

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 May 2009 (14.05.2009)

PCT

(10) International Publication Number
WO 2009/059350 A1

(51) International Patent Classification:

C08F 16/34 (2006.01) *A61P 35/00* (2006.01)
A61K 31/78 (2006.01) *A01N 61/00* (2006.01)
A61P 31/04 (2006.01) *A61P 29/00* (2006.01)
A01N 35/02 (2006.01) *C08G 2/00* (2006.01)
A61P 7/02 (2006.01)

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(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW.

(21) International Application Number:

PCT/AU2008/001140

(22) International Filing Date: 6 August 2008 (06.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2007906124 7 November 2007 (07.11.2007) AU
2007906829 14 December 2007 (14.12.2007) AU
2008903576 11 July 2008 (11.07.2008) AU

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,
NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— *with international search report*



WO 2009/059350 A1

(54) Title: ANTI-MICROBIAL POLYMERS AND THEIR COMPOSITIONS

(57) Abstract: Polymers derived directly from acrolein monomer that are substantially soluble in water and/or aqueous media, together with methods for preparing same and compositions containing such for use as an anti-microbial, anti-cancer, anti-inflammatory and/or anti-coagulant.

“Anti-Microbial Polymers and their Compositions”

Field of the Invention

The present invention relates to anti-microbial polymers and their compositions. The polymers are derived from the aqueous, base-catalysed polymerisation of acrolein and/or its acetals with hydroxy-alkanoic acids - optionally in the presence of ascorbic acid and/or anti-oxidant and/or alkanol. The present invention is in part directed to the manufacture of these compounds, and *in vitro* or *in vivo* uses of the compositions derived therefrom, especially as anti-microbial agents within the gastro-intestinal tracts of humans or animals.

10 Background Art

A “pure” polymer is inherently a mixture of different molecules. These molecules have different molecular weights, and often, different configurations – depending upon the polymerisation conditions by which the polymer was formed from its monomer(s). As a result, the mode of polymerisation of the monomer determines the chemical structure and hence, all properties of the polymer. It is groundless and most often wrong to assume that all polymers from the one monomer are either the same or react in the same manner. In particular, acrolein (2-propene-1-al) has alternative reaction-sites and every “polyacrolein” is not the same.

In this invention, polymerisations to yield a range of novel and useful polymers of acrolein and/or its acetals with hydroxy-alkanoic acids are described, so as to give distinct polymers of different and desired physical, chemical and anti-microbial properties.

The polymerisation of acrolein was first reported¹ in 1843 – providing a solid, insoluble in all common solvents, and of no significant use.

Much later in 1987, Melrose et al² first described the manufacture, compositions and uses of a range of polymers of acrolein as anti-microbial agents; by demonstrating a structural analogy between the polymers and the chemical sterilant glutaraldehyde (pentane-1,5-dial), the carbonyls were assigned as the anti-microbial sites in the polymers. Since water is the growth-domain of nearly all micro-organisms, water-solubility or at least an ability to disperse is essential for anti-microbial activity against these micro-organisms; therefore, usually, the polymers also contained hydrophilic co-monomers, so as to make the polymers more water-soluble. But still, anti-microbial activity of the polymers remained low, due to their high content of co-monomer which only contributed hydrophilicity.

In an attempt to circumvent this limiting insolubility in water – subsequent art³⁻⁷ always requires firstly, the anionic homo-polymerisation of acrolein monomer only, to yield an insoluble polyacrolein. Therefore, this was followed by secondly, filtration of the resulting water-insoluble polymer - then thirdly, prolonged autoxidation of the polymer by heating in air or oxygen over several days, to yield the acrolein-polymer, poly (2-propenal, 2-propenoic acid) having a content of 0.1 to 5 moles of (hydrophilic) carboxyl/Kg of polymer, so as to achieve water-solubility, albeit only⁴ at pHs above 5.5. Fourthly, the auto-oxidised polymer may be treated with polyethylene glycol (PEG) over a range including both weakly basic then weakly acidic conditions, to yield an acrolein-polymer having increased hydrophilicity, and acetal groups derived from reaction with the polyethylene glycol. However, this sequential synthesis is substantially limited, in that its autoxidation-step is so protracted - and tenuous, due to the well-known propensity of acrolein-polymers to revert to insoluble gums during filtration, and especially upon heating – a property⁸ which had inhibited their use for over one hundred years. As a direct consequence of these disadvantages, this process can not be repeated, successfully, on a regular basis.

Thus, it is one (first) objective of this invention, to provide novel, anti-microbial and water-soluble polymers of acrolein by a practical synthetic route – and in

particular, in so doing, to avoid the necessity of proceeding through an autoxidation-step of polymer.

Within the gastro-intestinal tract of humans, the bacterium *Helicobacter pylori*¹⁰ may be harboured in tooth-plaque; also surrounded by protective natural polymers, it is found in the stomach of about 50% of persons world-wide. In humans, it is unequivocally associated with stomach and duodenal ulcers and cancer; noteworthy, the bacterium thrives within the acidic pHs of the stomach. Therapy for infected patients necessarily includes a regime of a range of different antibiotics – since it is increasingly being frustrated by strains of *H. pylori* which are resistant to known antibiotics. In animals, but with less certainty, other *Helicobacter* have also been associated with gastro-intestinal disease.

Always, soluble polymers of acrolein have shown an exceptionally wide range of anti-microbial activity – even against antibiotic-resistant germs – and this is explained by the polymers' content of carbonyl groups which react destructively and indiscriminately with ever-present proteins in the outer membranes of all micro-organisms. Particularly, Melrose et al⁷ have reported anti-microbial activity of the acrolein-polymer, poly (2-propenal, 2-propenoic acid) against *H. pylori*, in vitro at pH 4 or pH 7 – but the polymer's water-solubility and anti-microbial activity is greatly reduced at the lower pHs associated with stomach-contents (that is, below pH 4).

Indeed, if tested, every acrolein-polymer which is soluble in aqueous solvents – has demonstrated anti-microbial activity. However, it is a central tenet of this invention that there has always been a challenging compromise to this latent anti-microbial property of all acrolein-polymers: It is solubility. Particularly, lack of solubility compromises the manifestation of the polymers' substantial and broad anti-microbial properties over low pH ranges in water.

Thus, it is a second objective of this invention to provide novel polymers from acrolein, such that the polymers are soluble over the low pH ranges found within the stomach of humans, and associated with the growth of especially, *H.pylori*.

