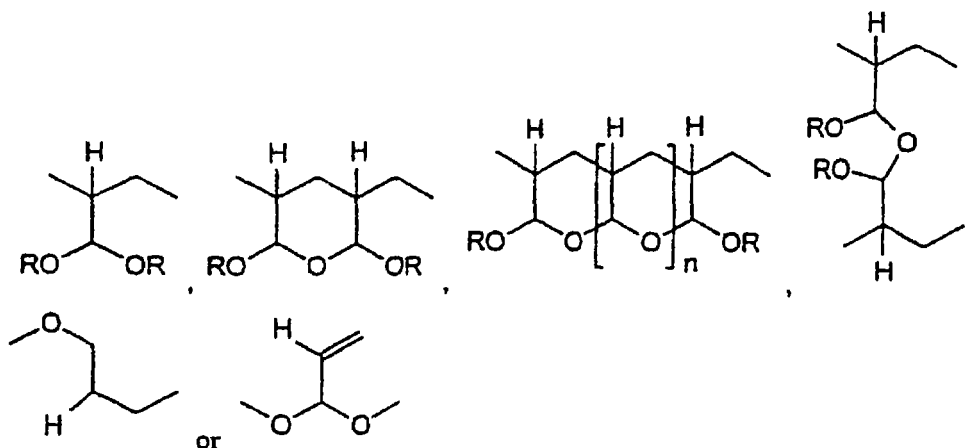
The present invention relates to polymeric compounds and methods of
5 formulating same, said polymeric compounds having a polyacrolein sub-unit in
aldehyde, hydrated, hemi-acetal or acetal form and having biostatic or biocidal
properties. More particularly, the present invention is directed to compositions
containing the above noted polymeric compounds and the biostatic and/or
biocidal uses of these compositions.

10 BACKGROUND ART

The broad-based antimicrobial properties of polymers having the repeating
polymeric unit:



15 ; or this unit in its hydrated, hemi-acetal or acetal form, represented by the
formulae:



kills a chosen quantum of vegetative micro-organisms within 10 minutes. That is, the antimicrobial activity of these compositions must be biocidal and quick. The formulations described herein are substantially aimed at these goals, but often achieve more, for example killing even extremely resistant bacterial spores within
5 the frequent standard of 24 hours.

Formulation of poly(2-propenal, 2-propenoic acid) simply by dissolution in dilute aqueous sodium carbonate, and then neutralisation to pH 7, has now been found to provide a composition that does not always kill micro-organisms fast enough to meet the above standards.

10 It is one object of the present invention to provide methods of preparing compositions containing compounds of the type described by the prior art and in particular poly(2-propenal, 2-propenoic acid), and which are useful disinfectants and/or antiseptics meeting these standards.

It is a further object of the present invention to provide a method of preparing
15 polymers and/or copolymers derived from acrolein in accordance with the above mentioned prior art for use as useful disinfectants and/or antiseptics.

It is a still further object of the present invention to provide a method of preparing polymers and/or copolymers derived from acrolein in accordance with the above mentioned prior art, for use in dermatological formulations, including sunscreens.

20 It is yet still a further object of the present invention to provide a method of preparing polymers and/or copolymers derived from acrolein in accordance with the above mentioned prior art for use in other applications including as a preservative or as an animal feed-additive.

Throughout this specification, unless the context requires otherwise, the word
25 "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

In a further form of the invention the composition exhibits reduced trans-dermal migration of low molecular weight components of the composition as a result of the presence of poly(2-propenal, 2-propenoic acid). The low molecular weight composition may contain a sunscreen agent, for example either or both of octyl methoxy cinnamate and octyl dimethyl p-aminobenzoate.

In a still further form of the invention the composition, especially for dermatological use, exhibits a sunscreensing effect as a result of the presence of poly(2-propenal, 2-propenoic acid).

In yet a further form of the invention the composition exhibits the formation of a continuous antimicrobial film on substrates, the method comprising the combination of poly(2-propenal, 2-propenoic acid) together with anionic surfactant and/or a phenol.

Preferably, the surfactant is sodium lauryl sulphate or disodium decyl (sulfophoxy) benzene sulfonate and disodium oxybis (decylsulfophenoxy) benzene sulfonate. The phenol is preferably o-phenyl-phenol.

