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(54) Title: METHOD OF PREPARING A STERILE ARTICLE

(57) Abstract

Disclosed is a method of preparing a sterile article. A poly(vinyl chloride) or polyvinylidene chloride polymer is produced that contains about 0.001 to about 5 wt.% of a metal complex having at least one anionic ligand that has at least one resonance structure in which the charge is localized on a carbon atom. An article is fabricated from the chlorinated polymer and the article is exposed to gamma radiation.

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METHOD OF PREPARING A STERILE ARTICLE

This invention relates to the preparation of sterile articles.

Poly(vinyl chloride) (PVC) has properties that make it desirable for use as medical devices and as packaging for medical applications. Articles that are used in the medical field have to be sterilized before they are used. Gamma radiation is often used for this purpose. It has been found, however, that gamma radiation causes PVC to become yellow and medical articles that have turned yellow may be rejected as being of inferior quality. Articles made of PVC that are re-used and sterilized after each use are especially likely to turn yellow.

A variety of substances have been added to PVC to stabilize it from gamma radiation and prevent yellowing, including organic Ca\Zn soap blends (JP 57,003,653), organo tin compounds (JP 02189352, JP 08073619, and EP 83112278), and sulfur compounds (JP 08151495, 07102142, and 01278551).

According to one aspect of the present invention there is provided a method of preparing a sterile article comprising

(A) producing a chlorinated polymer selected from polyvinyl chloride and polyvinylidene chloride that contains about 0.0001 to about 5 wt% of a metal complex having at least one anionic ligand that has at least one resonance structure in which the charge is localized on a carbon atom;

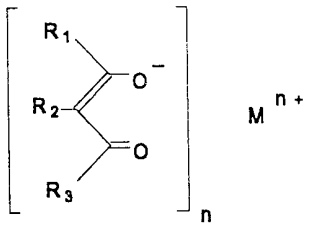
(B) fabricating said article from said chlorinated polymer;

and

(C) sterilizing said article with gamma radiation.

(D)

Preferably said metal complex has the general formula



wherein R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18}, and n is the valance of M.

Advantageously R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8.

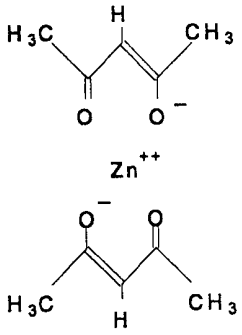
Conveniently R_2 is hydrogen.

Preferably M is divalent.

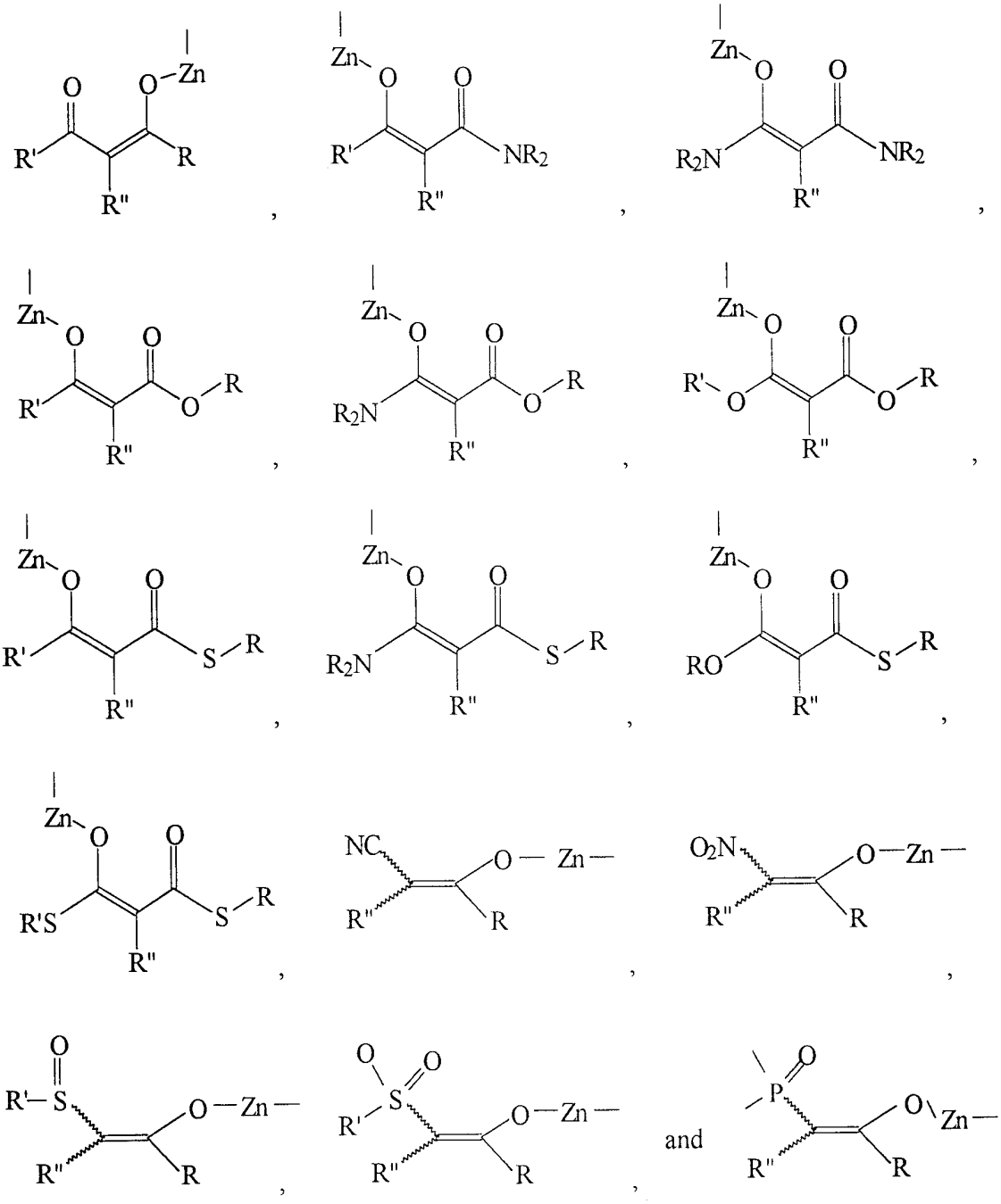
Conveniently M is calcium, barium, zinc, cadmium, lead, tin, or aluminium.