5 It is well-known^{3-7, 9} that acrolein can be a source of extreme irritation to humans or animals. It is generally recognised that any molecule having molecular weight less than 800, reasonably freely passes through natural membranes (skin or intestines); thus, irritating acrolein-monomer, low molecular weight oligomers of acrolein or its acetals have the propensity to penetrate protective membranes in humans or animals and hence, enter the vascular system, causing irritation.

10 Therefore, it is a third objective of this invention to provide polymers from acrolein which are novel, water-soluble at all pHs and anti-microbial - and also having structures with fewer propensities to migrate across membranes.

Specification WO 2005/044874 describes a method for the manufacture of what are referred to as soluble, microbiologically active and stable acrolein polymers.
15 Importantly, the polymer described is not derived directly from acrolein and is subject to the known problems associated with the initial filtration of a derived acrolein and is consequently limited by the formation of emulsions and gums. These issues have been highlighted in the prior art⁴. The polymers produced by this method are not significantly anti-microbial and the minimum kill
20 concentrations (MKC's) disclosed in the specification are known to involve a 24 hr exposure time. The method of manufacture described includes a number of limitation in addition to that noted immediately above. These include autoxidation/severe heating conditions at 65°C and above (which are described as essential), derivation in acidic conditions, a requirement for subsequent
25 treatment of the polymer with base to achieve stability, substantial degradation of the polymer as evidenced by the brown colour thereof, and the polymer derived in this manner is further poly-acetal and contains considerable carboxyl as is apparent from its dissolution in sodium carbonate solution (normally about pH 11) only giving a pH of 8 as the result of neutralisation of carboxyl.

This discussion of the background is only intended to facilitate an understanding of the present invention. The discussion is not an acknowledgement or admission that any of the material referred to is or was part of the common general knowledge as at the priority date of the application.

- 5 In this specification:
- (a) Unless specifically designated, always, an "alkanol" describes any compound having one or more hydroxyl groups, including hydroxy-derivatives of alkanes, alkenes, alkynes, aromatics, heterocycles, sugars, natural or synthetic polymers;
 - 10 (b) Unless specifically designated, always, an "hydroxy-alkanoic acid" or "alkanol containing carboxyl(s) groups" includes hydroxy-carboxylic acid-analogues related to alkanes, alkenes, alkynes, aromatics, heterocycles, sugars, natural or synthetic polymers - and as well as referring to mono-functional compounds in either one or both of these functional groups - may also
15 include such compounds containing more than one hydroxyl group and/or more than one carboxyl group and/or other groups which do not materially interfere with the functionality of either the hydroxyl or carboxyl groups;
 - (c) Unless specifically designated, always, "acetal" may describe mono-acetal and/or di-acetal;
 - 20 (d) Unless specifically designated, always, "polymerisation", may describe homo-polymerisation and/or co-polymerisation;
 - (e) Unless specifically designated, always, "olefinic monomer containing carboxyl group(s)" describes an olefin-monomer capable of polymerisation and containing one or more carboxyl groups in any state of ionisation;

- (f) Unless specifically designated, always, "acrolein" may describe and/or may include not only the free acrolein-monomer, but also in the same context, the acrolein-residue within a polymer;
- (g) Whilst *H.pylori* is discussed in particular herein, the invention is applicable to
5 other *Helicobacter* or other micro-organisms, especially amongst others, bacteria, fungi, yeasts, viruses and/or protozoa;
- (h) Whilst the present invention is described with reference to acrolein, it is not to be understood as limited thereto, but rather includes derivatives of acrolein (such as, methacrolein).
- 10 Throughout the specification and claims, unless the context requires otherwise, the word "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.

Disclosure of the Invention

- 15 In accordance with the present invention there are provided polymers derived directly from acrolein monomer that are substantially soluble in water and/or aqueous media.

Preferably, the polymers of the present invention are soluble at a pH of less than about 4.

- 20 Still preferably, no intermediate autoxidation step is employed in the preparation of the polymers of the present invention.

Still further preferably, the polymers of the present invention are substantially anti-microbial.

Yet still further preferably, the polymers of the present invention have an average molecular weight of greater than about 1000 Daltons. The polymers may be prepared so as to have fewer propensities to migrate through membranes as the result of having high levels of polarity and/or hydrophilicity due to included
5 carboxyl groups, either within hydroxy-alkanoic acids attached to the polymers as acetal groups, or within monomer-residues in the polymers – and whereby these polymers of average molecular weight greater than 1000 Daltons are substantially inhibited from passing through membranes which are designed to be transmissible to all molecules up to molecular weight 1000 Daltons.

10 The polymers of the present invention may additionally or further be prepared so as to have fewer propensities to migrate through membranes as the result of having within, structures resulting from the reaction between alkanol (and/or its ion) and proximate carbons to the carbonyl in acrolein-residues within the
15 1000 Daltons are substantially inhibited from passing through membranes which are designed to be transmissible to all molecules up to molecular weight 1000 Daltons.

The polymers of the present invention preferably have a carboxyl content of between about 0.1 and 25 moles/Kg of polymer.

20 In accordance with the present invention there is further provided a composition, being a solution, gel, emulsion or suspension of matter comprising at least in part polymers as defined hereinabove.

In accordance with the present invention there is still further provided an *in vitro* and/or *in vivo* anti-microbial composition comprising at least in part polymers as
25 defined hereinabove.

In accordance with the present invention there is yet still further provided a method for the synthesis of polymers defined hereinabove, the polymers having

been prepared so as to incorporate acetal-structures resulting from the reaction between acrolein (monomer or residue) and hydroxy-alkanoic acid (and/or its ion), or so as to incorporate within, structures resulting from the reaction between alkanol (and/or its ion) and proximate carbons to the carbonyl in acrolein-residues
5 within the polymers.

The method may further comprise the polymerisation, in basic aqueous solution in the presence of a basic catalyst, of acrolein, and/or acrolein plus alkanol, and/or other organic nucleophile, and/or acetal of acrolein with a hydroxy-alkanoic acid – optionally, in solution with other monomer, and/or ascorbic acid (and/or its ion)
10 and/or other antioxidant and/or other acid.

The basic aqueous medium is preferably aqueous sodium hydroxide at a pH of between 9 to 14, further preferably between pH 10 to 13.

The hydroxy-alkanoic acid is preferably tartaric acid and/or ascorbic acid. The acetal is preferably formed by acid-catalysis, further preferably using dilute sulphuric acid. The alkanol is preferably a polyalkylene glycol. The polyalkylene
15 glycol is preferably polyethylene glycol.