In a still yet further form of the present invention the composition, especially for dermatological use, exhibits a free-radical screening effect as the result of the presence of poly(2-propenal, 2-propenoic acid).

In accordance with the present invention there is further provided a composition adapted for antimicrobial uses and/or dermatological uses and/or uses as an animal feed additive, the composition comprising poly(2-propenal, 2-propenoic acid) and one or more of the following: an anionic surfactant, a phenol, ethylene diamine tetra acetic acid, a lower alkanol, isothiazolinones, glutaraldehyde, sunscreen agent, and an absence of low molecular weight components of the composition.

In one form of the invention the composition comprises an anionic surfactant chosen from either sodium lauryl sulphate or disodium decyl (sulfophoxy) benzene sulfonate and disodium oxybis (decylsulfophenoxy) benzene sulfonate. The phenol is preferably o-phenyl-phenol.

It has now been found that basic aqueous solutions of poly(2-propenal, 2-propenoic acid) kill micro-organisms more rapidly than do acidic solutions of the polymer. This discovery led to the further finding that formulations of more stable, acidic compositions containing poly(2-propenal, 2-propenoic acid) and preferably, anionic surfactant, could subsequently be made basic and hence, more antimicrobially active, immediately before use as, for example, either a disinfectant and/or antiseptic and/or preservative; see Example 10 hereinafter.

It has now been shown that if a solution of poly(2-propenal, 2-propenoic acid) which contains a phenol, with anionic surfactant is acidified, a surprisingly stable emulsion is formed, and in this heterogenous system, the poly(2-propenal, 2-propenoic acid) in the hydrophobic phase is protected from chemical degradation by the hydroxyl ions in the hydrophilic phase; see Example 2 hereinafter. o-Phenyl-phenol is particularly useful, and in equal weight ratio with the poly(2-propenal, 2-propenoic acid).

It has now been shown that the inclusion of phenols additionally to anionic surfactants in compositions containing poly(2-propenal, 2-propenoic acid) allows further acidification of these compositions before any precipitation of the poly(2-propenal, 2-propenoic acid) ie. further chemical stability with respect to hydroxyl ion and/or base is achieved; see Example 2 hereinafter. Further, it has now been shown that if the composition containing poly(2-propenal, 2-propenoic acid) only is firstly stood, for example for about 11 days at about pH 9, in an aqueous alkaline medium, before the addition of the anionic surfactant and then phenol - precipitation will not occur at all, upon acidification; see Example 2 hereinafter.

It has now been shown that co-formulation of the composition containing poly(2-propenal, 2-propenoic acid), with anionic surfactant, and optionally with additionally a phenol, produces a composition which provides a continuous antimicrobial film upon substrates, after application thereto, eg. skin, flooring, walls, furniture etc. Without these additives, the film is invariably discontinuous and hence only partially protects the substrate, antimicrobially. It has now been shown that these films retain moisture, facilitating their protective antimicrobial

presence of poly(2-propenal, 2-propenoic acid) in an emulsion with the UV sunscreen octyl methoxy cinnamate, or octyl dimethyl p-aminobenzoate, is shown to prevent the migration of either of the sunscreens through a membrane which is a model for the skin; see Example 8 hereinafter. Hence, it is apparent that
5 poly(2-propenal, 2-propenoic acid) may be used as a co-formulant to reduce potential toxicity and/or allergy and/or antigenicity and/or irritation and/or inflammation from sunscreen agents, or other compounds, eg. phenols, which results from trans-dermal migration of such constituents, in dermatological preparations, into the blood-stream.

- 10 It has been shown further, that the peak at 268 nm and below provides significant UVC absorption. UVC energy is greater than 50% of the energy in sunlight (Lide, D.R., "CRC Handbook of Chemistry and Physics", CRC Press, 73rd edition, 1992-93, page 14-8) and is in the wavelength to which the skin is most sensitive ("Harry's Cosmeticology", J.B. Wilkinson and R.J. Moore Eds., Chemical
15 Publishing Co. Inc., New York, 1982, page 228) and which induces changes that alter the structure of DNA (Kano R.J. and Colome J.S. "Microbiology", West Publishing Company, 1986, page 162). Thus, it has now been found that it is an advantage to include poly(2-propenal, 2-propenoic acid) in dermatological sunscreen preparations.
- 20 It has now been shown that compositions containing poly(2-propenal, 2-propenoic acid) and containing only polymeric ingredients (eg. polymeric solvents/emollients and/or polymeric surfactants and/or emulsifiers) and/or volatile ingredients provide compositions for dermatological applications, free of any components which, after spreading on the skin, may migrate trans-dermally
25 and into the bloodstream to cause toxicity, allergy etc; see Example 8 hereinafter.