Preferably M is Zn.

Conveniently said metal complex has the formula



Preferably said metal complex is selected from

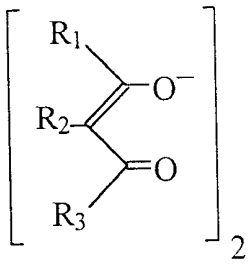


Advantageously said chlorinated polymer is poly(vinyl chloride).

Conveniently said chlorinated polymer is polyvinylidene.

According to another aspect of the present invention there is provided a method of preparing a sterile article comprising

(A) making poly(vinyl chloride) that contains about 0.001 to about 0.5 wt% of a zinc complex having the general formula

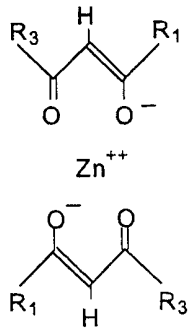


where Zn^{++} R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, and R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18};

(B) fabricating said article from said poly(vinyl chloride); and

(C) repeatedly sterilizing said article with gamma radiation.

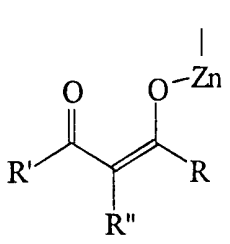
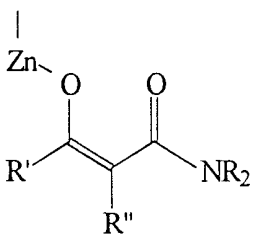
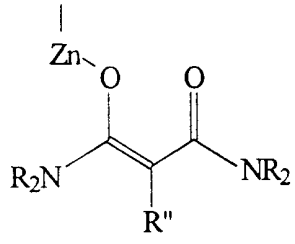
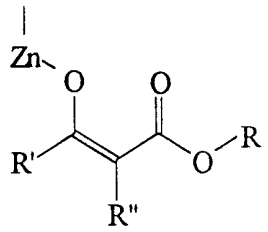
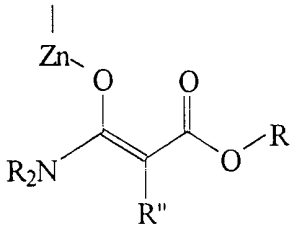
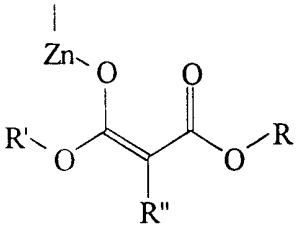
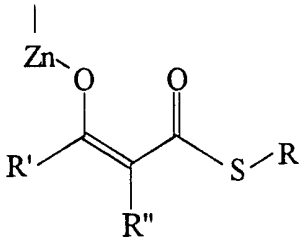
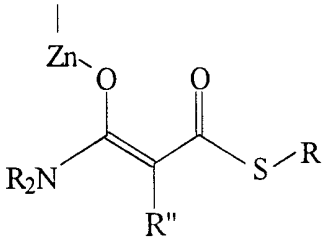
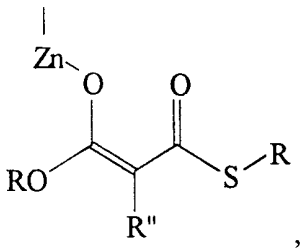
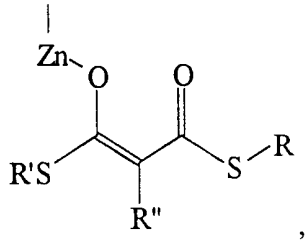
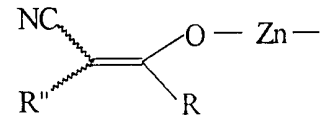
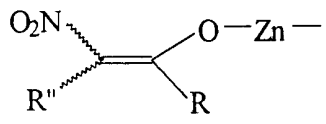
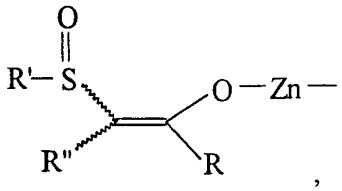
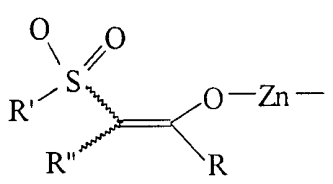
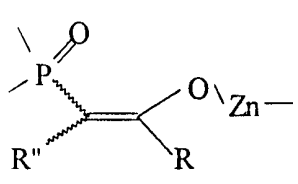
Preferably said zinc complex has the formula



where R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8.