The polyethylene glycol preferably has average molecular weight of 200 to 10,000 Daltons. The ratio of polyethylene glycol:acrolein or acrolein incorporated as its acetal, is preferably greater than 1:1 v/v, preferably greater than 4:1 v/v.

20 Preferably, the monomer is acrylic acid, further preferably at a ratio of acrylic acid:acrolein or acrolein incorporated as its acetal in the range of 0.05 to 0.10:1 w/w. The organic nucleophile is preferably a carboxylic acid. The ratio of ascorbic acid:acrolein or acrolein incorporated as its acetal is preferably in the range of about 0.01 to 10:1.00 w/w. Still preferably, the ratio of ascorbic acid:acrolein or
25 acrolein incorporated as its acetal is in the range 0.1 to 2.0 : 1.0 w/w - and preferably 0.6:1.0 w/w.

In accordance with the present invention there is still further provided methods for the treatment of cancer, disorders of coagulation, and/or inflammatory disorders, each method comprising the administration to a subject of a pharmaceutically acceptable amount of a polymer as described hereinabove, or a composition
5 containing such.

In accordance with the present invention there is yet still further provided the use of a polymer as described hereinabove in the preparation of a medicament for the treatment of one or more of cancer, disorders of coagulation, and/or inflammatory disorders or conditions.

10 It is hypothesized herein, that the ubiquitous, complete insolubility of polymers resulting from prior-art polymerisations of acrolein monomer³⁻⁷ – may be inhibited or prevented (and anti-microbial properties manifested) by either one, or a combination of two or three methods; primarily, it is hypothesized that the totality of the insolubility is only consistent with inter-molecular cross-linking within the
15 polymers:

Method 1: As this cross-linking was taking place at alkaline pHs, it was concluded that the rapidly-forming cross-links could not be acetal, since these form only under acidic conditions¹¹; hence, the links causing insolubility would likely be of radical-origin and could be inhibited during or after polymerisation
20 by ascorbic acid, (having the properties of a water-soluble anti-oxidant and as well, an acid).

Thus, this first method, using ascorbic acid and/or its ion (see Example 5(a) hereinafter), in accordance with objectives one and two of this invention has been successfully used – without an autoxidation step - to provide polymers which are
25 novel, anti-microbial and water-soluble at all pHs.

It is important to note that all three of the “polyacroleins” derived from prior art (see Example 1 hereinafter) and the polymer from the above polymerisation of

acrolein in the presence of ascorbic acid (Example 5(a)) - are very different: Obviously, the final polymer from either synthesis is derived from a different precursor – the prior art polymer, from a second intermediate-polymer (Example 1) – the polymer of this invention, directly from the monomer (Example 5(a));

5 furthermore, the prior-art polymer is insoluble below pH 4, has a carbonyl-content of 380% and is strongly coloured, indicating substantial conjugation within the molecule – whereas the polymer of this invention is soluble at all pHs below pH 4, has a carbonyl-content of only 40% and is without significant colour or apparently, conjugation. The prior art, first intermediate-polymer is totally

10 insoluble and is demonstrably, a different “polyacrolein”. Whereas the prior-art “polyacrolein”, termed the second intermediate-polymer (and being derived from autoxidation of the first intermediate-polymer) is substantially anti-microbial (only a small amount is required for inhibition of microbial growth) - the polymer from this invention is initially, eight-fold less anti-microbial; treatment of this second

15 intermediate-polymer from prior art with base and polyethylene glycol, *increased* by two-fold the amount of polymer required for inhibition (Example 1) – similar treatment of polyacrolein from the present invention, produced the opposite effect, *decreasing* forty-fold the amount of polymer required for inhibition (Example 5); further, this second intermediate-polymer is also obviously different from the

20 totally soluble polymer herein, in that it is not soluble below pH 5.5.

Method 2: If, during ionic polymerisation by base organic nucleophile, especially alkanol is included – it is hypothesized that the formation of inter-molecular bonds causing insolubility of polymer can be inhibited by steric hindrance between separate molecules – as the result of the alkanol or its ion

25 bonding by Michael-type reaction^{11A} to active (in the sense of active-propensity to lose attached hydrogen), proximate carbons to the carbonyl groups in the polymers - thus forming bulky side-groups in the separate polymer-molecules which inhibit cross-linking and insolubility.

Thus, this second method, using alkanol (see Examples 6 and 7 hereinafter) in

30 accordance with objectives one and two of this invention has been successfully

used – without an autoxidation step - to provide polymers which are novel, anti-microbial and water-soluble at all pHs.

The successful prevention of cross-linking and its resultant insolubility of acrolein-polymers in this way, herein (Examples 6 and 7), was initially unexpected, for the reason that previously, polymerisations between acrolein and alkanol have always yielded *insoluble* polymers⁹. Further, given the immediacy of the precipitations of polymer in the prior art⁴, it is additionally unexpected that the reaction brought about by the alkanol during the polymerisation herein is sufficiently fast, so as to prevent any precipitation or even clouding.

10 The difference between the polymer derived this way herein (Example 7), and the polymer (also treated with alkanol) in prior art⁵ (Example 1) is apparent: Firstly, the polymer of this invention (the former) has been synthesised directly from acrolein monomer – the polymer from prior art (the latter) has been synthesised from poly (2-propenal, 2-propenoic acid) ; secondly, the former, having been prepared entirely under basic conditions can not be of acetal structure^{11B} –
15 whereas, the latter prepared under conditions including acid-treatment, has been assigned an acetal structure with the alkanol; thirdly, the former is soluble at pHs below 4 – the latter is not; fourthly, the former is colourless – the latter is deep red, indicating considerable un-saturation within the molecule; fifthly, the former has a
20 carbonyl-content of 20% - the latter has 380%; sixthly, the former is many-fold more anti-microbially active, inhibiting mixed microbes at 100 ppm and killing 10⁶ E.coli in 3 minutes – whereas for the latter, the parameters were 500ppm and 3 hours, respectively.

25 Additionally, the polymer (Example 6) of the present invention has similar differences to the polymer of prior art (Example 1).

In summary, as well as being many-fold more anti-microbial than the “super-activated” polymer of prior-art⁵ – the polymers of the present invention are water-soluble over a broad range of pHs, whilst the prior art polymer is not.

Method 3: If, before the polymerisation, at least a portion of the acrolein was converted to its acetal derivative with a hydroxy-alkanoic acid – it is hypothesized that the formation of the inter-molecular bonds causing insolubility can be inhibited, especially under the basic conditions, as the result of inter-molecular repulsion between the ionized carboxyls within the polymer-molecules of the present invention.