It has now been shown that the formulation of such compositions (eg free of conventional surfactants) is facilitated by the surfactant properties of poly(2-propenal, 2-propenoic acid).

3. Sporicidal Test

Add 1 mL of spore suspension of *B. subtilus var niger* (cfu 10^7 /mL) to 10 mL of solution of the sample in a sterile bottle, and vortex. Immediately remove 0.020 mL and add to recovery broth; repeat 5 times. Vortex and incubate at 37°C for 14 days. Confirm by "heat shock" to all tests.

4 Sporicidal Efficacy Test

Inoculate sterile glass slides with a suspension of *B. subtilus var niger* (cfu 10^7 /mL). Dry under vacuum for 24 hours at 30°C. Add 4mL sample solution to slide. After 10 min contact time, dry slides at 30°C for 72 hours. Sonicate and vortex slides into deactivation broth. Enumerate by performing 4 serial 1 in 10 dilutions in agar and incubate for 48 hours at 30°C.

5. Modified Kelsey Sykes Test

Add 1 mL of culture of test organism (2×10^8 - 2×10^9) cfu/mL containing 1% yeast to 3 mL of test solution. At 8 minutes, subculture 0.02 mL into each of 5 tubes containing recovery broth, and vortex. Incubate at 37° C for 48 hours

6. Stability Test

Poly(2-propenal, 2-propenoic acid) (1 g) was dissolved in 0.5% w/w aqueous sodium carbonate, and stood at room temperature. The stability was measured by the UV method.

The stability of aqueous solutions of polymers were followed by the disappearance of a UV peak near 268nm, and the appearance of a peak near 232nm; ca. absorbance at 268nm, of 0.02% solution = 1.5.

(c) Without hydroquinone; closed vessel

As above for (a), except hydroquinone was excluded, and the reaction vessel was a stoppered 1 litre flask; this resulted in a crystalline product - yield 21.0 g.

(d) Without hydroquinone; open to the air

- 5 As above for (a), except hydroquinone was excluded; this resulted in a crystalline product - yield 26.0 g.

After 3 days at room temperature, the diluted samples (0.25% w/w), being the product of examples 1(a) to 1(b), were tested by the Biocidal Test. The results are shown in Table 1:

10

Table 1

cfu/mL (i.e. Colony forming units/mL)

<u>Sample</u>	<u>1 minute</u>	<u>5 minutes</u>	<u>15 minutes</u>	<u>30 minutes</u>
1 (a)	6.6×10^5	1.6×10^5	50	0
1 (b)	7.7×10^5	4.7×10^5	8.2×10^3	0
1 (c)	9.0×10^5	8.1×10^5	6.2×10^3	0
1 (d)	8.3×10^5	2.1×10^5	60	0

Example 2

- 15 A series of tests were conducted to examine the impact of surfactant, and/or water, and/or buffer, and/or phenol on precipitation state and pH. Results are shown in Table 2:

- 15 -

with hydrochloric acid to pH5, was shown by the UV test to be more stable than a solution without the sodium lauryl sulphate over 4 days/room temperature.

5 Results are shown in Table 3:

Table 3

Sample	Sodium Lauryl Sulphate (2% w/w)	pH	Absorbance Ratio $\frac{A_{232}}{A_{268}}$		
			0hrs	96hrs	264hrs
3(a)	No	9.8	0	-	∞
3(a)	Yes	9.8	0	-	1.36
3(b)	No	5.0	0	1.05	-
3(b)	Yes	5.0	0	0	-

Example 4

10

A series of tests were conducted to examine the impact of the incorporation of EDTA or SLS on the antimicrobial activity of a 2% w/w solution of poly(2-propenal, 2-propenoic acid). Results of the Biocidal Test are shown in Table 4:

15

Table 4

cfu/mL

<u>Sample</u>	<u>1 minute</u>	<u>5 minutes</u>	<u>15 minutes</u>	<u>30 minutes</u>
Control	3.7×10^6	5.1×10^6	9.2×10^4	0
plus EDTA (0.25%)	3.7×10^6	0	0	0
plus SLS (0.25%)	3.7×10^6	2.7×10^6	0	0

Example 6

A series of tests were conducted to examine the impact of poly(2-propenal, 2-propenoic acid) on the odours of compositions containing phenols and/or glutaraldehyde. Results are shown in Table 6:

5 Solution A - 1g poly(2-propenal, 2-propenoic acid) was dissolved in 50mL of 1% w/w sodium carbonate.

Solution B - 1g of 4-tert-amylphenol and 2g of sodium hydroxide was dissolved in 40mL of water.

Solution C - 25% w/w glutaraldehyde in water.

10

Table 6

<u>Sample</u>	<u>1 minute</u>	<u>5 minutes</u>
Solution A + Water	15 min	little or no odour
Solution B + Water	15 min	medium phenolic odour
Solution C + Water	15 min	strong pungent, irritating odour
Solution B + Solution A	15 min	little or no phenolic odour
Solution C + Solution A	15 min	medium pungent, irritating odour

Example 7

A series of tests were conducted to examine any synergy between the antimicrobial activity of solutions containing poly(2-propenal, 2-propenoic acid) and EDTA and/or phenols, and/or isothiazolinones, and/or glutaraldehyde.

15

a	polymer		625				625
b	thiazolinone		1000				60
m	polymer+		625				80
	thiazolinone						
S			3				9

phenol = DOWICIDE A; thiazolinone = KATHON

Example 8

The effects of the presence of poly(2-propenal, 2-propenoic acid) on the migration of various agents across a model for skin were studied as follows

5 Results are shown in Table 8:

- 10 (a) poly(2-propenal, 2-propenoic acid) (0.5 g) was dissolved in polyethylene glycol 1000 (10 g) by stirring at 70°C, then sodium hydroxide micro-pellets (50 mg) were added and stirred for 2 minutes, and then octyl methoxy cinnimate (10 g; sunscreen agent) was added, followed by a mixture of the polymeric emulsifiers PEMULIN TR1 and CARBOPOL 2984 (0.5g; equal parts) whilst maintaining the temperature at 70°C/15 minutes. This resulting composition was then poured with stirring into water (79 g; at room temperature) and then the pH adjusted to 7.
- 15 (b) The same as (a) above, except the octyl methoxy cinnimate was substituted by octyl dimethyl p-aminobenzoate.
- (c) The same as (a) above, except the 1 : 1 mixture of polymeric emulsifiers were substituted by a 1 : 1 mixture of TWEEN 80 and stearic acid.
- 20 (d) The same as (a) above, except the 1 : 1 mixture of polymeric emulsifiers were substituted by a 1 : 1 mixture of TWEEN 80 and stearic acid - followed by CARBOPOL 2984 (0.25 g).

Firstly a solution of 1% w/w poly(2-propenal, 2-propenoic acid) in aqueous sodium carbonate, adjusted to pH 7.1, was treated with two successive additions of Fenton's reagent comprising 0.1% w/w ferrous sulphate (3 mL) and 30% v/v hydrogen peroxide (3 mL), and stirred; bubbles of oxygen were observed and the
5 typical golden colour of the solution of poly(2-propenal, 2-propenoic acid), disappeared.

Secondly, the following were mixed, as shown in Table 9:

Table 9 —

	Sample 1	Sample 2
Linseed oil (12.5 g)	yes	yes
Light petroleum bp 70-90°C (25 g)	yes	yes
Ethanol (20 g)	no	yes
Polymer (0.25 g) in ethanol (20 g)	yes	no
Cobalt (II) acetate (1%) in ethanol (0.1 g)	yes	yes

10 Yes = included in sample
No = NOT included in sample

The inhibition by the poly(2-propenal, 2-propenoic acid) of the cobalt catalysed free-radical autoxidation of the linseed oil was demonstrated by the speed of each of the samples becoming "tacky" after drawing as films upon glass, namely,
15 sample 2>sample 1.

