PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Mixtures of Polymeric N-Vinyl Pyrrolidone and Halogens or Halogen Compounds

We, GENERAL ANILINE & FILM CORPORATION, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 230 Park Avenue, New York, County and State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to improved novel compositions containing halogens and polymeric N-vinyl pyrrolidone.

We have discovered that polymeric N-vinyl pyrrolidone of the type described in U.S.P. No. 2,265,450 in combination with halogens and organic and inorganic substances derived from and containing halogens or capable of setting free halogens in solution materially lower the toxicity and sensitizing effects of the halogens on animal life without affecting and, in fact, in many cases enhancing the killing effect of such halogen compounds on microorganisms, i.e., bacteria, yeasts, molds, fungi, protozoa, and metazoa.

This discovery makes possible the formulation of a wide variety of compositions containing such halogen compounds in conjunction with polyvinyl pyrrolidone which are of value in substantially the same use as the unmodified halogen compounds but are free of many of the objectionable properties of such unmodified halogen compounds and thus may be employed in with greater safety than the unmodified compounds and in more effective concentrations.

The present invention does not relate to any novel halogen compounds *per se* but instead relates to the combination of known halogen compounds having bactericidal, therapeutic or diagnostic uses with polyvinyl pyrrolidone, such combinations having decreased toxicity and substantially less irritation and sensitization effects than the halogen compounds *per se*, but in many cases showing synergistic effect. Such combinations, depending upon the particular halogen compound employed, may be employed for local application to the skin, in ointments, creams, jellies, suppositories and the like, or may be employed as parenteral or intramuscular injections. In addition to decreasing the toxicity and irritation and sensitization effects of the halogen compounds, it has been found that the presence of polyvinyl pyrrolidone substantially prolongs the application of the halogen when it is used therapeutically or otherwise *in situ*.

As stated above the polymeric N-vinyl pyrrolidone compounds which we found to be useful combined with halogens and halogen containing compounds in the compositions of the present inventions are the polymeric N-vinyl pyrrolidones of the type described in the U.S. Patent No. 2,265,450. We have found that the water soluble polymers of N-vinyl pyrrolidone as a class are effective in the compositions of this invention and that the degree of polymerisation (i.e. molecular weight of the polymer) has no apparent effect on its detoxifying action However, for particular uses polymers of particular molecular weight range may be preferred for reasons other than their detoxifying effect. The Fikentscher K value as defined by H. Fikentscher Cellulose Chemie XIII, 58, 1932 is a convenient designation of relative degree of polymerization or relative molecular weight and will therefore be used to designate specific polymers in this specification. Thus, polymers having a K

value below 15, and particularly below 10, are rapidly excreted from the body in the urine when administered in parenteral fluids, and when it is desired to detoxify a halogen compound and to have that compound excreted normally such low K value polymers will usually be preferred. Polymers having K values within the range of 15, to say 75 and preferably 25, to 50, appear to be excreted from the body more slowly. Moreover, the osmotic pressure of solutions of polymers within this range of K values appear to be better suited for the preparation of parenteral fluids and therefore such polymers will usually be preferred in compositions intended for use in parenteral fluids or where it is desired to prolong the presence and effect of the composition. The higher polymers i.e. those having a K value above 50 and especially above 75, to say 90, appear to be stored in the liver for appreciable periods of time and such high molecular weight products may therefore be preferred in compositions intended for therapy of the liver or where it is desired to have the therapeutic or diagnostic agent incorporated either then remain in the body for long periods of time. The water soluble polymers of N - vinyl pyrrolidone have been extensively employed as blood plasma substitutes and appear to be entirely innocuous. While for certain purposes a polymer for a particular weight range may be desired, the detoxifying effect does not appear to be related to the molecular weight and the range of molecular weight of a particular polymer to be employed in any given application will be governed by considerations other than this detoxifying action. Such considerations are well known in the medical profession and the proper choice of polymer may readily be made. For external use the molecular weight (K value) of the polymer appears to be without effect save for its effect on the viscosity of the composition.

The present invention will first be described in detail in connection with its use with inorganic irritating forms of halogens. Thus the addition of a small amount of polyvinyl pyrrolidone to elemental iodine was effective in decreasing the toxicity of iodine solutions very substantially. The inorganic forms of iodine with which polyvinyl pyrrolidone may be used include elemental iodine, Lugol's solution, colloidal iodine suspensions, salts of iodine, iodides, iodates and iodites and acids of oidine, HI and HIO.