Thus, in accordance with objectives one and two of this invention there is provided a third method – without an autoxidation step - for the preparation of polymers which are novel, anti-microbial and water-soluble at all pHs, derived from the polymerisation of acrolein, its derivatives and/or its acetals with hydroxy-alkanoic acid (see Example 3 hereinafter) - optionally, additionally performed in the presence of ascorbic acid, the method also giving in substantial yield, polymers which are water-soluble at all pHs, and anti-microbial (see Example 4 hereinafter).

Further, the novel, anti-microbial polymers of acrolein provided by all three methods have practical levels of stability under simulated pH and resident-time within the stomach.

By design herein, another important advantage in forming the acetals with hydroxy-alkanoic acid is that it renders the polymers more hydrophilic, causing the polymers to have fewer propensities to migrate across biological membranes *in vivo*; it is well-known in the art that increased hydrophilicity slows migration.

Thus, in accordance with a third objective of the present invention, there are provided polymers of acrolein which are novel, anti-microbial, soluble at all pHs - and which have a reduced propensity to migrate across biological membranes.

The polymers derived from the co-polymerisation of an acetal, according to the present invention have a carboxyl-content of about 0.1 to 15 moles/Kg of polymer - preferably about 5 to 10 moles carboxyl/Kg of polymer. That is, usually, the

novel polymers have higher carboxyl contents than those of prior art – and a reduced propensity to migrate across biological membranes.

During dialyses, these polymers were inhibited from travel through membrane which is designed to be permeable to all molecules up to 10,000 Daltons.

- 5 Herein, for estimations of anti-microbial activity, an assay of inhibition of growth of micro-organisms in milk was chosen, as milk contains a wide range of different micro-organisms, and contains proteinaceous materials which usually, readily bind-with and de-activate acrolein-polymers. The Examples provided hereinafter show that this invention provides substantially anti-microbial polymers – in these
10 demanding conditions. Also, the polymers were estimated against diarrhoea-producing bacteria, *Escherichia coli*.

The polymers of Examples 4 and 7 hereinafter are two preferred polymers of the present invention – both are prepared without an autoxidation step – are soluble at all pHs – and have structures designed to give minimal migration across
15 membranes relative to that of prior art acrolein polymers. Additionally, a summary of results from these estimations for these polymers, and the best prior art polymer (Example 1) shows that there is also provided herein, polymers which are considerably more anti-microbial than any acrolein-polymers of the prior art:

20 TABLE 1: Comparison of Polymeric Anti-microbials (See “Examples” section for details of methods)

Example	Minimum amount for total kill (ppm)	Time to kill <i>E.coli</i> (mins.)
4	250	180
7	50	3
1	500	180

Best Mode(s) for Carrying Out the Invention

In chronological order, the method of the present invention comprises the following, outline steps:

- 5 1. Optionally, partial conversion, using acid-catalyst, of acrolein monomer to its acetal derivative with an hydroxy-alkanoic acid;
2. Polymerisation in basic aqueous solution and providing a basic catalyst, of acrolein, and/or acrolein plus alkanol and/or other organic nucleophile(s) (and/or its ion), and/or the product from Step 1 above – optionally, in solution with other monomer(s), and/or ascorbic acid (and/or its ion) and/or 10 other antioxidant and/or other acid ; and
3. Adjustment of the resulting solution to pH 7 with acid.

15 Additionally, at the commencement of Step 3 (before adjustment to pH 7), it will be apparent that all the preparations of this invention are amenable to dialysis against water; especially, this totally removes any low molecular weight fractions which may penetrate membranes, in vivo. However, when applying this technique to the polymer (see Example 4 hereinafter), some loss of anti-microbial activity was observed; alternatively, this can be prevented by dialysis against sodium tartrate solution, adjusted to pH 6. A decrease in carbonyl-content accompanies 20 this alternative and the recovery of anti-microbial activity – and suggests that this acetal-polymer has a different site which causes the anti-microbial activity, other than carbonyl.

25 The combination of methods (of Examples 4 and 7 hereinafter) within Example 8, discussed hereinafter, represents an additional, preferred methodology of the present invention, and yields a polymer of substantial anti-microbial activity. However, an analogous combination of the methods of Examples 4 and 6 yields a polymer of only insignificant anti-microbial activity (see Example 9 hereinafter). The common element of Examples 8 and 9 is that the carbonyls of polymers from both are hindered by acetal-formation (by inclusion of the common method of

acetal-formation from Example 4); the reason for their difference is apparent when it is concluded that the site of anti-microbial activity in the polymer of Example 7 is at its remaining and active carbon atoms with which the PEG reacts – whereas in the polymer of Example 6, all active carbons are reacted with PEG, and the carbonyl groups remain exclusively as the sole site of anti-microbial activity. (Following alternative dialysis-conditions of polymer derived in Example 4 – the resultant-polymer which is the more active anti-microbial, has the lower carbonyl-content; this also indicates an alternative site of activity to the carbonyl groups.) Thus, it is apparent that the method of the present invention has the additional advantage of providing polymers having two different anti-microbial sites – for example, from Examples 4 or 7 – or from Example 6, respectively. Particularly, this presents an alternative defence against germs evolving anti-microbial resistance. In Step 1, usually a stoichiometric excess of acrolein over hydroxy-alkanoic acid is used, so that in Step 2, co-polymerisation occurs between the acetal of acrolein and the remaining, excess acrolein.

In Step 1, the hydroxy-alkanoic acid is, for example, tartaric acid, lactic acid, glyceric acid, glycolic acid, citric acid or 2-hydroxy-butanoic acid - or other hydroxy-carboxylic acid conceptually derived from the selective oxidation of a diol, an alkan-diol, a polyol, a poly(oxyalkene), a sugar or other molecule containing multiple hydroxyls, such as ethane-1,2-diol, glycerol or polyethylene glycol. A thiol-analog of a hydroxy-alkanoic acid, for example, glutathione, may also be used.

In Step 1, amongst other evidence herein, acetal-formation is confirmed by contrasting the properties of polymers without acetal (Examples 1 and 5(a)) with polymers containing acetal (Examples 3 and 4, respectively).

As they form cyclic acetals with acrolein - which are more favoured (than linear acetals) in their equilibrium-forming reaction¹³ - preferred hydroxy-alkanoic acids are tartaric acid or ascorbic acid, especially the former. Within practical limits, in

polymers, the acetal of tartaric acid was stable at pH 2 at 37° C for 4 hours – conditions associated with the resident period of contents in the stomach.