Example 10

Shown in Tables 10A, 10B and 10C are results obtained for the following typical compositions derived from the present invention:

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Table 10A

Modified Kelsey Sykes Test:

<u>Sample</u>	<u>Organism</u>	<u>Inoculum (cfu/mL)</u>	<u>Fraction negative tubes</u>
10(a)	<i>E.coli</i>	5.3×10^8	5/5
	<i>S.aureus</i>	4.2×10^8	4/5
	<i>Ps. aeruginosa</i>	4.5×10^8	5/5
	<i>P.vulgaris</i>	2.7×10^8	5/5
10(b)	<i>E.coli</i>	5.3×10^8	5/5
	<i>S.aureus</i>	3.8×10^8	5/5
	<i>Ps.aeruginosa</i>	4.2×10^8	5/5
	<i>P.vulgaris</i>	3.3×10^8	5/5
10(c)	<i>E.coli</i>	4.3×10^8	5/5
	<i>S.aureus</i>	4.9×10^8	5/5
	<i>Ps.aeruginosa</i>	5.8×10^8	5/5
	<i>P.vulgaris</i>	2.8×10^8	5/5

Table 10B5 Sporicidal Test

<u>Sample</u>	<u>Time (hours)</u>	<u>Fraction Negative Tube</u>
10(a)	3	5/5
10(a)	7	5/5
10(a)	24	5/5

CLAIMS

1. A method for the preparation of compositions of poly(2-propenal, 2-propenoic acid), whereby the compositions exhibit one or more of the properties of increased stability, increased antimicrobial activity, reduced trans-dermal migration of low molecular weight components of the composition, and the formation of continuous antimicrobial film on substrates, the property or properties making the composition suitable for one or more of antimicrobial use, dermatological use, and/or use as an animal feed additive.
2. A method according to Claim 1 wherein the composition exhibits increased stability, the method comprising the acidification of compositions of poly(2-propenal, 2-propenoic acid) to which has been added one or more anionic surfactant and/or one or more phenol.
3. A method according to Claim 2 wherein the composition containing poly(2-propenal, 2-propenoic acid) is firstly stored in basic composition.
4. A method according to Claim 2 or 3 wherein the anionic surfactant is selected from either sodium lauryl sulphate or disodium decyl (sulfophoxy) benzene sulfonate and disodium oxybis (decylsulfophenoxy) benzene sulfonate.
5. A method according to Claims 2 to 4 wherein the phenol is o-phenyl-phenol.
6. A method according to Claim 1 wherein the composition exhibits increased antimicrobial activity, the method comprising preparation of the poly(2-propenal, 2-propenoic acid) in the presence of air and/or oxygen, with or without inhibitor.
7. A method according to Claim 1 wherein the composition exhibits increased antimicrobial activity, the method comprising the making of the composition of poly(2-propenal, 2-propenoic acid) into a basic composition.

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- 17 A method according to Claim 1 wherein the composition, especially for dermatological use exhibits a free-radical screening effect as the result of the presence of poly(2-propenal, 2-propenoic acid).
- 5 18. A composition adapted for antimicrobial uses and/or dermatological uses and/or uses as an animal feed additive, the composition comprising poly(2-propenal, 2-propenoic acid) and one or more of the following: an anionic surfactant, a phenol, ethylene diamine tetra acetic acid, a lower alkanol, isothiazolinones, glutaraldehyde, sunscreen agent, and an absence of low molecular weight components of the composition.
- 10 19. A composition according to Claim 18, wherein the composition comprises an anionic surfactant chosen from either sodium lauryl sulphate or disodium decyl (sulfophoxy) benzene sulfonate and disodium oxybis (decylsulfophenoxy) benzene sulfonate.
20. A composition according to Claim 18 wherein the phenol is o-phenyl-phenol.
- 15 21. A composition according to Claims 18 to 20 wherein the composition is an emulsion.
22. The use of compositions according to any one of Claims 18 to 21 for antimicrobial uses.
- 20 23. The use of compositions according to any one of Claims 18 to 21 for dermatological uses.
24. The use of compositions according to any one of Claims 18 to 21 as an animal feed additive.
- 25 25. A method for the preparation of compositions of poly(2-propenal, 2-propenoic acid) substantially as hereinbefore described with reference to any one or more of examples 1 to 10.