It was found that in such combinations of iodine and polyvinyl pyrrolidone, the acute toxicity of iodine was lowered approximately 10-fold average, and the lowering of the chronic toxicity resulted in very substantial increase in the average daily consumption. The irritation and sensitization effects of iodine were completely absent in iodine polyvinyl pyrrolidone combinations. The objectionable staining properties of the iodine were overcome, and the odor of iodine was not noticeable. At the same time, it was noted that the presence of a polyvinyl pyrrolidone in the composition did not affect the bactericidal function of the iodine as free elemental iodine and in fact it was found that combinations of iodine and polyvinyl pyrrolidone were more active bactericidally than free iodine itself. It was found that while there was no conclusive evidence of any chemical combination between the iodine and the polyvinyl pyrrolidone, it appears that such combination possesses distinctive properties which possibly may be due to the formation of a new form of matter. Thus when a small amount of polyvinyl pyrrolidone is added to Lugol's solution and the thus formed mixture heated on a steam bath, a starch test for iodine could not be obtained on paper suspended over the bath and no odor of iodine could be detected, the vapor pressure of iodine being substantially reduced to 0. This mixture of polvinyl-a-pyrrolidone and Lugol's solution was subjected to standard culture tube tests as illustrated in Series A of Table I below using 1 ml. 24 hour Staph. aureus broth culture to each tube of test broth culture and 1 per cent Lugol's iodine was added to the culture broth to the indicated dilution.

In the tables polyvinyl pyrrolidone is abbreviated as PVP.

Table I.

Series A.

Nutrient Broth in	1/25	1/50	1/100	1/150	1/300	1/400	1/600
H_2O-base							
24 hours	−	+	+ +	+ +	+ +	+ +	+ +
48 hours		+ +	+ +	+ +	+ +	+ +	+ +
1% PVP H_2O-base							
24 hours	−	−	−	−	−	+	+ +
48 hours	−	−	+ +	+ +	+ +	+ +	+ +

Series B.

Nutrient Broth in	1/20	1/40	1/80	1/160	1/320
H_2O-base					
24 hours	−	+ +	+ +	+ +	
48 hours	−	+ +	+ +	+ +	
1% PVP H_2O-base					
24 hours	−	−	−	−	+ +
48 hours	−	−	−	+ +	+ +
72 hours	−	−	+ +	− +	+ +

It will be noted that the Lugol's solution was effective at a dilution of 1 to 25, whereas the same solution containing 1 per cent polyvinyl-n-pyrrolidone having a K value of about 25 and a molecular weight of from 30,000 to 40,000 was effective at dilutions of 1 to 300. Substantially similar results were obtained in agar cup plate tests as indicated by the following tables in which 2.0 ml. of a 24 hour Staph. aureus culture was used per 100 ml. agar.

Table II.

Dilutions in H_2O	Width of Zones	Dilutions in 2.5% PVP	Width of Zones
1/2	10. mm	1/2	13. mm
1/10	3. mm	1/10	8. mm
1/50	0.5 mm	1/50	2. mm
1/100	0.0 mm	1/100	0.0 mm

Table III.

Concentrations of PVP	Width of Zone
2.5%	7. mm
1.25%	7. mm
0.63%	6. mm
0.313%	3. mm
H_2O Control	3. mm
2.5% Gelatin	1.5 mm
2.5% Gelatin (no Iodine)	0.0 mm

The effect of adding polyvinyl-n-pyrrolidone to inorganic forms of chlorine, both elemental chlorine, hypochlorites, hydrochloric acid, toxic salts of chlorine, were substantially similar to its effect with iodine in that the killing effect of chlorine on microorganisms was enhanced, while the toxicity, irritation and sensitization effects were decreased or eliminated in the case of irritation and sensitization effects. Thus it will be noted from Series B of Table I above that whereas a commercial solution of sodium

hypochlorite (Chlorox) was effective in broth tube test at a dilution of 1 to 20, the same hypochlorite solution containing 1 per cent of polyvinyl-n-pyrrolidone having a value of about 25 and a molecular weight of from 30,000 to 40,000 was effective at a dilution of 1 to 160. Table IV below illustrates the enhanced effect obtained in agar cup plate tests, particularly at low concentrations of chlorine.

Table IV.

Concentrations of Chlorine in H_2O	Width of Zones	Concentrations of Chlorine in 1% PVP	Width of Zones
0.5%	9. mm	0.5%	10. mm
0.1%	5. mm	0.1%	10. mm
0.05%	4. mm	0.05%	8. mm
0.01%	2. mm	0.01%	3. mm

It was also found that the stability of the hypochlorite was materially increased.

It has been found that compositions of polyvinyl-n-pyrrolidones and free iodine are most readily formed by adding a solution of polyvinyl pyrrolidone to a solution of iodine rather than using the reverse procedure of adding a solution of iodine to a solution of polyvinyl pyrrolidone since when the iodine is added to the polyvinyl pyrrolidone there is a tendency for a precipitate to be formed and difficulty may be encountered in obtaining a uniform composition. Such difficulties are not encountered when the polyvinyl pyrrolidone is added to the iodine nor were such difficulties encountered on mixing solutions containing free chlorine with solutions of polyvinyl-n-pyrrolidone regardless of which order of mixing was employed.