In Step 2, the preferred base is aqueous sodium hydroxide solution – having a pH between 10 and 13.

- 5 In Step 2, the preferred organic nucleophile is an alkanol, although a carboxylic acid may be used; a more preferred alkanol is a polyalkylene glycol, especially polyethylene glycol; the preferred molecular weight of the polyethylene glycol is in the range 200-2000 Daltons. For a given weight-ratio of acrolein to alkanol, higher molecular weights of the alkanol give more hindrance and, polymers which
- 10 have fewer propensities to migrate through membranes; conversely, lower molecular weight alkanols may be preferred in order for the acrolein polymers to penetrate natural polymers surrounding target-germs. The preferred ratio of polyethylene glycol: acrolein (or its acetal) is greater than 1:1 w/w – and more preferably, greater than 4:1 w/w.
- 15 In Step 2, and in keeping with discussion hereinabove, a relatively low stoichiometric ratio of hydroxyl groups with the polyethylene glycol (brought about by a high molecular weight and/or a low concentration of the polyethylene glycol) will leave un-reacted active carbons within the resulting polymer – and favour anti-microbial activity at this site in the polymer; the converse will favour anti-microbial
- 20 activity at the carbonyl groups within the polymer.

In Step 2, if both tartaric acid and polyethylene glycol are used - MW 2000 of the latter, without heating is much preferred (see Example 8 hereinafter).

- In Step 2, ascorbic acid (and/or its ion) is preferred; water-soluble antioxidants other than those known in the art may be used. Ascorbic acid (neutralized with
- 25 base to prevent the formation of acetal) – when used without augmentation of alkanol as the means of preventing insolubility, should be used at greater than about 0.15 part by weight to every 1.00 part of acrolein or acrolein incorporated as

its acetal. Ascorbic acid may contribute as an antioxidant, alkanol or carboxylic acid, to inhibit cross-linking between polymers.

In Step 2, the optional co-monomer (if used) is usually an olefinic monomer containing carboxyl groups – preferably, acrylic acid at about 0.05 to 0.10 part by weight to every 1.00 part of acrolein or acrolein incorporated as its acetal. Also,
5 the co-monomer may contain more than one carboxyl group e.g. maleic acid. The usual purpose in the inclusion of monomer is to provide either repulsion between the molecules (or their ions) during polymerisation, and/or hydrophilicity in the product-polymer.

10 Polymers of this invention have been provided either as their aqueous solutions (see Examples 2, 5, 8) – or after dialysis, isolated as the dry liquid-polymers (see Examples 4, 6, 7).

The polymers of this invention have physical and anti-microbial stability which makes them practical for their intended uses – and in particular, under the
15 conditions (pH 2/37°C/4 hours) which simulate residence-time in the stomach.

Being free of the protracted autoxidation step – in contrast to prior art, there is now provided, syntheses of water-soluble and substantially anti-microbial polymers, amenable to the greatly improved economies of continuous-flow manufacture (over the batch-wise manufacture required of the prior art).

20 It will be apparent that the examples herein contain laboratory methods; industrially, they will be varied considerably, in ways which are readily apparent to those skilled in the art – and which remain within the spirit and scope of the present invention.

Throughout the description of the present invention, in all methods, the solvent is
25 either aqueous or entirely water. However, the preparations are amenable to heterogeneous techniques - including emulsion, dispersion or suspension techniques.

It is also apparent that the reactions described herein, with free acrolein monomer and/or its derivatives, especially with hydroxy-alkanoic acids – are amenable to the same reactions with fixed acrolein- residues within polymers.

5 It will be apparent to those skilled in the art that the polymers of this invention may be formulated in controlled-release compositions and/or with other materials as solids, solutions, emulsions, suspensions or gels, into compositions suitable for use in human or animal health care, especially within the gastro-intestinal tract.

EXAMPLES

10 EXAMPLE 1; PRIOR ART⁵; PREPARATION OF POLY (2-PROPENAL, 2-PROPENOIC ACID)

With continued stirring at room-temperature, in chronological order:

1. Freshly distilled and inhibitor-free acrolein (15g) was added to water (180g); and
2. The pH was adjusted to 10.5 by addition of aqueous sodium hydroxide (ca 15 5ml; 0.8% w/w).

After 30 minutes, the insoluble precipitate of the first intermediate-polymer (which had formed within the first minutes) was filtered, then air-dried, firstly at room-temperature for 1 day (dry weight 7.62g; polymerisation-yield 50%; softening around 80°C) and then by successive heat-increments to 75°C over 2 days, 20 followed by heating at 85°C for 1 day. This resulting second intermediate-polymer dissolved in basic, aqueous solvent to give a deep red solution – but precipitated at pHs below 6; Microbiological Assay showed, minimally, inhibition at 250ppm of polymer.

25 A sample of this autoxidized, second intermediate-polymer (5g) was partly dissolved by stirring and heating at 65°C in polyethylene glycol (60g; MW ca 200), and then aqueous sodium hydrogen carbonate (30g; 1% w/w). The resulting, deep-red solution (pH 8) was heated at 100°C for 4 hours to yield a solution (final

pH 6) of the required (third) acrolein-polymer, namely, poly (2-propenal, 2-propenoic acid).

Microbiological Assay (see all methodologies, below) showed, minimally, inhibition at 500ppm of polymer, and kill of *E. coli* after 180 minutes; oxidation-products were indicated by a carbonyl assay-result of 380% within the polymer; the polymer precipitated from solution, below pH 4.

The invention is illustrated by the following examples, which should not be regarded as restricting the scope of the invention:

ESTIMATE OF ANTI-MICROBIAL ACTIVITY

10 (a) Microbiological Assay: Inhibition of micro-organisms: Duplicate samples, in serial 50% dilutions, were made-up in aqueous solution (5ml) and each added to separate stoppered test-tubes containing pasteurised, whole-milk (20ml) in which sucrose (3g) had been dissolved. Each resulting sample in the test-tubes was placed in a water-bath at 32-38°C, for 20-24 hours; a “positive” test-tube was prepared and contained water (5ml) instead of sample-solution (5ml). The pH of the contents of each was measured before and after these protocols. “Inhibition” was noted when there was greater than 0.5 pH difference between the contents of a test and the “positive”; results are reported as ppm w/w of polymer (assuming polymerisation had proceeded in 100% yield).