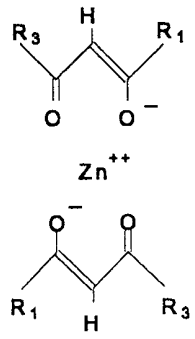
Advantageously R_1 and R_3 are CH_3.

Conveniently said zinc complex is selected from


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and

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According to a further alternative embodiment of the present invention there is provided a method of preparing a sterile article comprising

(A) making poly(vinyl chloride) that contains about 0.001 to about 0.5 wt% of a zinc complex having the general formula



where R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8;

(B) fabricating said article from said poly(vinyl chloride); and

(C) repeatedly sterilizing said article with gamma radiation.

Preferably R_1 and R_3 are methyl.

According to a further preferred embodiment of the present invention there is provided a sterile article prepared according to any of the methods described above.

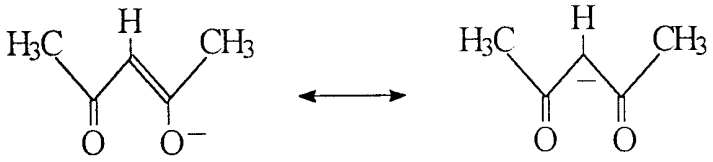
The article may be a medical article.

The addition of certain metal complexes to PVC and polyvinylidene chloride has been found to stabilize the polymers against gamma radiation. The metal complexes can be easily added to the polymers during polymerization or processing so that no additional procedural steps are required. The articles can be sterilized with gamma radiation without significant yellowing.

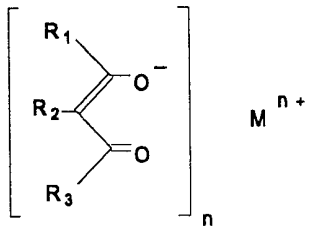
In the method of this invention, a sterile medical article or sterile packaging is prepared by first producing a chlorinated polymer with a metal complex additive. The chlorinated polymer may be either PVC or polyvinylidene chloride. The metal complex can be added to the polymer at any stage, such as, for example, to the monomer, to the partially polymerized monomer, during the drying of the polymer, or during processing of the polymer into the medical article. However, it is preferably added at the earliest possible stage after the monomer has at least partially polymerized in order to avoid any extra procedural steps and to ensure its complete incorporation into the polymer.

The metal complex that is added to the polymer to stabilize it against gamma radiation contains at least one anionic ligand that has at least one resonance structure in which the charge is localized on a carbon atom. That is, the anionic ligand resonates between two structures and, in at least one of those structures, the negative charge is localized on a carbon atom. For

example, if the anionic ligand is acetylacetonate the following two structures resonate, where the negative charge is on the carbon atom in one of the two structures.

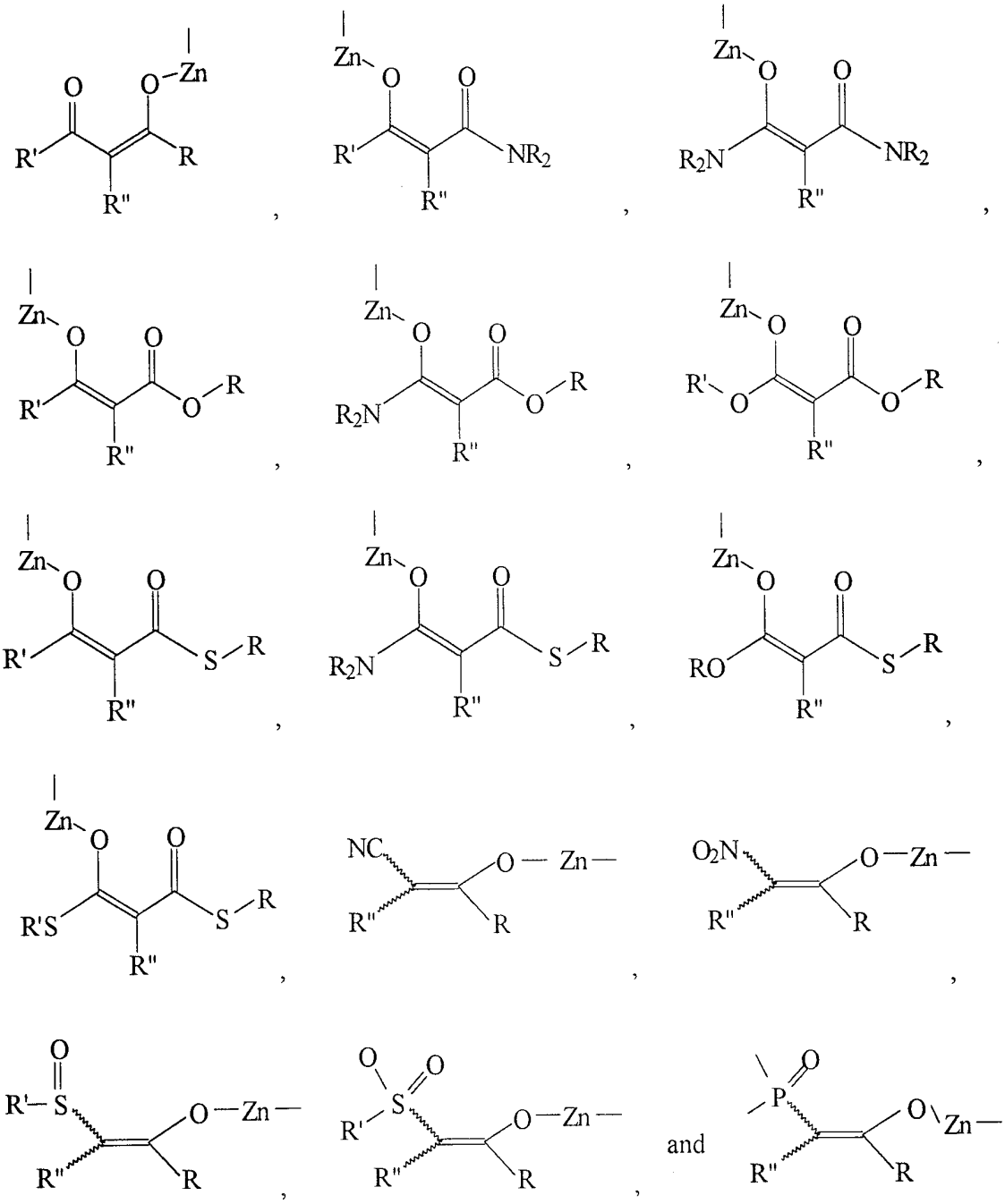


Generally, the metal complex can have the general formula



where M is a metal, R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18}, and n is the valence of M. Preferably, R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8 and are the same as that simplifies synthesis of the complex. Preferably, R_2 is hydrogen as those compounds are more readily available. Examples of metals that can be used include calcium, barium, zinc, cadmium, lead, tin, and aluminum. Divalent metals (n=2) are preferred as the Lewis acidity of those complexes is in the desirable range and adjustments to acidity can be avoided. Zinc is the preferred metal as zinc complexes have less toxicity and are less expensive.

Examples of more preferred zinc complexes include.



The amount of metal complex added can be about 0.0001 wt% to about 5 wt%, based on the weight of the polymer; the preferred range is about 0.001 to about 0.5 wt%.

In addition, plasticizers, heat stabilizers, epoxidized soybean oil, lubricants, and other additives can be mixed in with the PVC as is well known in the art.

The following examples further illustrate this invention.

Examples 1 to 5

To mixtures of 150.00 g PVC (sold by Occidental Chemical Corp. as "Oxy 240"), 0.30 g stearic acid, 0.23 g of a soap thermal stabilizer sold by Witco as "Mark 152 S," 97.50 g dioctyl phthalate, and 15.00 g epoxidized soybean oil sold by Witco as "Drapex 6.8" was added various amounts of different zinc salts of β-biscarbonyl compounds. The mixtures were thoroughly blended and hot milled at 300°F (149°C) for 5 minutes. The resulting PVC sheets were pressed at 330°F (166°C) and cut into 4"x3"x1/4" (10 cm x 8 cm x 0.6 cm) plaques. The plaques were divided into two smaller pieces. One piece was saved for the purpose of comparison and the other one was subjected to 5.0 Mrad of γ radiation at 50 kGy. The irradiated piece was again divided into two pieces and one piece was oven aged at 50°C for 48 hours. All three pieces were measured for yellowness index with a Mascbeth 2020 Plus Color Eye Spectrometer. The control materials were similarly prepared, but without a zinc complexe of a β-biscarbonyl compound. The following table gives the results:

Example	Metal Complex	Yellowness		
		With Metal Complex		Without Metal Complex
1	0.35 g Zn acetylacetonate	Initial	11.3	12.4
		After γ	29.4	45.0
		Aged	37.2	72.0
2	0.60 g Zn acetylacetonate	Initial	21.6	19.8
		After γ	34.1	52.8
		Aged	38.8	73.3
3	0.91 g Zn acetylacetonate	Initial	34.5	19.8
		After γ	35.1	52.8
		Aged	37.4	73.3
4	0.35 g Zn bis(2,2,6,6-tetramethyl-3,5-heptanedionate	Initial	16.4	12.4
		After γ	39.5	45.0
		Aged	57.7	72.0
5	0.31 g Zn hexafluoroacetylacetonate	Initial	11.6	12.4
		After γ	36.8	45.0
		Aged	55.0	72.0

The table shows that the PVC that contain zinc salts of β-biscarbonyl compounds had significantly less discoloration after γ radiation compared with the control samples, which did not contain those compounds.

Examples 6 to 9

Example 1 was repeated using various zinc salts as γ radiation stabilizers or the same molar equivalent amount of the corresponding ketone (see JP 02263853). The following table gives the stabilizers tested and the results:

Example	Zinc Salt (g) Ketone	Yellowness		
		Initial	After γ Rays	After Aging
6	Zinc Acetylacetonale (0.40)	19.1	38.6	45.9
	2,4-pentanedione	16.9	55.8	76.3
7	Zinc 1-benzoylacetonate (0.59)	18.9	39.4	44.9
	1-benzoylacetone	15.6	50.9	72.6
8	Zinc(methoxyethoxy)carbonyl acetonate (0.58)	19.0	40.6	49.1
	2-methoxyethoxy acetoacetate	18.0	54.0	73.3
9	Zinc 3-(2'-ethylcarboxyethyl)-2,4-petanedionate (0.70)	21.9	45.0	52.9
	Ethyl 4-acetyl-5-oxohexanoate	17.1	49.6	61.5

The above table shows that the zinc salts are more effective in reducing yellowness than the corresponding ketones.

In the present specification the word "comprise" or "comprises" means "includes or consists of" and "comprising" means "including or consisting of".

CLAIMS:

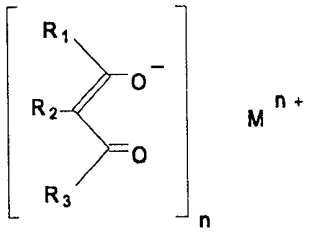
1. A method of preparing a sterile article comprising

(A) producing a chlorinated polymer selected from polyvinyl chloride and polyvinylidene chloride that contains about 0.0001 to about 5 wt% of a metal complex having at least one anionic ligand that has at least one resonance structure in which the charge is localized on a carbon atom;

(B) fabricating said article from said chlorinated polymer; and

(C) sterilizing said article with gamma radiation.

2. A method according to Claim 1 wherein said metal complex has the general formula



wherein R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18}, and n is the valance of M.

3. A method according to Claim 2 wherein R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8.

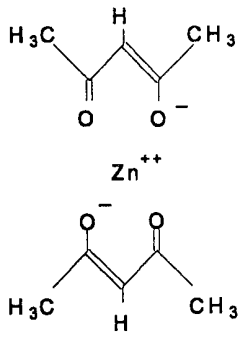
4. A method according to Claim 2 or Claim 3 wherein R_2 is hydrogen.

5. A method according to any one of Claims 2 to 4 wherein M is divalent.

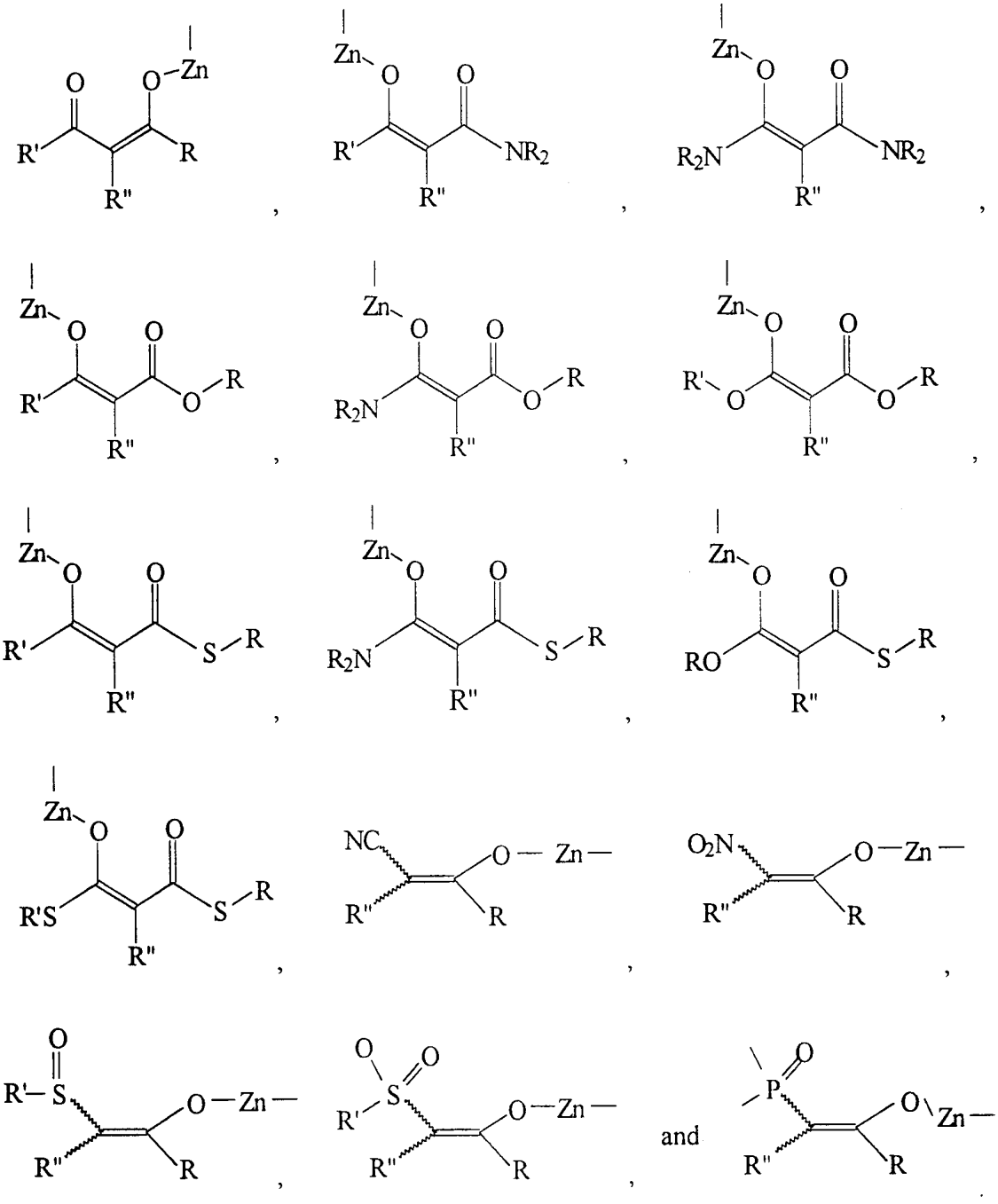
6. A method according to any one of Claims 2 to 6 wherein M is calcium, barium, zinc, cadmium, lead, tin, or aluminum.

7. A method according to any one of Claims 2 to 6 wherein M is Zn.

8. A method according to Claim 7 wherein metal complex has the formula



9. A method according to Claim 3 or any one of Claims 4 to 7 dependent thereon wherein said metal complex is selected from

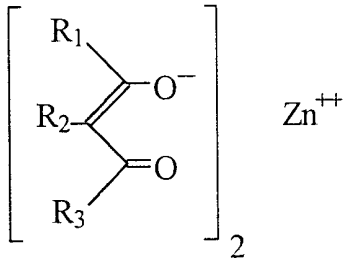


10. A method according to any one of the preceding claims wherein said chlorinated polymer is poly(vinyl chloride).

11. A method according to any one of the preceding claims wherein said chlorinated polymer is polyvinylidene.

12. A method of preparing a sterile article comprising

(A) making poly(vinyl chloride) that contains about 0.001 to about 0.5 wt% of a zinc complex having the general formula

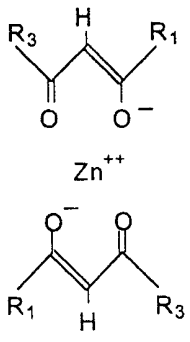


where R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, and R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18};

(B) fabricating said article from said poly(vinyl chloride); and

(C) repeatedly sterilizing said article with gamma radiation.

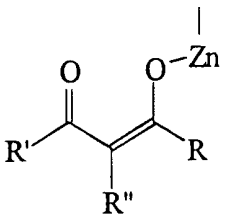
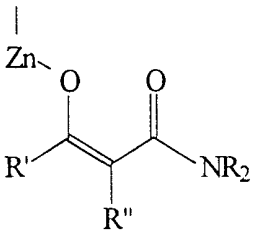
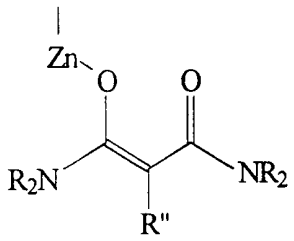
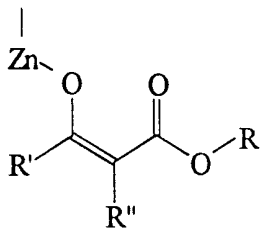
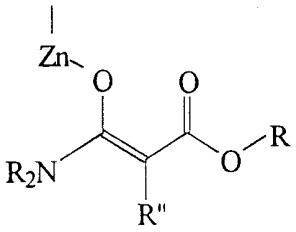
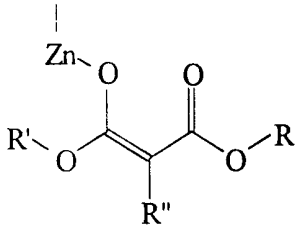
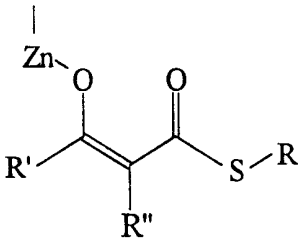
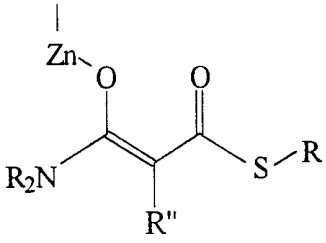
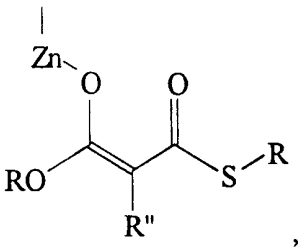
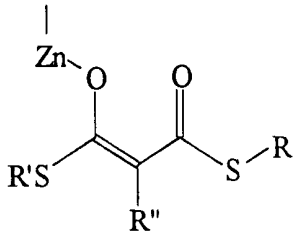
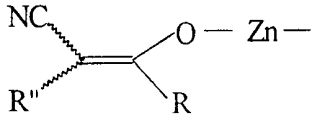
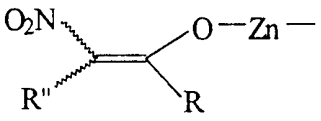
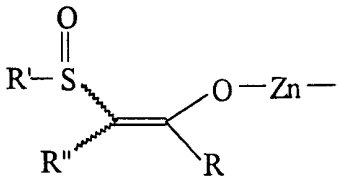
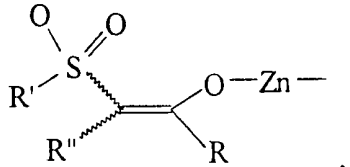
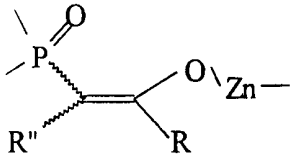
13. A method according to Claim 12 wherein said zinc complex has the formula



where R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8.

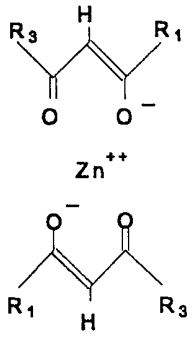
14. A method according to Claim 12 or Claim 13 wherein R_1 and R_3 are CH_3.

15. A method according to Claim 12 wherein said zinc complex is selected from


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and

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16. A method of preparing a sterile article comprising

(A) making poly(vinyl chloride) that contains about 0.001 to about 0.5 wt% of a zinc complex having the general formula



where R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8;

(B) fabricating said article from said poly(vinyl chloride); and

(C) repeatedly sterilizing said article with gamma radiation.

17. A method according to Claim 16 wherein R_1 and R_3 are methyl.

18. A sterile article prepared according to the method of any one of the preceding claims.

AMENDED CLAIMS

[received by the International Bureau on 17 January 2000 (17.01.00);
original claims 1-18 replaced by amended claims 1-15 (6 pages)]

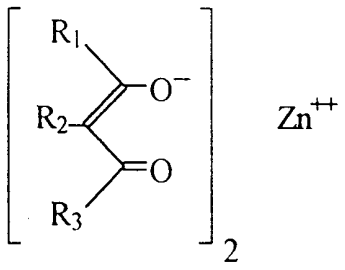
1. A method of preparing a sterile article comprising

   (A) producing a chlorinated polymer selected from polyvinyl chloride and polyvinylidene chloride that contains about 0.0001 to about 5 wt% of a zinc complex having at least one anionic ligand that has at least one resonance structure in which the charge is localized on a carbon atom;

   (B) fabricating said article from said chlorinated polymer; and

   (C) sterilizing said article with gamma radiation.

2. A method according to Claim 1 wherein said metal complex has the general formula

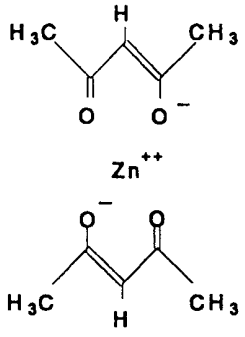


wherein R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18}.

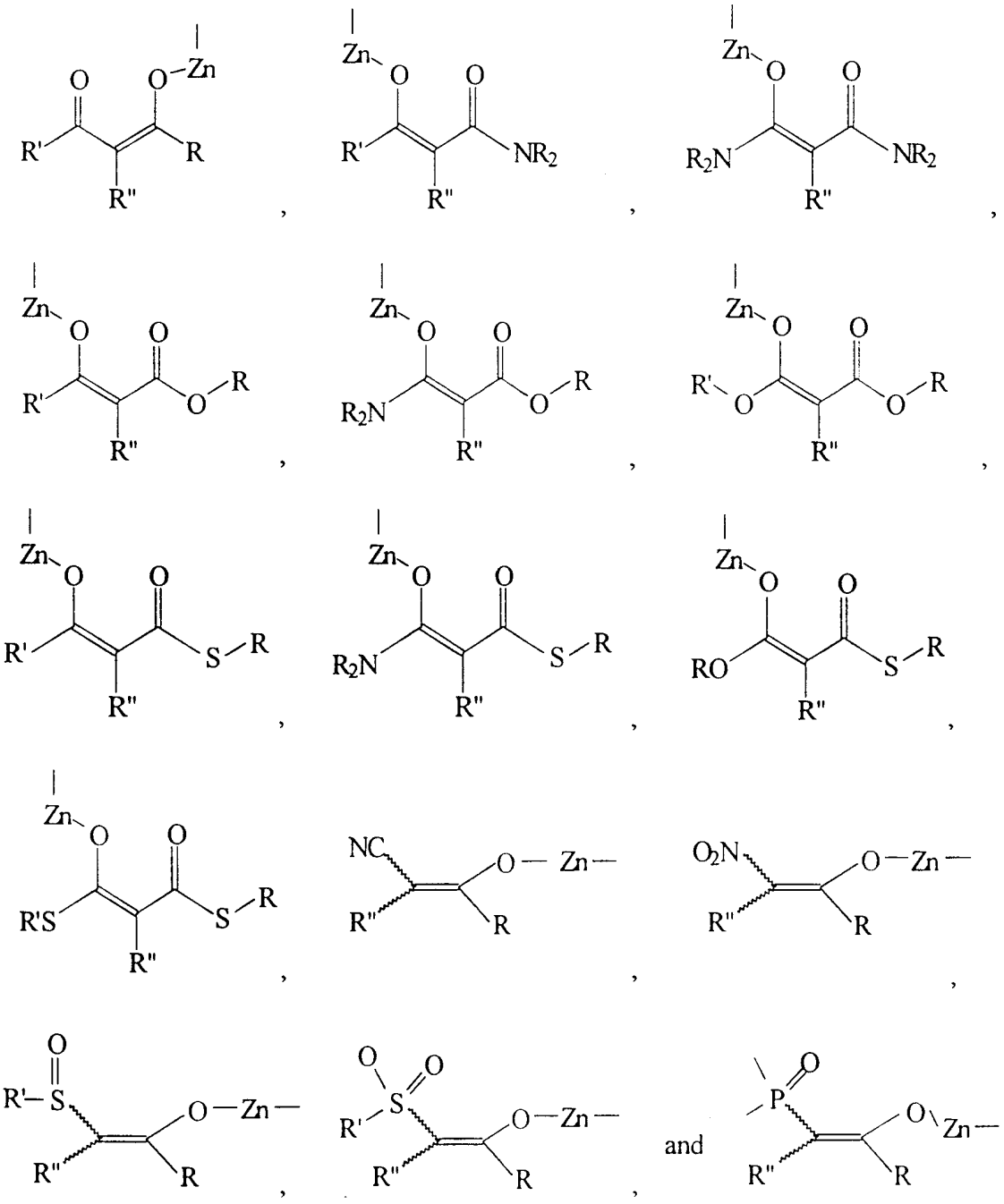
3. A method according to Claim 2 wherein R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8.

4. A method according to Claim 2 or Claim 3 wherein R_2 is hydrogen.

5. A method according to Claim 4 wherein metal complex has the formula



6. A method according to Claim 5 wherein said metal complex is selected from

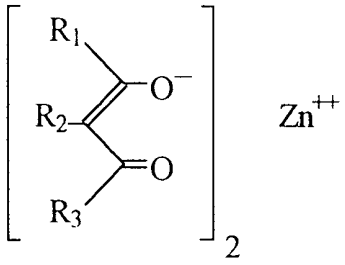


7. A method according to any one of the preceding claims wherein said chlorinated polymer is poly(vinyl chloride).

8. A method according to any one of the preceding claims wherein said chlorinated polymer is polyvinylidene chloride.

9. A method of preparing a sterile article comprising

(A) making poly(vinyl chloride) that contains about 0.001 to about 0.5 wt% of a zinc complex having the general formula

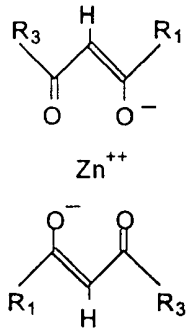


where R_1, R_2, and R_3 are each independently selected from R, OR, SR, and $N(R)_2$, and R is hydrogen, alkyl from C_1 to C_{12}, or aryl from C_6 to C_{18};

(B) fabricating said article from said poly(vinyl chloride); and

(C) repeatedly sterilizing said article with gamma radiation.

10. A method according to Claim 9 wherein said zinc complex has the formula



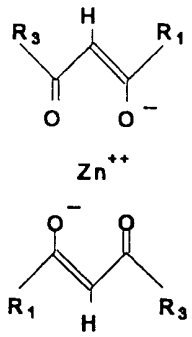
where R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8.

11. A method according to Claim 9 or Claim 10 wherein R_1 and R_3 are CH_3.

12. A method according to Claim 11 wherein said zinc complex is selected from

13. A method of preparing a sterile article comprising

(A) making poly(vinyl chloride) that contains about 0.001 to about 0.5 wt% of a zinc complex having the general formula



where R_1 and R_3 are each independently selected from alkyl and alkoxide from C_1 to C_8;

(B) fabricating said article from said poly(vinyl chloride); and

(C) repeatedly sterilizing said article with gamma radiation.

14. A method according to Claim 13 wherein R_1 and R_3 are methyl.

15. A sterile article prepared according to the method of any one of the preceding Claims.

INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/GB 99/02484

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08K5/00 A61L2/00

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 7 C08K A61L

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 345 662 A (GOODRICH CO B F) 13 December 1989 (1989-12-13) claims 8,11,15; examples	1-18
Y	FR 1 546 264 A (GRACE & CO) 15 November 1968 (1968-11-15) column 1, paragraph 3; claim 3; example 3; tables	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 November 1999	16/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Friederich, P

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 99/02484

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2043245 A	13-02-1990
FR 1546264 A		GB 1156879 A	02-07-1969