The effect of the addition of polyvinyl-n-pyrrolidones to elemental and inorganic solutions of bromine and fluorine are substantially parallel to its effects with iodine and chlorine.

It has also been found that the combination of polyvinyl-n-pyrrolidone with organic forms of halogens produces substantially similar effects in that the acute and chronic toxicity are materially lowered and irritation and sensitization effects are greatly decreased or completely eliminated and other objectionable properties attributable to the sharp pungent irritating and in some cases lachrymating odors of halogen compounds are overcome. Thus, ethyl bromo acetate which is used as a lachrymator when dissolved in polyvinyl pyrrolidone no longer has this effect.

Among the organic forms of iodine with which polyvinyl pyrrolidone may be used may be mentioned such organic compounds as sold under the registered trade mark "Diodrast", which is used intravenously for radiological purposes. Also combinations of polyvinyl pyrrolidone with products derived from the thyroid gland, such as thyroxin and di-iodo tyrosine and the soluble iodine fraction found in whole desiccated thyroid are valuable for therapeutic applications and for diagnostic purposes. It has been found that the presence of the polyvinyl pyrrolidone together with organic forms of iodine compounds commonly employed for therapeutic and diagnostic purposes does not interfere with their use for such purposes but substantially decreases the toxicity and irritation and sensitization effect thus permitting freer and more effective use of such iodine compounds.

The use of such combinations of polyvinyl pyrrolidone and iodine and other halogen containing compounds is not limited to but extends into parenteral use, intramuscular use, intraperitoneal uses and use *per os*. Some halogen compositions because of lower toxicity and the synergistic effect can be used orally for therapeutic and diagnostic purposes.

The combination of polyvinyl pyrrolidone and halogens both organic and inorganic forms thereof is not limited to any single concentration but concentrations up to the maximum solubility of the polyvinyl pyrrolidone together with the maximum solubility of the particular halogen compound may be used. In other words, these cover hypo-, hyper- and isotonic solutions as well as stoichiometric propositions of halogens and polyvinyl pyrrolidone.

It will be understood that the combination of halogen and polyvinyl-n-pyrrolidone may be combined with other materials to enhance or permit its use in special applications. Thus, the novel

polyvinyl pyrrolidone-halogen combinations of the present invention may be formulated along with surface active materials to provide novel compositions useful industrially and therapeutically. The addition of the novel polyvinyl pyrrolidone sodium hypo-chlorite or elemental iodine combinations of the present invention to known surface active agents such as soaps, synthetic organic detergents such as organic sulfonates and sulfates, non-ionic detergents such as polyglycol ether detergents and cationic detergents, are effective in sterilizing and sanitizing and cleaning operations. In therapeutic applications, the novel combination of polyvinyl pyrrolidone and halogen compounds may be combined with other agents such as enzymes, for instance, hyalouronidase, are effective for carrying the polyvinyl pyrrolidone halogen combination into the cell body proper, the enzyme being effective to penetrate the cell wall.

What we claim is:—

1. A method of detoxifying halogen containing pharmaceutical products selected from the group consisting of normally toxic organic iodine containing pharmaceutical products and normally toxic inorganic halogen containing pharmaceutical products supplying free halogen ions in solution which comprises mixing such halogen containing pharmaceutical products having a normal toxicity with a polymeric N-vinyl-α-pyrrolidone.

2. Detoxified halogen containing pharmaceutical products selected from the group consisting of normally toxic organic iodine containing pharmaceutical products and normally toxic inorganic halogen containing pharmaceutical products supplying free halogen ions in solution having a normal toxicity comprising a mixture of a polymeric N-vinyl-α-pyrrolidone and such halogen containing pharmaceutical products.

3. The method of reducing the toxicity of free-iodine solutions which comprises mixing a polymeric N-vinyl-α-pyrrolidone with a solution containing free iodine.

4. A solution containing free iodine and a polymeric N-vinyl-α-pyrrolidone.

5. The method of reducing the toxicity of solutions of alkali hypohalites which comprises mixing such solutions with a polymeric N-vinyl-α-pyrrolidone.

6. Method as defined in claim 5 wherein the alkali hypohalite is sodium hypochlorite.

7. A composition comprising a mixture of alkali hypohalite and a polymeric N-vinyl-α-pyrrolidone.

8. A composition comprising a mixture of sodium hypochlorite and a polymeric N-vinyl-α-pyrrolidone.

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6. Method as defined in claim 5 wherein the alkali hypohalite is sodium hypochlorite.

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