20 Essentially, this assay measures anti-microbial capacity to inhibit a wide range of micro-organisms, and is designed to have relevance to the circumstances of an anti-microbial in the presence of food constituents, at body-temperatures. The accuracy of the assay is considered to be within 1 dilution.

25 (b) Kill of *Escherichia coli* : In duplicate, samples were dissolved in 1% aqueous sodium bicarbonate so as to give a polymer solution (0.125% w/w of the polymer – assuming 100% polymerisation). A sample of the solution (20 ml) was mixed with 0.1 ml of 10xE6 viable haemolytic *E. coli* (serotype O149, K88). At time

intervals 0, 3, 10, 30 and 180 minutes, an aliquot (in duplicate) was plated on blood agar plates and the counts estimated semi-quantitatively.

ESTIMATE OF CARBONYL

This estimate is based upon an established method by Smith¹⁴. The aqueous sample (1g) was weighed to an accuracy of 0.01g - water (9g) was added, and then the solution of the sample was brought to pH 6.00 by the addition of either 0.01M hydrochloric acid or 0.01M aqueous sodium hydroxide, as appropriate.

A 1% solution of hydroxylamine hydrochloride (50ml) was brought to pH 6.00 with 0.01M aqueous sodium hydroxide.

10 The above sample-solution and reagent-solution were mixed and stood at room-temperature for 30 minutes; the reactants were back-titrated with 0.01M aqueous sodium hydroxide (V ml) to pH 6.00.

15 Then, the w/w% carbonyl content of the original sample (W g) – estimated as acrolein, equals: $(V \times 0.10 \times 5.6)/(W \times f)$ where f is the weight-fraction (expressed as decimal) of polymer within the aqueous sample (assuming a polymerisation yield of 60% which herein, was found in practice, and gave results of carbonyl-content in polymers, comparable and similar to prior art). Results of duplicate determinations were averaged.

QUANTITATIVE ANALYSIS OF POLYMER SOLUTIONS BY DIALYSIS

20 In duplicate, the aqueous solution of polymer (1.00g) was dialysed in magnetically-stirred, single-sided micro-dialysis chambers (SIGMA-ALDRICH) against water (1L) for 4 to 5 hours – using low-binding cellulose acetate membranes (SIGMA-ALDRICH) - as applicable, of upper molecular weight permeability of either 1,000 Daltons or 10,000 Daltons. The dialysates were dried
25 at room-temperature to constant weight, to recover the polymer-fraction.

IN VITRO SIMULATION OF ACIDIC, RESIDENT-CONDITIONS IN THE STOMACH

In duplicate, the aqueous sample (1.00g) was dissolved in water (9g) and then made pH2 by the addition of 10% hydrochloric acid; also in duplicate, as the
5 blank, the sample was similarly treated – but substituting the same volume of water for the hydrochloric acid.

All were heated at 37°C/4 hours – then, adjusted to pH 6.00, before analysis of their physical, chemical or microbiological properties.

EXAMPLE 2

10 With continued stirring at room-temperature, in chronological order:

1. Freshly distilled acrolein (5g; inhibited with hydroquinone 0.1% w/w) was slowly added to an aqueous solution of ascorbic acid (8.25g) in water (33g) containing 1% sulphuric acid (0.25ml) ;
- 15 2. After 2 hours, the solution was slowly added over 30 minutes to water (100ml) which was maintained at a pH of ca. 11 by incremental additions of 10% aqueous sodium hydroxide; and
3. After a further 30 minutes, the pH of the clear solution of polymer was adjusted to 7 with 10% hydrochloric acid.

Microbiological Assay showed inhibition minimally at 250ppm of polymer.

20 EXAMPLE 3

With continued stirring at room-temperature, in chronological order:

1. Freshly distilled acrolein (5g; inhibited with hydroquinone 0.1% w/w) was slowly added to an aqueous solution of tartaric acid (7g) in water (33g) containing 1% sulphuric acid (0.25ml);
- 5 2. After 2 hours, the solution was slowly added over 30 minutes to water (100ml) which was maintained at a pH of ca. 11 by incremental additions of 10% aqueous sodium hydroxide; and
- 10 3. After a further 30 minutes, the pH was adjusted to 7 with 10% hydrochloric acid, and a minor precipitate of polymer was filtered, washed with a little water, and dried (1.75g; the polymer did not soften below 125°C). Most of the polymer remained in solution; its minimum inhibition-quantity was 250ppm of polymer.

EXAMPLE 4

With continued stirring at room-temperature, in chronological order:

- 15 1. Freshly distilled acrolein (5g; inhibited with hydroquinone 0.1% w/w) was slowly added to an aqueous solution of tartaric acid (7g) in water (30ml) containing 1% sulphuric acid (0.25ml);
- 20 2. After 2 hours, the solution was slowly added over 30 minutes to ascorbic acid (5g) in water (30ml) which had been brought to, and then maintained at a pH of ca. 11 by incremental additions of 10% aqueous sodium hydroxide; and
3. After a further 30 minutes, the pH was adjusted with 10% hydrochloric acid to give a clear, almost colourless solution of pH 7.5.

When tested down to pH 1, the polymer remained soluble. Microbiological Assay showed inhibition minimally at 250ppm of polymer - which was unchanged after storage at 7°C/6 months. All *E.coli* were killed after 180

minutes (see method, above). The polymer-solution was dialysed using either a 1,000 Dalton or 10,000 Dalton membrane to isolate the dry liquid-polymer (polymerisation-yield 60%) which inhibited at 500ppm. Alternatively, the sample inhibited at 500ppm-1000ppm after exposure to the simulation of resident-conditions within the stomach at pH 2/37°C/4 hours.

The carbonyl-content within the polymer was 25% - both before and after exposure to simulation of resident-conditions within the stomach at pH 2/37°C/4 hours. The carbonyl-content of the polymer was 55%, and it minimally inhibited at 2000ppm after dialysis against water, pH 6; the carbonyl-content of the polymer was 5% after dialysis against aqueous sodium tartrate solution (16% w/w; pH 6) and the Microbiological Assay showed inhibition minimally at 500ppm of polymer.

EXAMPLE 5

With continued stirring, in chronological order:

(a) Freshly distilled acrolein (5g; inhibited with hydroquinone 0.1% w/w) was slowly added to a pH 11 aqueous solution of ascorbic acid (5g) in water (19ml) plus 10% aqueous sodium hydroxide (12ml); an additional aliquot of the sodium hydroxide solution (1ml) was added to maintain the pH at 11 during the addition. A small aliquot of this clear, slightly gold solution did not inhibit when tested in the Microbiological Assay until 2000ppm of polymer.

(b) After 15 minutes, polyethylene glycol 200 (60ml) was added, and then the clear solution was heated at 50 to 60°C over 1 hour. The pH was then adjusted to 8 with 10% hydrochloric acid.

A small portion of the clear solution did not precipitate/cloud down to pH 1; Microbiological Assay showed inhibition minimally at 50ppm of polymer; the carbonyl-content within the polymer was 40%.

EXAMPLE 6

With continued stirring at room-temperature, in chronological order:

- 5 1. Freshly distilled acrolein (5g; 89mMole; inhibited with hydroquinone 0.1% w/w) was slowly added to water (20ml) plus polyethylene glycol (60ml; 330mMole; MW 200), rendered pH 12 to 13 by the addition of 10% aqueous sodium hydroxide (2 drops) ; and
2. After 30 minutes, water (10ml) was added to the clear, colourless solution, and the pH adjusted to 7 with several drops of 10% hydrochloric acid.

10 When tested down to pH 1, the polymer remained soluble. Microbiological Assay showed inhibition minimally at 50ppm of polymer. The recovery of dry liquid-residues after dialyses of polymer-solution, using 1,000 Dalton membranes, gave weights indicating a 1:1 ratio of PEG:acrolein residues.

EXAMPLE 7

With continued stirring at room-temperature, in chronological order:

- 15 1. Freshly distilled acrolein (5g; 89mMole; inhibited with hydroquinone 0.1% w/w) was slowly added to water (30ml) plus polyethylene glycol (30g; 15mMole; MW 2000), rendered pH 12 to 13 by the addition of 10% aqueous sodium hydroxide (2 drops); and
- 20 2. After 60 minutes, the pH of the clear solution was adjusted to 7 with several drops of 10% hydrochloric acid.

When tested down to pH 1, the polymer remained soluble. Microbiological Assay showed inhibition minimally at 100ppm of polymer, and which was re-produced after storage at 7°C/6 months. All *E.coli* were killed after 3 minutes (see method, above). The inhibition of the polymer was 250ppm after treatment in the

simulation (see above) at pH 2/37°C/4 hours. Dialysis of the polymer-solution, using 10,000 Dalton membrane, then recovery, yielded dry, liquid polymer of weight indicating a 60% polymerisation-yield and approximately 1:6 ratio of PEG:acrolein within the polymer. The dialysis-residue of polymer exhibited
5 microbiological inhibition at 250ppm; carbonyl-content was determined as 20%.

EXAMPLE 8

With continued stirring at room-temperature, in chronological order:

- 10 1. Freshly distilled acrolein (5g; 89mMole; inhibited with hydroquinone 0.1% w/w) was slowly added to an aqueous solution of tartaric acid (2.5g) in water (25ml) containing 1% sulphuric acid (0.25ml);
- 15 2. After 2 hours, the above solution was slowly added over 15 minutes to ascorbic acid (1g) plus polyethylene glycol (30g; 15mMole; MW 2000) in water (30ml), pre-rendered to pH 12 - and then the reaction maintained at pH 12 to 13 during the addition (by further increments of 10% aqueous sodium hydroxide solution) ; and
3. After 30 minutes the pH of the clear, pale-golden solution of polymer was adjusted to 7 with 10% hydrochloric acid.

The Microbiological Assay (see above) showed a minimum-inhibition amount at 250ppm of polymer. The polymer remained soluble in dilute hydrochloric acid of
20 pH 1. Dialysis of the polymer-solution against water, pH 2, gave rise to a solution having a minimum-inhibition amount of 500ppm of polymer; the recovery of dry polymer gave weights indicating a ratio of 1:11 of PEG:acrolein within the polymer.

EXAMPLE 9

25 With continued stirring at room-temperature, in chronological order:

1. Freshly distilled acrolein (5g; 89mMole; inhibited with hydroquinone 0.1% w/w) was slowly added to an aqueous solution of tartaric acid (2.5g) in water (25ml) containing 1% sulphuric acid (0.25ml);
- 5 2. After 2 hours, the above solution was slowly added over 15 minutes to ascorbic acid (1g) plus polyethylene glycol (30g; 300mMole; MW 200) in water (30ml), pre-rendered to pH 12 - and then the reaction maintained at pH 12 to 13 during the addition (by further increments of 10% aqueous sodium hydroxide solution) ; and
- 10 3. After 30 minutes the pH of the clear, golden solution of polymer was adjusted to 7 with 10% hydrochloric acid.

The Microbiological Assay (see above) did not show a minimum-inhibition amount at 2000ppm of polymer. The polymer remained soluble in dilute hydrochloric acid of pH 1. Recovery of polymer, following dialysis against water, pH 7, gave weights indicating a 1:3 ratio of PEG:acrolein.

- 15 It is envisaged that the polymers of the present invention, as a direct result of the properties thereof evident above, will prove effective in the treatment of cancer, disorders of coagulation and inflammation. In turn, it is envisaged that the polymers of the present invention will prove useful and effective when used in anti-cancer, anti-coagulant and anti-inflammatory compositions in a
- 20 pharmaceutically acceptable amount.

Modifications and variations such as would be apparent to the skilled addressee are considered to fall within its scope.

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The Claims Defining the Invention are as Follows:

1. Polymers derived directly from acrolein monomer that are substantially soluble in water and/or aqueous media.
2. Polymers according to claim 1, wherein the polymers are soluble at a pH of less than about 4.
5
3. Polymers according to claim 1 or 2, wherein no intermediate autoxidation step is employed in their preparation.
4. Polymers according to any one of the preceding claims, wherein the polymers are substantially anti-microbial.
- 10 5. Polymers according to any one of the preceding claims, wherein the polymers have an average molecular weight of greater than about 1000 Daltons.
6. Polymers according to any one of the preceding claims, wherein the polymers have a low propensity to migrate through membranes as the result of having high levels of polarity and/or hydrophilicity due to included carboxyl groups, either within hydroxy-alkanoic acids attached to the polymers as acetal
15 groups, or within monomer-residues in the polymers.
7. Polymers according to claim 6, wherein the polymers are of average molecular weight greater than 1000 Daltons and are substantially inhibited from passing through membranes which are designed to be transmissible to
20 all molecules up to molecular weight 1000 Daltons.

8. Polymers according to any one of claims 1 to 5, wherein the polymers exhibit a low propensity to migrate through membranes as the result of having within, structures resulting from the reaction between alkanol (and/or its ion) and proximate carbons to the carbonyl in acrolein-residues within the polymers.
- 5 9. Polymers according to claim 8, wherein the polymers are of average molecular weight greater than 1000 Daltons and are substantially inhibited from passing through membranes which are designed to be transmissible to all molecules up to molecular weight 1000 Daltons.
- 10 10. Polymers according to any one of the preceding claims, wherein the polymers have a carboxyl content of between about 0.1 and 25 moles/Kg of polymer.
11. A composition comprising at least in part polymers according to any one of the preceding claims, the composition being a solution, gel, emulsion or suspension of matter.
- 15 12. An *in vitro* and/or *in vivo* anti-microbial composition comprising at least in part polymers according to any one of the preceding claims.
- 20 13. A method for the synthesis of polymers according to any one of claims 1 to 10, wherein the polymers are prepared so as to incorporate acetal-structures resulting from the reaction between acrolein (monomer or residue) and hydroxy-alkanoic acid (and/or its ion), or so as to incorporate within, structures resulting from the reaction between alkanol (and/or its ion) and proximate carbons to the carbonyl in acrolein-residues within the polymers.
- 25 14. A method according to claim 13, wherein the method further comprises the polymerisation, in basic aqueous solution in the presence of a basic catalyst, of acrolein, and/or acrolein plus alkanol and/or other organic nucleophile, and/or acetal of acrolein with a hydroxy-alkanoic acid – optionally, in solution with other monomer, and/or ascorbic acid (and/or its ion) and/or other antioxidant and/or other acid.

15. A method according to claim 14, wherein the basic aqueous solution is preferably aqueous sodium hydroxide at a pH of between about 9 to 14, further preferably between pH 10 to 13.
16. A method according to claim 14 or 15, wherein the hydroxy-alkanoic acid is tartaric acid and/or ascorbic acid.
17. A method according to any one of claims 14 to 16, wherein the acetal is formed by acid-catalysis,
18. A method according to claim 17, wherein the acid-catalysis uses dilute sulphuric acid.
19. A method according to any one of claims 14 to 18, wherein the alkanol is a polyalkylene glycol.
20. A method according to claim 19, wherein the polyalkylene glycol is polyethylene glycol.
21. A method according to claim 20, wherein the polyethylene glycol has an average molecular weight of about 200 to 10,000 Daltons.
22. A method according to claim 20 or 21, wherein the ratio of polyethylene glycol:acrolein or acrolein incorporated as its acetal, is greater than 1:1 w/w.
23. A method according to claim 20, 21 or 22, wherein the ratio of polyethylene glycol:acrolein or acrolein incorporated as its acetal, is greater than 4:1 w/w.
24. A method according to any one of claims 13 to 23, wherein the monomer is acrylic acid.
25. A method according to claim 24, wherein the ratio of acrylic acid:acrolein or acrolein incorporated as its acetal is in the range of about 0.05 to 0.10:1 w/w.

26. A method according to any one of claims 14 to 25, wherein the organic nucleophile is a carboxylic acid.
27. A method according to any one of claims 14 to 26, wherein the ratio of ascorbic acid:acrolein or acrolein incorporated as its acetal is in the range of about 0.01 to 10:1.00 w/w.
28. A method according to any one of claims 14 to 27, wherein the ratio of ascorbic acid:acrolein or acrolein incorporated as its acetal is in the range of about 0.1 to 2.0:1.0 w/w.
29. A method according to any one of claims 14 to 28, wherein the ratio of ascorbic acid:acrolein or acrolein incorporated as its acetal is in the range of about 0.6:1.0 w/w.
30. A method for the treatment of cancer comprising the administration to a subject of a pharmaceutically acceptable amount of a polymer according to any one of claims 1 to 10, or a composition containing such.
31. A method for the treatment of disorders of coagulation comprising the administration to a subject of a pharmaceutically acceptable amount of a polymer according to any one of claims 1 to 10, or a composition containing such.
32. A method for the treatment of inflammatory disorders comprising the administration to a subject of a pharmaceutically acceptable amount of a polymer according to any one of claims 1 to 10, or a composition containing such.
33. The use of a polymer according to any one of claims 1 to 10 in the preparation of a medicament for the treatment of cancer.

34. The use of a polymer according to any one of claims 1 to 10 in the preparation of a medicament for the treatment of disorders of coagulation.
35. The use of a polymer according to any one of claims 1 to 10 in the preparation of a medicament for the treatment of inflammatory disorders or conditions.
- 5 36. Polymers substantially as hereinbefore described with reference to Examples 6 or 7.
37. A method for the synthesis of polymers substantially as hereinbefore described with reference to Examples 6 or 7.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2008/001140

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

<i>C08F 16/34</i> (2006.01)	<i>A61K 31/78</i> (2006.01)	<i>A61P 31/04</i> (2006.01)
<i>A01N 35/02</i> (2006.01)	<i>A61P 7/02</i> (2006.01)	<i>A61P 35/00</i> (2006.01)
<i>A01N 61/00</i> (2006.01)	<i>A61P 29/00</i> (2006.01)	<i>C08G 2/00</i> (2006.01)

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)

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 practicable, search terms used)

WPI, EPODOC & Keywords acrolein, anti-microbial, anti-oxidant and the like

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1996/038186 A1 (CHEMEQ PTY LTD) 05 December 1996 See whole document	1, 4-7, 10-12, 30-35
X	WO 2001/060874 A1 (CHEMEQ LTD) 23 August 2001 See whole document	1, 4-15, 19-21
X	WO 2000/003723 A1 (CHEMEQ LTD) 27 January 2000 See whole document	1-2, 4-7
X	WO 2005/044874 A1 (CHEMEQ LTD) 19 May 2005 See whole document	1, 3-15, 17, 19-23

Further documents are listed in the continuation of Box C See patent family annex

* Special categories of cited documents:		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 September 2008	Date of mailing of the international search report 17 SEP 2008
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INTERNATIONAL SEARCH REPORT

International application No.

Information on patent family members

PCT/AU2008/001140

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member					
WO 9638186	AU	14733/02	AU	57557/96	BR	9609166
	CN	1186436	CN	1397283	EP	0828498
	EP	1393735	HK	1010490	US	6723336
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WO 0160874	AU	26512/00	BR	0009423	CN	1347425
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WO 2005044874	AU	2004287510	BR	PI0416298	CN	1875039
	EP	1689795	KR	2007000041	US	2007083031

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX