

ABSORBABLE DUSTING POWDER DERIVED FROM STARCH

5

BACKGROUND OF THE INVENTIONField of The Invention

The present invention relates to dusting powders of the type used for lubricating surgical gloves. More particularly, the invention has to do with absorbable dusting powders made from starches having reduced protein content, a low level of carboxyl groups generated through the slight oxidation of hydroxyl groups, and other hydroxyl groups cross-linked using a relatively low level of phosphorus oxychloride (POCl_3).

Description of Related Art

15 Dusting powders used by the medical profession have been associated with numerous problems. Such powders have traditionally been based on talc. However, it has been discovered that talc causes granulomas in the body. Talc also has come under increasing scrutiny as possibly containing
20 asbestos, a carcinogenic substance. While pure mineral talc is composed of a group of hydrous magnesium silicates, commercial talc has varying compositions depending on the source and method of production. Some of these compositions may be contaminated with asbestos.

25 Talc has effectively been replaced by starch-based powders, but the starch-based powders have a number of

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disadvantages too. The use of starch has been associated with peritonitis flowing from the use of corn starch on or in surgeons' gloves and has been associated with infections which occur from glove-borne particles during optical surgery which may cause the cornea to turn opaque. Microbial problems are associated with starch because it is an excellent nutrient medium for virtually all vegetative bacteria such as various pathogenic microorganisms.

Despite the aforementioned disadvantages associated with starch-based powders, they are still used by the medical profession because starch is an inexpensive and readily available raw material. There is a need, therefore, for improved starch dusting powders which overcome many of the foregoing problems.

Starch-based dusting powders used for surgical gloves and other medical apparatus (e.g., tubing, catheters and drains) which may be exposed to internal parts of the body, such as the peritoneal cavity during surgery, must meet strict United States Pharmacopoeia (USP) standards for Absorbable Dusting Powders. These standards are published by the United States Pharmacopeial Convention, Inc., 12601 Twin Brook Parkway, Rockville, MD 20852 USA. All references to the USP or to USP Standards are to the official standards from January 1, 1990 entitled "USP XXII, NF XVII, The United States Pharmacopeia, The National Formulary." The USP Standards require cross-linking of the starch to prevent gelatinization which would



otherwise occur during sterilization when an autoclave is used.

Epichlorohydrin can be used for cross-linking as disclosed in U.S. Patent No. 4,853,978 to Stokum. The patent relates to antimicrobial medical gloves which can be coated with
5 epichlorohydrin cross-linked corn starch. The starch serves as an antimicrobial agent and a donning assist. The starch powder is believed to be bioabsorbable if left in a wound site. In some applications, antimicrobials (e.g., compositions having fungicidal, bactericidal and/or bacteriostatic properties)
10 having an affinity for the cross-linked starch can be absorbed on the starch.

When epichlorohydrin is used for cross-linking, there is some risk that residual quantities of toxic chlorohydrins can remain in the product. Thus, alternative types of absorbable
15 dusting powders have been developed. U.S. Patent No. 4,540,407 to Dunn, for example, discloses the use of a polyol powder which also avoids the problem of starch peritonitis.

A chitin-derived, finely divided biodegradable powder is described in U.S. Patent No. 4,064,564 to Casey for use as a
20 lubricant on surgical gloves. Derivatized chitin, however, is believed to be expensive relative to modified starch and is difficult to obtain in commercial quantities.

Other medical lubricants are disclosed in U.S. Patent No. 4,773,902 to Lentz et al. which is directed to the use of
25 oxidized cellulose, and U.S. Patent No. 4,152,783 to Choski which is directed to a surgeon's glove provided with a sodium



bicarbonate powder.

It has now been discovered in accordance with the present invention that a new modified starch can be prepared which meets USP Standards for absorbable dusting powders while
5 avoiding many of the problems associated with prior art products. The starch is modified in two steps. First, it is treated with sodium hypochlorite to remove protein, oxidize some of the hydroxyl groups and whiten the product. Second, the hypochlorite treated starch is cross-linked with POCl_3 at a
10 low level to allow better assimilation while meeting USP Standards. The use of POCl_3 for cross-linking avoids any risk of residual chlorohydrins associated with the use of epichlorohydrin.

U.S. Patent No. 4,562,086 to Smolka et al. discloses a
15 modified starch for use in food applications which is prepared by etherification with an alkylene oxide followed by cross-linking. Phosphorus oxychloride is disclosed as a cross-linking agent. Treatment of corn starch with hypochlorite is disclosed in U.S. Patent No. 2,070,776 to Bochslandl, U.S.
20 Patent No. 2,951,776 to Scallet et al. and U.S. Patent No. 2,989,521 to Serti et al. The Serti et al. patent describes a process whereby starch is first cross-linked with epichlorohydrin followed by treatment with sodium hypochlorite. These patents do not disclose the processing conditions, or the
25 products of the present invention and none of them relate to the preparation of modified starches for medical uses.



SUMMARY OF THE INVENTION

The absorbable dusting powder composition of the invention is made by modifying starch, preferably corn starch, in two steps. In the first step, the starch is treated with a hypochlorite to remove most of the protein and oxidize some of the hydroxyl groups. This step also causes whitening of the product. It has been found that protein from plant sources can cause allergic response in humans. To reduce any possible allergic reaction from the protein in starch, treatment, using hypochlorite, is important in the development of an absorbable dusting powder.

In the second step, the hypochlorite modified starch is partially cross-linked with POCl_3 to allow better assimilation while meeting USP Standards. A sufficiently low level of cross-linking with POCl_3 prevents gelatinization during heat-pressure based sterilization. The low levels of cross-linking also increase the opportunity for assimilation by normal physiological functions. The USP requires that sedimentation, a measure which depends on the degree of cross-linking, not exceed a value of 75 milliliters (which, for the product of the present invention, is approximately equivalent to bound phosphorus levels of about 400 parts per million (ppm) as explained later in this specification).

Magnesium oxide (MgO) can be added to the hypochlorite-modified cross-linked starch if desired. Magnesium oxide is



commonly used to increase the flowability of dry starch products. When the starch materials formulated with MgO are placed in water, the MgO becomes magnesium hydroxide, an alkaline substance. The USP has limits on the maximum quantities of magnesium oxide that can be used as well as a maximum pH specification that would be indicative of the generation of magnesium hydroxide in solution.

DETAILED DESCRIPTION OF THE INVENTION

The starting material starch used in accordance with the present invention can be derived from various cereal and root materials including corn, milo, wheat, rice, arrowroot, beet, potato, tapioca, waxy corn and waxy milo. Granular corn starch which is made in the corn wet-milling process is preferred because it is readily available, inexpensive and relatively pure as it is produced so that it does not have to be heavily refined after it comes from a corn-wet milling plant.

Corn starch is a carbohydrate polymer derived from corn of various types and composed of about 25% amylose and about 75% amylopectin. It is generally in the form of a fine white powder having a granule size from about 5 to about 25 microns with the average granule size being about 13.9 microns. Bulk density ranges from about 38 to 47 pounds per cubic foot depending on the drying technique used. Flash dried and spray dried starches have bulk densities at the low end of the range and belt dried starches have bulk densities at the high end. Moisture content of corn starch is generally about 12%, but



varies with ambient relative humidity. The gelatinization temperature, as defined by the loss of birefringence, is from about 68 to 72° C.

5 The starting material starch can be unmodified or modified. Suitable modified starches include oxidized starches such as those prepared with hypochlorite or peroxide.

The hypochlorite used in accordance with the invention may be a hypochlorite of sodium, potassium, calcium or magnesium. Sodium hypochlorite (NaOCl) is preferred because it is more
10 readily commercially available.

The phosphorus oxychloride (POCl_3) used in accordance with the invention is a technical grade compound which generally has a specification of 99.5% purity. Phosphorus oxychloride, which is also known as phosphorus oxytrichloride or phosphoryl
15 chloride, is a colorless to pale yellow fuming liquid. It reacts exothermically with water to produce phosphoric and hydrochloric acids.

If magnesium oxide is used in accordance with the invention, it should meet the requirements of USP Standards.

20 The process of the invention can be carried out in a continuous or batchwise manner. The first process step comprises treating a slurried starting material starch with a hypochlorite to remove most of the protein and oxidize some of the hydroxyl groups. The slurried starting material starch
25 should have a dry substance (d.s.) from about 10% to about 45%.

The hypochlorite used can have a concentration from about



5% to about 25% by weight (w/w) chlorine. If necessary, an acid or alkali is added with the hypochlorite to maintain the pH of the reaction mixture at from about 5 to about 10.

Suitable reagents for this purpose are hydrochloric acid, sulfuric acid, phosphoric acid, sodium hydroxide and potassium hydroxide.

The starch is preferably reacted with hypochlorite at a temperature from about 100°F. to about 150°F. for a period of time sufficient to remove the protein to a level of less than about 0.15% w/w, with levels of about 0.05% w/w or less being particularly preferred, and oxidize from about 0.5% w/w to about 0.05% w/w of the hydroxyl groups. Typical reaction times are from about 15 minutes to about 2 hours. The degree of oxidation is determined by measuring the carboxyl content of the starch using standard analytical methods such as those set forth in Whistler et al., STARCH: Chemistry and Technology, Vol II (Academic Press 1967) Chapter XXV entitled "Characterization and Analysis of Starches" pp. 620-621; and Bernetti et al., Modern Methods of Analysis of Food Starches, Cereal Foods World, Vol. 35, No. 11, November 1990 (American Association of Cereal Chemists Inc. 1990) p. 1102.

Following the reaction with hypochlorite, any free chlorine present in the reaction slurry should be neutralized; otherwise the reaction can continue, even in the dry form, although at a reduced rate. Neutralization, if needed, can be accomplished by admixing a neutralizing compound such as sodium



bisulfite, sodium sulfite, potassium bisulfite, potassium sulfite or sulfur dioxide gas in a sufficient quantity to achieve a value of no detectable chlorine as determined by suitable analytical methods for residual oxidants such as that set forth in the USP Standards for starch, page 1986 [9005-25-8] under "Oxidizing Substances".

At this stage, the reaction slurry can either be directed to the next reaction step, or dewatered and the hypochlorite treated starch can be dried by conventional means and saved for subsequent processing. If the material is to be saved, reaction slurry pH is adjusted to from about 5 to about 8 before dewatering and drying. Suitable pH adjustment agents include sodium hydroxide, potassium hydroxide; hydrochloric, sulfuric or phosphoric acid; or any other acid or base that will yield non-toxic soluble salts. Suitable dewatering techniques include centrifugation and filtration. Drying can be carried out in a flash dryer, ring dryer, spray dryer, belt dryer or the like.

The reaction slurry from the hypochlorite treatment stage is adjusted by the addition or removal of water, if necessary, to a d.s. from about 10% to about 45%. If dried hypochlorite treated starch is used, it is reslurried with the addition of water to a d.s. within the same range and mixed to prepare a uniform dispersion. Slurry temperature at this stage is preferably maintained at from about 100°F. to about 150°F.

A salt can be added at a level from about 1% to about 5%



dry basis (d.b.) to the slurry as a gelation suppressant to reduce the tendency of starch granules to swell in the presence of base or alkali and to retard hydrolysis of the POCl_3 reagent. Commonly used salts include sodium chloride and sodium sulfate. Then the pH is adjusted by adding caustic to attain a slurry pH from about 11.5 to about 12.5. Suitable caustic agents include sodium hydroxide and potassium hydroxide. Phosphorus oxychloride is then added at a concentration from about 0.05% to about 1.1% w/w, preferably from about 0.5% to about 1.0% w/w, based on dry substance, to cross-link the starch. Typical reaction times are from about 15 to about 45 minutes. At higher slurry temperatures shorter times might be used and longer times may be suitable for lower slurry temperatures. Higher concentrations will result in more cross-linking and lower concentrations will result in less cross-linking.

The degree of cross-linking of the product of the invention is characterized by bound phosphorus levels from about 1200 to about 200 ppm, preferably from about 475 to about 200 ppm and most preferably from about 475 to about 400 ppm. Bound phosphorus levels are determined by standard analytical methods such as published in "Standard Analytical Methods of the Member Companies of the Corn Refiners Association, Inc." Tentative Standard, 10-16-69, pages C-46-1 through C-46-6.

The degree of cross-linking of the product of the invention can also be expressed as that which will yield a USP



sedimentation value in milliliters (ml.) of about 45 to about 95, preferably about 70-95, and most preferably from about 70-75. (The most preferred range is based on present USP standards. However, compositions having higher sedimentation values may be more desirable since they are more easily assimilated by the body.) Excessive cross-linking, yielding a sedimentation value of less than about 45 ml. is detrimental to physiological assimilation which becomes difficult or reduced at such levels.

The cross-linked product is then washed and neutralized. Washing can be carried out either before or after neutralizing, but it is preferred to neutralize first because it reduces the presence of ash before washing. (Neutralization is necessary because it converts hydroxides to salts and salts are easier to remove.) Neutralization is accomplished by adding acid to bring the slurry to a pH of from about 6 to about 8. Suitable neutralizing acids include hydrochloric, sulfuric and phosphoric acids. Hydrochloric acid is preferred because it is readily available and essentially all of the resulting salts are soluble.

Washing is necessary to remove residual inorganic and organic components and is accomplished by dewatering and reslurrying in one or more cycles until acceptable levels (preferably the lowest possible levels) of such residual components are reached. Dewatering can be carried out by means of a filter or centrifuge. Reslurrying following dewatering



should be to about 10 to about 20% w/w solids. Slurry washing can also be accomplished using successive stages of hydroclones.

5 The washed, neutralized slurry is then dried to a moisture content from about 8% to about 14% using a spray dryer, flash dryer, ring dryer, belt dryer or the like.

The dried modified starch product is a free flowing white powder and is characterized by a protein content of less than about 0.15%, preferably about 0.05% or less, hydroxyl groups
10 oxidized to a level of from about 0.05% w/w to about 0.5% w/w and a degree of cross-linking of hydroxyl groups characterized by bound phosphorus levels from about 200 to about 1200 ppm.

The modified starch composition can be used as a medical dusting powder for various applications including surgical
15 gloves, catheters, tubing, drains and the like. It can be admixed with magnesium oxide if desired or if necessary to meet regulatory standards. The magnesium oxide can be added in an amount less than about 2% w/w dry substance and preferably from about 0.5% to about 2% w/w dry substance, with the maximum
20 being based on USP specifications. When magnesium oxide is added, the objective is to obtain an end product having USP sedimentation values within the range of about 45 to about 95 ml., preferably about 70-95 ml. and most preferably about 70-75 ml.

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EXAMPLES

Six samples of absorbable dusting powder were prepared.



The final processing steps were conducted in a batch process using a 100 gallon tank provided with an agitator. A high level of agitation was attained by adjusting a portable mixer so that the impeller was near the liquid surface. Agitation was continuous during all of the process steps from preparation of the starch slurry through completion of the cross-linking reaction. Each batch was made in the same way except for variations in concentrations and quantities as indicated below.

Reaction Sequence

One hundred pounds of BUFFALO® food grade granular starch available from Corn Products, Box 345, Summit-Argo, Illinois 60501 USA, is treated with sodium hypochlorite in a continuous process. The starch is slurried at 41% d.s. and combined with sodium hypochlorite having a concentration of 15% w/w chlorine and 31% w/w hydrochloric acid. The starch slurry is added to a reaction hold tank at a rate of 10.2 liters per minute, sodium hypochlorite is added at a rate of 14.5 liters per hour and hydrochloric acid is added at a rate of 0.69 liters per hour. The reaction mixture in the reaction hold tank is maintained at a temperature of 47°C. (117°F.) and a pH of 6.4 ± 0.3 . Residence time in the reaction hold tank is 30 minutes.

Sodium bisulfite (having a concentration of 15% w/w) is admixed with the product leaving the reaction hold tank to neutralize free chlorine. The addition takes place in a neutralization pipeline on the way into a neutralization tank. The flow of sodium bisulfite is adjusted as necessary to



achieve no detectable free chlorine.

Soda ash (having a concentration of 5% w/w) is added to the product leaving the neutralization tank. The addition takes place in a neutralization pipeline on the way to a basket
5 centrifuge for dewatering. The flow rate of soda ash is adjusted as necessary to achieve a slurry pH of 5.0-5.5.

The slurry is dewatered in the basket centrifuge and the dewatered hypochlorite-treated starch is dried in a flash dryer to a moisture content of 12% w/w.

10 Alternatively, one hundred pounds of oxidized starch having a protein content of about 0.15% d.s. is treated with hypochlorite in the same manner as set forth above except that sodium hypochlorite containing about 4% w/w free sodium
hydroxide is added at a comparable rate and no hydrochloric
15 acid is added.

For each reaction batch, 45 gallons of water were added to a 100 gallon tank and heated to a temperature of about 110°F. (43°C.) For each of five samples, 300 pounds of BUFFALO starch (not hypochlorite-treated) was added to prepare starch slurries
20 having 40% starch solids while maintaining the temperature at about 110° F. For the sixth sample, 100 pounds of the hypochlorite-treated BUFFALO starch was added to 30 gallons of water to prepare a starch slurry having 20% starch solids. There was no other adjustment or control of temperature during
25 subsequent processing steps. Each starch slurry was mixed for from about 15 to 30 minutes before further processing. The



objective of the mixing was to prepare a uniform dispersion.

Sodium chloride (NaCl) was added to each starch slurry as a dry solid at a level of 3% based on starch dry substance. About 15 minutes after NaCl addition, sodium hydroxide (NaOH) was added as a 4% by weight solution. (The 4% NaOH solution was prepared by adding 50% by weight NaOH to dilution water.) NaOH addition was gradual over a period of about 20 minutes until a concentration of 2.05% by weight NaOH based on starch dry substance was attained. The NaOH addition point was into an area of high agitation on the liquid surface in the reaction tank. Slurry pH after NaOH addition was from about 12.0 to about 12.4.

About 10 minutes after NaOH addition was completed, POCl_3 was measured in a graduated cylinder before addition. Of the six samples prepared, two were at a POCl_3 concentration of 0.6% by weight based on starch dry substance, two at 0.8% and two at 1.0%. The concentrations were varied to achieve different levels of cross-linking. POCl_3 was added gradually over a period of 30-60 seconds. Vapors were controlled with a vat hose connected to an exhaust fan. The cross-linking reaction was considered completed 10 minutes after POCl_3 addition. Reaction slurry pH following cross-linking was from about 11.3 to about 11.9.

Washing and Neutralization

Some of the reaction slurries were separated into two fractions with about one-third being neutralized before



washing. The remaining two-thirds were neutralized after washing. Neutralization was accomplished by adding 1% w/w hydrochloric acid to the slurries to bring the pH to about 7.

The cross-linked reaction product was washed in three steps using a 36 inch diameter gravity nutsche filter. (A nutsche filter is a tank equipped with a false bottom, perforated or porous, that may support a filter medium or may itself act as the septum.) Two different tightly woven filter cloths were used in separate trials. One was a white polyamide-nylon fabric made from a monofilament source having a mesh of -3-53/21 xx and a width of 40-42 inches. This cloth is sold under the trademark MITEX by Tetko Incorporated, 333 S. Highland Avenue, Briarcliff Manor, New York 10523 USA. The other was a gray cotton fabric made from a twisted multifilament thread and sold under the Style Number EMPH 101 by TestFabrics Inc., 200 Blackford Avenue, Middlesex, NJ 08846 USA. Both filter cloths gave satisfactory results. A vacuum generated by a vacuum pump at a level of 15 inches mercury (Hg) was used. Each filtration cycle was conducted for about 5-15 minutes resulting in filter cakes about 1-3 inches thick having a moisture content of about 50%. The filter cakes were reslurried to about 35-40% by weight solids between each step and after the last filtration step.

Drying

The washed, neutralized slurries were each separately spray dried in a DeLaval spray dryer (DeLaval, Inc.,



Lawrenceville, New Jersey USA). Dryer inlet air at a temperature of 300°F (50°F wet bulb) was obtained from a gas furnace. Supply slurry was atomized through a high pressure nozzle at 2600 p.s.i.g. at a rate of 15 gallons/hour. Outlet
 5 air temperature was controlled at about 150°F. for a target product moisture of 10%. The drying rate was about 50 pounds of product per hour.

The spray dried product was free flowing with low dust generation when handled and had a somewhat granular texture.
 10 Microscopic examination revealed roughly spherical agglomerates ranging in size from a few to several hundred individual starch granules. In the presence of water, the agglomerates immediately and totally dispersed.

Product Analyses

15 Analytical results are summarized in Tables I and II below.

TABLE I

		POC1 ₃	%		Ash, ¹	Sedi-
20	<u>Sample</u>	<u>dose</u>	<u>moist.</u>	<u>pH</u>	<u>% d.b.</u>	<u>mentation</u> ²
	1A	0.6	6.7	8.9	1.6	52
	1B	0.6	6.8	9.3	1.0	51
	2A	0.8	7.7	9.2	1.8	47
	2G	0.8	9.9	9.3	0.7	59
25	3A ³	1.0	8.3	8.8	1.5	45
	3B	1.0	10.0	9.3	1.1	50



1 % d.b. means % dry basis. Dry basis is calculated by
multiplying the sample weight by the dry substance (d.s.)
Dry substance is calculated by dividing the dried weight
5 (without moisture) of a sample by the total weight (with
moisture) of the sample before drying.

2 USP Sedimentation in milliliters based on the method
associated with the USP specifications.

3 This sample was tested for heavy metals as
10 representative of the others and 1 ppm heavy metals was
detected.

The POCl_3 dose was a percentage based on total starch, dry
substance.

The "A" samples and the "G" sample were washed before the
15 neutralization step and the "B" samples were washed after
neutralization. The "A" and "B" samples were made using the
BUFFALO starch starting material and the "G" sample was made
using the hypochlorite-treated BUFFALO starch starting
material.

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TABLE II

	<u>Sample</u>	<u>Na, ppm d.b.</u>	<u>Protein, % d.b.</u>	<u>Solubles, % d.b.</u>	<u>Bact.</u>	<u>Mold/ Yeast</u>
5	1A	6900	0.21	1.6	3500	5
	1B	2700	0.34	1.0	5200	180
	2A	7000	0.20	1.9	4800	70
	2G	2800	0.05	1.3	7800	40
	3A	4300	0.26	1.2	350	10
7	3B	1500	0.29	0.9	--	--

Microbial analytical values for bacteria (Bact.) and mold and yeast are in colony forming units per gram (cfu/g).

15 Sample Formulation With MgO

Each of the six samples was formulated in the laboratory with 0.25, 0.50 and 0.75 percent magnesium oxide to determine the effect on pH and sedimentation volume shown in Table III. A magnesium level of about 0.5% was enough to reach the minimum
 20 10.0 pH for all of the samples and still be within the sedimentation specification.



TABLE III

	<u>Sample</u>	<u>MgO, % on d.s.</u>	<u>pH</u>	<u>U.S.P. Sedi- mentation, ml</u>
5	1A	0	8.9	52
		0.25	9.65	68
		0.50	9.95	70
		0.75	10.0	70
	1B	0	9.3	51
		0.25	9.9	58
		0.50	10.05	62
		0.75	10.1	65
10	2A	0	9.2	47
		0.25	9.9	60
		0.50	10.05	63
		0.75	10.2	70
	2G	0	9.3	59
		0.25	10.2	73
		0.50	10.25	74
		0.75	10.35	76
15	3A	0	8.8	45
		0.25	10.05	60
		0.50	10.2	62
		0.75	10.3	64
	3B	0	9.3	50
		0.25	10.05	64
		0.50	10.25	66
		0.75	10.3	68
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Having set forth the general nature and some specific examples of the present invention, the scope is now more specifically set forth in the appended claims.





WE CLAIM:

1. A modified starch composition comprising a protein content of less than about 0.15% by weight, from about 0.5 to about 0.05% by weight oxidized hydroxyl groups and a degree of cross-linking of hydroxyl groups characterized by bound phosphorus levels from about 200 to about 1200 ppm.
2. The composition of claim 1 further comprising magnesium oxide in an amount less than about 2% by weight dry substance.
3. The use of the composition of claim 1 as a medical lubricant.
4. A modified starch composition comprising a protein content of less than about 0.15% by weight, from about 0.5 to about 0.05% by weight oxidized hydroxyl groups and having a USP sedimentation value from about 45 to about 95 milliliters.
5. The composition of claim 4 further comprising magnesium oxide in an amount less than about 2% by weight dry substance.
6. The use of the composition of claim 4 as a medical lubricant.
7. A process for preparing a modified starch composition comprising treating a starch with a hypochlorite to remove protein to a level less than about 0.15% by weight and oxidize from about 0.5 to about 0.05% by weight of the hydroxyl groups, and then partially cross-linking the hypochlorite treated





starch with phosphorus oxychloride to a degree of cross-linking characterized by bound phosphorus levels from about 200 to about 1200 ppm.

8. The process of claim 7 wherein the hypochlorite is sodium hypochlorite.

9. The process of claim 7 wherein a starch slurry having a dry substance from about 10% to about 45% is first reacted with a hypochlorite at a pH from about 5 to about 10 and a temperature from about 100 to about 150°F. for a period of time sufficient to reduce the protein content of the starch to a level of less than about 0.15% by weight and oxidize from about 0.5 to about 0.05% by weight of the hydroxyl groups, followed by reacting with phosphorus oxychloride at a pH from about 11.5 to about 12.5 and a temperature from about 100 to about 150°F. for a period of time sufficient to cross-link the hydroxyl groups to a level characterized by bound phosphorus levels from about 200 to about 1200 ppm.

10. A process for preparing a modified starch composition comprising treating a starch with a hypochlorite to remove protein to a level less than about 0.15% by weight and oxidize from about 0.5 to about 0.05% by weight of the hydroxyl groups, and then partially cross-linking the hypochlorite treated starch with phosphorus oxychloride to obtain a composition having a USP sedimentation value from about 45 to about 95 milliliters.



ABSORBABLE DUSTING POWDER DERIVED FROM STARCH**ABSTRACT**

5 Absorbable dusting powders suitable for medical
applications such as lubricating surgical gloves are prepared
by treating starch with a hypochlorite to remove protein and
oxidize some of the hydroxyl groups, and partially cross-
linking the hypochlorite-treated starch with phosphorus
10 oxychloride. The modified starch dusting powders are free
flowing and are characterized by a protein content of less than
about 0.15% by weight, hydroxyl groups oxidized to a level of
from about 0.5 to about 0.05% by weight and a degree of cross-
linking of other hydroxyl groups characterized by bound
15 phosphorus levels of from about 200 to about 1200 ppm.

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ABSORBABLE DUSTING POWDER DERIVED FROM STARCH

BACKGROUND OF THE INVENTION

Field of The Invention

The present invention relates to dusting powders of the type used for lubricating surgical gloves. More particularly, the invention has to do with absorbable dusting powders made from starches having reduced protein content, a low level of carboxyl groups generated through the slight oxidation of hydroxyl groups, and other hydroxyl groups cross-linked using a relatively low level of phosphorus oxychloride (POCl_3).

Description of Related Art

Dusting powders used by the medical profession have been associated with numerous problems. Such powders have traditionally been based on talc. However, it has been discovered that talc causes granulomas in the body. Talc also has come under increasing scrutiny as possibly containing asbestos, a carcinogenic substance. While pure mineral talc is composed of a group of hydrous magnesium silicates, commercial talc has varying compositions depending on the source and method of production. Some of these compositions may be contaminated with asbestos.

Talc has effectively been replaced by starch-based powders, but the starch-based powders have a number of

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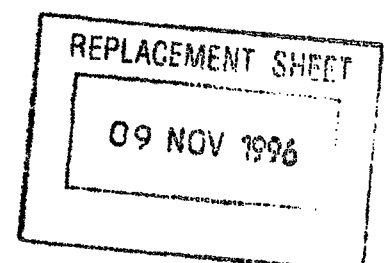
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disadvantages too. The use of starch has been associated with peritonitis flowing from the use of corn starch on or in surgeons' gloves and has been associated with infections which occur from glove-borne particles during optical surgery which may cause the cornea to turn opaque. Microbial problems are associated with starch because it is an excellent nutrient medium for virtually all vegetative bacteria such as various pathogenic microorganisms.

Despite the aforementioned disadvantages associated with starch-based powders, they are still used by the medical profession because starch is an inexpensive and readily available raw material. There is a need, therefore, for improved starch dusting powders which overcome many of the foregoing problems.

Starch-based dusting powders used for surgical gloves and other medical apparatus (e.g., tubing, catheters and drains) which may be exposed to internal parts of the body, such as the peritoneal cavity during surgery, must meet strict United States Pharmacopoeia (USP) standards for Absorbable Dusting Powders. These standards are published by the United States Pharmacopeial Convention, Inc., 12601 Twin Brook Parkway, Rockville, MD 20852 USA. All references to the USP or to USP Standards are to the official standards from January 1, 1990 entitled "USP XXII, NF XVII, The United States Pharmacopeia, The National Formulary." The USP Standards require cross-linking of the starch to prevent gelatinization which would

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otherwise occur during sterilization when an autoclave is used.

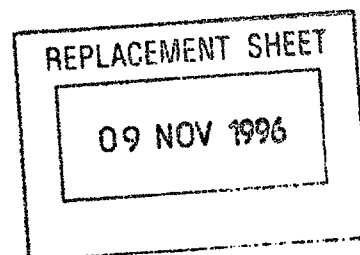
Epichlorohydrin can be used for cross-linking as disclosed in U.S. Patent No. 4,853,978 to Stokum. The patent relates to antimicrobial medical gloves which can be coated with epichlorohydrin cross-linked corn starch. The starch serves as an antimicrobial agent and a donning assist. The starch powder is believed to be bioabsorbable if left in a wound site. In some applications, antimicrobials (e.g., compositions having fungicidal, bactericidal and/or bacteriostatic properties) having an affinity for the cross-linked starch can be absorbed on the starch.

When epichlorohydrin is used for cross-linking, there is some risk that residual quantities of toxic chlorohydrins can remain in the product. Thus, alternative types of absorbable dusting powders have been developed. U.S. Patent No. 4,540,407 to Dunn, for example, discloses the use of a polyol powder which also avoids the problem of starch peritonitis.

A chitin-derived, finely divided biodegradable powder is described in U.S. Patent No. 4,064,564 to Casey for use as a lubricant on surgical gloves. Derivatized chitin, however, is believed to be expensive relative to modified starch and is difficult to obtain in commercial quantities.

Other medical lubricants are disclosed in U.S. Patent No. 4,773,902 to Lentz et al. which is directed to the use of oxidized cellulose, and U.S. Patent No. 4,152,783 to Choski which is directed to a surgeon's glove provided with a sodium

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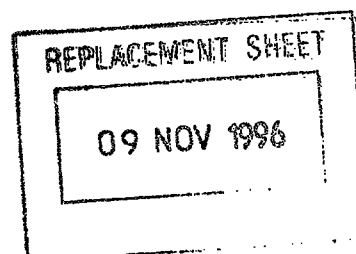


bicarbonate powder.

It has now been discovered in accordance with the present invention that a new modified starch can be prepared which meets USP Standards for absorbable dusting powders while avoiding many of the problems associated with prior art products. The starch is modified in two steps. First, it is treated with sodium hypochlorite to remove protein, oxidize some of the hydroxyl groups and whiten the product. Second, the hypochlorite treated starch is cross-linked with POCl_3 at a low level to allow better assimilation while meeting USP Standards. The use of POCl_3 for cross-linking avoids any risk of residual chlorohydrins associated with the use of epichlorohydrin.

U.S. Patent No. 4,562,086 to Smolka et al. discloses a modified starch for use in food applications which is prepared by etherification with an alkylene oxide followed by cross-linking. Phosphorus oxychloride is disclosed as a cross-linking agent. Treatment of corn starch with hypochlorite is disclosed in U.S. Patent No. 2,070,776 to Bochskaendl, U.S. Patent No. 2,951,776 to Scallet et al. and U.S. Patent No. 2,989,521 to Serti et al. The Serti et al. patent describes a process whereby starch is first cross-linked with epichlorohydrin followed by treatment with sodium hypochlorite. These patents do not disclose the processing conditions, or the products of the present invention and none of them relate to the preparation of modified starches for medical uses.

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SUMMARY OF THE INVENTION

The absorbable dusting powder composition of the invention is made by modifying starch, preferably corn starch, in two steps. In the first step, the starch is treated with a hypochlorite to remove most of the protein and oxidize some of the hydroxyl groups. This step also causes whitening of the product. It has been found that protein from plant sources can cause allergenic response in humans. To reduce any possible allergenic reaction from the protein in starch, treatment, using hypochlorite, is important in the development of an absorbable dusting powder.

In the second step, the hypochlorite modified starch is partially cross-linked with POCl_3 to allow better assimilation while meeting USP Standards. A sufficiently low level of cross-linking with POCl_3 prevents gelatinization during heat-pressure based sterilization. The low levels of cross-linking also increase the opportunity for assimilation by normal physiological functions. The USP requires that sedimentation, a measure which depends on the degree of cross-linking, not exceed a value of 75 milliliters (which, for the product of the present invention, is approximately equivalent to bound phosphorus levels of about 400 parts per million (ppm) as explained later in this specification).

Magnesium oxide (MgO) can be added to the hypochlorite-modified cross-linked starch if desired. Magnesium oxide is

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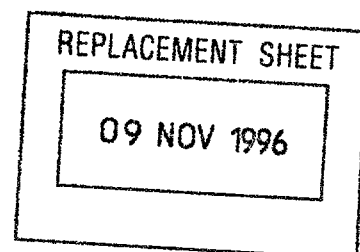
commonly used to increase the flowability of dry starch products. When the starch materials formulated with MgO are placed in water, the MgO becomes magnesium hydroxide, an alkaline substance. The USP has limits on the maximum quantities of magnesium oxide that can be used as well as a maximum pH specification that would be indicative of the generation of magnesium hydroxide in solution.

DETAILED DESCRIPTION OF THE INVENTION

The starting material starch used in accordance with the present invention can be derived from various cereal and root materials including corn, milo, wheat, rice, arrowroot, beet, potato, tapioca, waxy corn and waxy milo. Granular corn starch which is made in the corn wet-milling process is preferred because it is readily available, inexpensive and relatively pure as it is produced so that it does not have to be heavily refined after it comes from a corn-wet milling plant.

Corn starch is a carbohydrate polymer derived from corn of various types and composed of about 25% amylose and about 75% amylopectin. It is generally in the form of a fine white powder having a granule size from about 5 to about 25 microns with the average granule size being about 13.9 microns. Bulk density ranges from about 38 to 47 pounds per cubic foot depending on the drying technique used. Flash dried and spray dried starches have bulk densities at the low end of the range and belt dried starches have bulk densities at the high end. Moisture content of corn starch is generally about 12%, but

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varies with ambient relative humidity. The gelatinization temperature, as defined by the loss of birefringence, is from about 68 to 72° C.

The starting material starch can be unmodified or modified. Suitable modified starches include oxidized starches such as those prepared with hypochlorite or peroxide.

The hypochlorite used in accordance with the invention may be a hypochlorite of sodium, potassium, calcium or magnesium. Sodium hypochlorite (NaOCl) is preferred because it is more readily commercially available.

The phosphorus oxychloride (POCl_3) used in accordance with the invention is a technical grade compound which generally has a specification of 99.5% purity. Phosphorus oxychloride, which is also known as phosphorus oxytrichloride or phosphoryl chloride, is a colorless to pale yellow fuming liquid. It reacts exothermically with water to produce phosphoric and hydrochloric acids.

If magnesium oxide is used in accordance with the invention, it should meet the requirements of USP Standards.

The process of the invention can be carried out in a continuous or batchwise manner. The first process step comprises treating a slurried starting material starch with a hypochlorite to remove most of the protein and oxidize some of the hydroxyl groups. The slurried starting material starch should have a dry substance (d.s.) from about 10% to about 45%.

The hypochlorite used can have a concentration from about

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5% to about 25% by weight (w/w) chlorine. If necessary, an acid or alkali is added with the hypochlorite to maintain the pH of the reaction mixture at from about 5 to about 10. Suitable reagents for this purpose are hydrochloric acid, sulfuric acid, phosphoric acid, sodium hydroxide and potassium hydroxide.

The starch is preferably reacted with hypochlorite at a temperature from about 100°F. to about 150°F. for a period of time sufficient to remove the protein to a level of less than about 0.15% w/w, with levels of about 0.05% w/w or less being particularly preferred, and oxidize from about 0.5% w/w to about 0.05% w/w of the hydroxyl groups. Typical reaction times are from about 15 minutes to about 2 hours. The degree of oxidation is determined by measuring the carboxyl content of the starch using standard analytical methods such as those set forth in Whistler et al., STARCH: Chemistry and Technology, Vol II (Academic Press 1967) Chapter XXV entitled "Characterization and Analysis of Starches" pp. 620-621; and Bernetti et al., Modern Methods of Analysis of Food Starches, Cereal Foods World, Vol. 35, No. 11, November 1990 (American Association of Cereal Chemists Inc. 1990) p. 1102.

Following the reaction with hypochlorite, any free chlorine present in the reaction slurry should be neutralized; otherwise the reaction can continue, even in the dry form, although at a reduced rate. Neutralization, if needed, can be accomplished by admixing a neutralizing compound such as sodium

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bisulfite, sodium sulfite, potassium bisulfite, potassium sulfite or sulfur dioxide gas in a sufficient quantity to achieve a value of no detectable chlorine as determined by suitable analytical methods for residual oxidants such as that set forth in the USP Standards for starch, page 1986 [9005-25-8] under "Oxidizing Substances".

At this stage, the reaction slurry can either be directed to the next reaction step, or dewatered and the hypochlorite treated starch can be dried by conventional means and saved for subsequent processing. If the material is to be saved, reaction slurry pH is adjusted to from about 5 to about 8 before dewatering and drying. Suitable pH adjustment agents include sodium hydroxide, potassium hydroxide; hydrochloric, sulfuric or phosphoric acid; or any other acid or base that will yield non-toxic soluble salts. Suitable dewatering techniques include centrifugation and filtration. Drying can be carried out in a flash dryer, ring dryer, spray dryer, belt dryer or the like.

The reaction slurry from the hypochlorite treatment stage is adjusted by the addition or removal of water, if necessary, to a d.s. from about 10% to about 45%. If dried hypochlorite treated starch is used, it is reslurried with the addition of water to a d.s. within the same range and mixed to prepare a uniform dispersion. Slurry temperature at this stage is preferably maintained at from about 100°F. to about 150°F.

A salt can be added at a level from about 1% to about 5%

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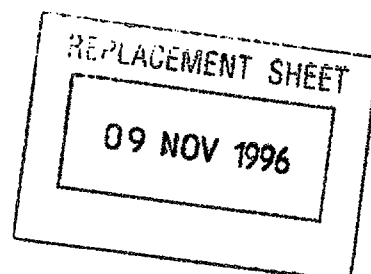
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dry basis (d.b.) to the slurry as a gelation suppressant to reduce the tendency of starch granules to swell in the presence of base or alkali and to retard hydrolysis of the POCl_3 reagent. Commonly used salts include sodium chloride and sodium sulfate. Then the pH is adjusted by adding caustic to attain a slurry pH from about 11.5 to about 12.5. Suitable caustic agents include sodium hydroxide and potassium hydroxide. Phosphorus oxychloride is then added at a concentration from about 0.05% to about 1.1% w/w, preferably from about 0.5% to about 1.0% w/w, based on dry substance, to cross-link the starch. Typical reaction times are from about 15 to about 45 minutes. At higher slurry temperatures shorter times might be used and longer times may be suitable for lower slurry temperatures. Higher concentrations will result in more cross-linking and lower concentrations will result in less cross-linking.

The degree of cross-linking of the product of the invention is characterized by bound phosphorus levels from about 1200 to about 200 ppm, preferably from about 475 to about 200 ppm and most preferably from about 475 to about 400 ppm. Bound phosphorus levels are determined by standard analytical methods such as published in "Standard Analytical Methods of the Member Companies of the Corn Refiners Association, Inc." Tentative Standard, 10-16-69, pages C-46-1 through C-46-6.

The degree of cross-linking of the product of the invention can also be expressed as that which will yield a USP

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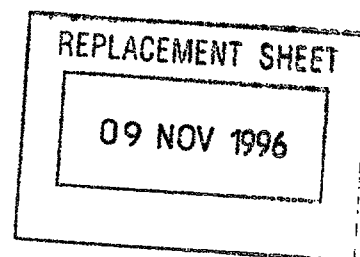


sedimentation value in milliliters (ml.) of about 45 to about 95, preferably about 70-95, and most preferably from about 70-75. (The most preferred range is based on present USP standards. However, compositions having higher sedimentation values may be more desirable since they are more easily assimilated by the body.) Excessive cross-linking, yielding a sedimentation value of less than about 45 ml. is detrimental to physiological assimilation which becomes difficult or reduced at such levels.

The cross-linked product is then washed and neutralized. Washing can be carried out either before or after neutralizing, but it is preferred to neutralize first because it reduces the presence of ash before washing. (Neutralization is necessary because it converts hydroxides to salts and salts are easier to remove.) Neutralization is accomplished by adding acid to bring the slurry to a pH of from about 6 to about 8. Suitable neutralizing acids include hydrochloric, sulfuric and phosphoric acids. Hydrochloric acid is preferred because it is readily available and essentially all of the resulting salts are soluble.

Washing is necessary to remove residual inorganic and organic components and is accomplished by dewatering and reslurrying in one or more cycles until acceptable levels (preferably the lowest possible levels) of such residual components are reached. Dewatering can be carried out by means of a filter or centrifuge. Reslurrying following dewatering

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should be to about 10 to about 20% w/w solids. Slurry washing can also be accomplished using successive stages of hydroclones.

The washed, neutralized slurry is then dried to a moisture content from about 8% to about 14% using a spray dryer, flash dryer, ring dryer, belt dryer or the like.

The dried modified starch product is a free flowing white powder and is characterized by a protein content of less than about 0.15%, preferably about 0.05% or less, hydroxyl groups oxidized to a level of from about 0.05% w/w to about 0.5% w/w and a degree of cross-linking of hydroxyl groups characterized by bound phosphorus levels from about 200 to about 1200 ppm.

The modified starch composition can be used as a medical dusting powder for various applications including surgical gloves, catheters, tubing, drains and the like. It can be admixed with magnesium oxide if desired or if necessary to meet regulatory standards. The magnesium oxide can be added in an amount less than about 2% w/w dry substance and preferably from about 0.5% to about 2% w/w dry substance, with the maximum being based on USP specifications. When magnesium oxide is added, the objective is to obtain an end product having USP sedimentation values within the range of about 45 to about 95 ml., preferably about 70-95 ml. and most preferably about 70-75 ml.

EXAMPLES

Six samples of absorbable dusting powder were prepared.

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The final processing steps were conducted in a batch process using a 100 gallon tank provided with an agitator. A high level of agitation was attained by adjusting a portable mixer so that the impeller was near the liquid surface. Agitation was continuous during all of the process steps from preparation of the starch slurry through completion of the cross-linking reaction. Each batch was made in the same way except for variations in concentrations and quantities as indicated below.

Reaction Sequence

One hundred pounds of BUFFALO® food grade granular starch available from Corn Products, Box 345, Summit-Argo, Illinois 60501 USA, is treated with sodium hypochlorite in a continuous process. The starch is slurried at 41% d.s. and combined with sodium hypochlorite having a concentration of 15% w/w chlorine and 31% w/w hydrochloric acid. The starch slurry is added to a reaction hold tank at a rate of 10.2 liters per minute, sodium hypochlorite is added at a rate of 14.5 liters per hour and hydrochloric acid is added at a rate of 0.69 liters per hour. The reaction mixture in the reaction hold tank is maintained at a temperature of 47°C. (117°F.) and a pH of 6.4 ± 0.3 . Residence time in the reaction hold tank is 30 minutes.

Sodium bisulfite (having a concentration of 15% w/w) is admixed with the product leaving the reaction hold tank to neutralize free chlorine. The addition takes place in a neutralization pipeline on the way into a neutralization tank. The flow of sodium bisulfite is adjusted as necessary to

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achieve no detectable free chlorine.

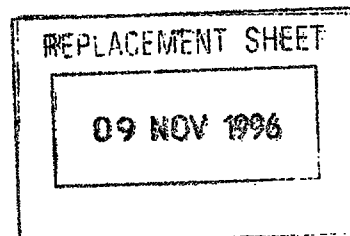
Soda ash (having a concentration of 5% w/w) is added to the product leaving the neutralization tank. The addition takes place in a neutralization pipeline on the way to a basket centrifuge for dewatering. The flow rate of soda ash is adjusted as necessary to achieve a slurry pH of 5.0-5.5.

The slurry is dewatered in the basket centrifuge and the dewatered hypochlorite-treated starch is dried in a flash dryer to a moisture content of 12% w/w.

Alternatively, one hundred pounds of oxidized starch having a protein content of about 0.15% d.s. is treated with hypochlorite in the same manner as set forth above except that sodium hypochlorite containing about 4% w/w free sodium hydroxide is added at a comparable rate and no hydrochloric acid is added.

For each reaction batch, 45 gallons of water were added to a 100 gallon tank and heated to a temperature of about 110°F. (43°C.) For each of five samples, 300 pounds of BUFFALO starch (not hypochlorite-treated) was added to prepare starch slurries having 40% starch solids while maintaining the temperature at about 110° F. For the sixth sample, 100 pounds of the hypochlorite-treated BUFFALO starch was added to 30 gallons of water to prepare a starch slurry having 20% starch solids. There was no other adjustment or control of temperature during subsequent processing steps. Each starch slurry was mixed for from about 15 to 30 minutes before further processing. The

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objective of the mixing was to prepare a uniform dispersion.

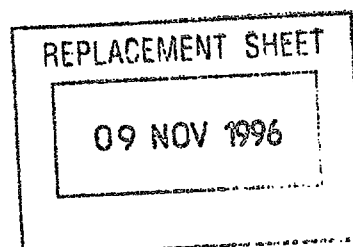
Sodium chloride (NaCl) was added to each starch slurry as a dry solid at a level of 3% based on starch dry substance. About 15 minutes after NaCl addition, sodium hydroxide (NaOH) was added as a 4% by weight solution. (The 4% NaOH solution was prepared by adding 50% by weight NaOH to dilution water.) NaOH addition was gradual over a period of about 20 minutes until a concentration of 2.05% by weight NaOH based on starch dry substance was attained. The NaOH addition point was into an area of high agitation on the liquid surface in the reaction tank. Slurry pH after NaOH addition was from about 12.0 to about 12.4.

About 10 minutes after NaOH addition was completed, POCl_3 was measured in a graduated cylinder before addition. Of the six samples prepared, two were at a POCl_3 concentration of 0.6% by weight based on starch dry substance, two at 0.8% and two at 1.0%. The concentrations were varied to achieve different levels of cross-linking. POCl_3 was added gradually over a period of 30-60 seconds. Vapors were controlled with a vat hose connected to an exhaust fan. The cross-linking reaction was considered completed 10 minutes after POCl_3 addition. Reaction slurry pH following cross-linking was from about 11.3 to about 11.9.

Washing and Neutralization

Some of the reaction slurries were separated into two fractions with about one-third being neutralized before

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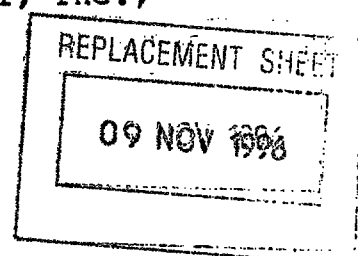
washing. The remaining two-thirds were neutralized after washing. Neutralization was accomplished by adding 1% w/w hydrochloric acid to the slurries to bring the pH to about 7.

The cross-linked reaction product was washed in three steps using a 36 inch diameter gravity nutsche filter. (A nutsche filter is a tank equipped with a false bottom, perforated or porous, that may support a filter medium or may itself act as the septum.) Two different tightly woven filter cloths were used in separate trials. One was a white polyamide-nylon fabric made from a monofilament source having a mesh of -3-53/21 xx and a width of 40-42 inches. This cloth is sold under the trademark MITEK by Tetko Incorporated, 333 S. Highland Avenue, Briarcliff Manor, New York 10523 USA. The other was a gray cotton fabric made from a twisted multifilament thread and sold under the Style Number EMPH 101 by TestFabrics Inc., 200 Blackford Avenue, Middlesex, NJ 08846 USA. Both filter cloths gave satisfactory results. A vacuum generated by a vacuum pump at a level of 15 inches mercury (Hg) was used. Each filtration cycle was conducted for about 5-15 minutes resulting in filter cakes about 1-3 inches thick having a moisture content of about 50%. The filter cakes were reslurried to about 35-40% by weight solids between each step and after the last filtration step.

Drying

The washed, neutralized slurries were each separately spray dried in a DeLaval spray dryer (DeLaval, Inc.,

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Lawrenceville, New Jersey USA). Dryer inlet air at a temperature of 300°F (50°F wet bulb) was obtained from a gas furnace. Supply slurry was atomized through a high pressure nozzle at 2600 p.s.i.g. at a rate of 15 gallons/hour. Outlet air temperature was controlled at about 150°F. for a target product moisture of 10%. The drying rate was about 50 pounds of product per hour.

The spray dried product was free flowing with low dust generation when handled and had a somewhat granular texture. Microscopic examination revealed roughly spherical agglomerates ranging in size from a few to several hundred individual starch granules. In the presence of water, the agglomerates immediately and totally dispersed.

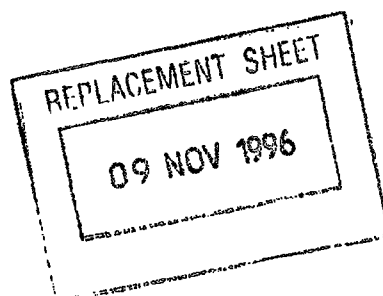
Product Analyses

Analytical results are summarized in Tables I and II below.

TABLE I

<u>Sample</u>	<u>POCl₃ dose</u>	<u>% moist.</u>	<u>pH</u>	<u>Ash, ¹ % d.b.</u>	<u>Sedi- mentation ²</u>
1A	0.6	6.7	8.9	1.6	52
1B	0.6	6.8	9.3	1.0	51
2A	0.8	7.7	9.2	1.8	47
2G	0.8	9.9	9.3	0.7	59
3A ³	1.0	8.3	8.8	1.5	45
3B	1.0	10.0	9.3	1.1	50

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- ¹ % d.b. means % dry basis. Dry basis is calculated by multiplying the sample weight by the dry substance (d.s.) Dry substance is calculated by dividing the dried weight (without moisture) of a sample by the total weight (with moisture) of the sample before drying.
- ² USP Sedimentation in milliliters based on the method associated with the USP specifications.
- ³ This sample was tested for heavy metals as representative of the others and 1 ppm heavy metals was detected.

The POCl_3 dose was a percentage based on total starch, dry substance.

The "A" samples and the "G" sample were washed before the neutralization step and the "B" samples were washed after neutralization. The "A" and "B" samples were made using the BUFFALO starch starting material and the "G" sample was made using the hypochlorite-treated BUFFALO starch starting material.

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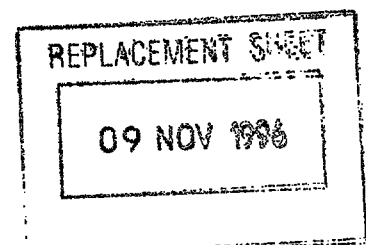


TABLE II

<u>Sample</u>	<u>Na, ppm d.b.</u>	<u>Protein, % d.b.</u>	<u>Solubles, % d.b.</u>	<u>Bact.</u>	<u>Mold/ Yeast</u>
1A	6900	0.21	1.6	3500	5
1B	2700	0.34	1.0	5200	180
2A	7000	0.20	1.9	4800	70
2G	2800	0.05	1.3	7800	40
3A	4300	0.26	1.2	350	10
3B	1500	0.29	0.9	--	--

Microbial analytical values for bacteria (Bact.) and mold and yeast are in colony forming units per gram (cfu/g).

Sample Formulation With MgO

Each of the six samples was formulated in the laboratory with 0.25, 0.50 and 0.75 percent magnesium oxide to determine the effect on pH and sedimentation volume shown in Table III. A magnesium level of about 0.5% was enough to reach the minimum 10.0 pH for all of the samples and still be within the sedimentation specification.

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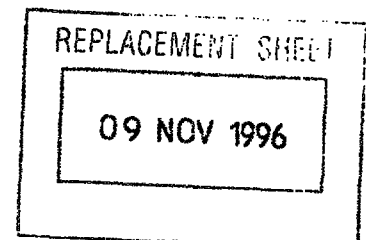
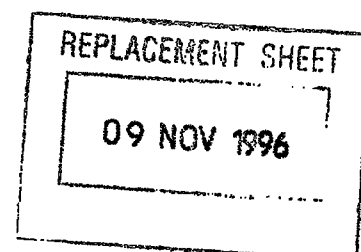


TABLE III

<u>Sample</u>	<u>MgO, % on d.s.</u>	<u>pH</u>	<u>U.S.P. Sedi- mentation, ml</u>
1A	0	8.9	52
	0.25	9.65	68
	0.50	9.95	70
	0.75	10.0	70
1B	0	9.3	51
	0.25	9.9	58
	0.50	10.05	62
	0.75	10.1	65
2A	0	9.2	47
	0.25	9.9	60
	0.50	10.05	63
	0.75	10.2	70
2G	0	9.3	59
	0.25	10.2	73
	0.50	10.25	74
	0.75	10.35	76
3A	0	8.8	45
	0.25	10.05	60
	0.50	10.2	62
	0.75	10.3	64
3B	0	9.3	50
	0.25	10.05	64
	0.50	10.25	66
	0.75	10.3	68

Having set forth the general nature and some specific examples of the present invention, the scope is now more specifically set forth in the appended claims.

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WE CLAIM:

1. A modified starch composition comprising a protein content of less than about 0.15% by weight, from about 0.5 to about 0.05% by weight oxidized hydroxyl groups and a degree of cross-linking of hydroxyl groups characterized by bound phosphorus levels from about 200 to about 1200 ppm.

2. The composition of claim 1 further comprising magnesium oxide in an amount less than about 2% by weight dry substance.

3. The use of the composition of claim 1 as a medical lubricant.

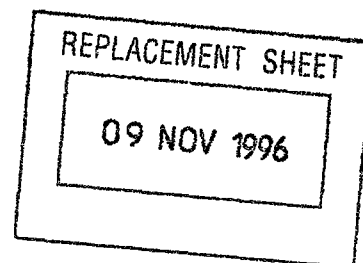
4. A modified starch composition comprising a protein content of less than about 0.15% by weight, from about 0.5 to about 0.05% by weight oxidized hydroxyl groups and having a USP sedimentation value from about 45 to about 95 milliliters.

5. The composition of claim 4 further comprising magnesium oxide in an amount less than about 2% by weight dry substance.

6. The use of the composition of claim 4 as a medical lubricant.

7. A process for preparing a modified starch composition comprising treating a starch with a hypochlorite to remove protein to a level less than about 0.15% by weight and oxidize from about 0.5 to about 0.05% by weight of the hydroxyl groups, and then partially cross-linking the hypochlorite treated

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starch with phosphorus oxychloride to a degree of cross-linking characterized by bound phosphorus levels from about 200 to about 1200 ppm.

8. The process of claim 7 wherein the hypochlorite is sodium hypochlorite.

9. The process of claim 7 wherein a starch slurry having a dry substance from about 10% to about 45% is first reacted with a hypochlorite at a pH from about 5 to about 10 and a temperature from about 100 to about 150°F. for a period of time sufficient to reduce the protein content of the starch to a level of less than about 0.15% by weight and oxidize from about 0.5 to about 0.05% by weight of the hydroxyl groups, followed by reacting with phosphorus oxychloride at a pH from about 11.5 to about 12.5 and a temperature from about 100 to about 150°F. for a period of time sufficient to cross-link the hydroxyl groups to a level characterized by bound phosphorus levels from about 200 to about 1200 ppm.

10. A process for preparing a modified starch composition comprising treating a starch with a hypochlorite to remove protein to a level less than about 0.15% by weight and oxidize from about 0.5 to about 0.05% by weight of the hydroxyl groups, and then partially cross-linking the hypochlorite treated starch with phosphorus oxychloride to obtain a composition having a USP sedimentation value from about 45 to about 95 milliliters.

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REPLACEMENT SHEET

09 NOV 1996

ABSORBABLE DUSTING POWDER DERIVED FROM STARCH**ABSTRACT**

Absorbable dusting powders suitable for medical applications such as lubricating surgical gloves are prepared by treating starch with a hypochlorite to remove protein and oxidize some of the hydroxyl groups, and partially cross-linking the hypochlorite-treated starch with phosphorus oxychloride. The modified starch dusting powders are free flowing and are characterized by a protein content of less than about 0.15% by weight, hydroxyl groups oxidized to a level of from about 0.5 to about 0.05% by weight and a degree of cross-linking of other hydroxyl groups characterized by bound phosphorus levels of from about 200 to about 1200 ppm.

11/21/90

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REPLACEMENT SHEET

09 NOV 1996

ABSORBABLE DUSTING POWDER DERIVED FROM STARCH

5

BACKGROUND OF THE INVENTIONField of The Invention

10

The present invention relates to dusting powders of the type used for lubricating surgical gloves. More particularly, the invention has to do with absorbable dusting powders made from starches having reduced protein content, a low level of carboxyl groups generated through the slight oxidation of hydroxyl groups, and other hydroxyl groups cross-linked using a relatively low level of phosphorus oxychloride (POCl_3).

Description of Related Art

15

20

Dusting powders used by the medical profession have been associated with numerous problems. Such powders have traditionally been based on talc. However, it has been discovered that talc causes granulomas in the body. Talc also has come under increasing scrutiny as possibly containing asbestos, a carcinogenic substance. While pure mineral talc is composed of a group of hydrous magnesium silicates, commercial talc has varying compositions depending on the source and method of production. Some of these compositions may be contaminated with asbestos.

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Talc has effectively been replaced by starch-based powders, but the starch-based powders have a number of

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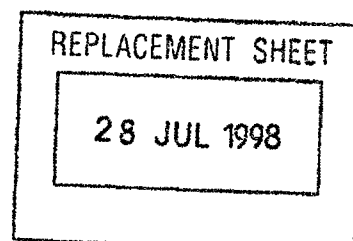
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disadvantages too. The use of starch has been associated with peritonitis flowing from the use of corn starch on or in surgeons' gloves and has been associated with infections which occur from glove-borne particles during optical surgery which may cause the cornea to turn opaque. Microbial problems are associated with starch because it is an excellent nutrient medium for virtually all vegetative bacteria such as various pathogenic microorganisms.

Despite the aforementioned disadvantages associated with starch-based powders, they are still used by the medical profession because starch is an inexpensive and readily available raw material. There is a need, therefore, for improved starch dusting powders which overcome many of the foregoing problems.

Starch-based dusting powders used for surgical gloves and other medical apparatus (e.g., tubing, catheters and drains) which may be exposed to internal parts of the body, such as the peritoneal cavity during surgery, must meet strict United States Pharmacopoeia (USP) standards for Absorbable Dusting Powders. These standards are published by the United States Pharmacopeial Convention, Inc., 12601 Twin Brook Parkway, Rockville, MD 20852 USA. All references to the USP or to USP Standards are to the official standards from January 1, 1990 entitled "USP XXII, NF XVII, The United States Pharmacopeia, The National Formulary." The USP Standards require cross-linking of the starch to prevent gelatinization which would



otherwise occur during sterilization when an autoclave is used.

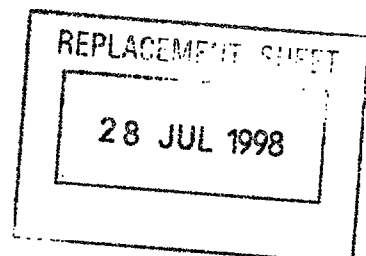
Epichlorohydrin can be used for cross-linking as disclosed in U.S. Patent No. 4,853,978 to Stokum. The patent relates to antimicrobial medical gloves which can be coated with

5 epichlorohydrin cross-linked corn starch. The starch serves as an antimicrobial agent and a donning assist. The starch powder is believed to be bioabsorbable if left in a wound site. In some applications, antimicrobials (e.g., compositions having fungicidal, bactericidal and/or bacteriostatic properties)
10 having an affinity for the cross-linked starch can be absorbed on the starch.

When epichlorohydrin is used for cross-linking, there is some risk that residual quantities of toxic chlorohydrins can remain in the product. Thus, alternative types of absorbable
15 dusting powders have been developed. U.S. Patent No. 4,540,407 to Dunn, for example, discloses the use of a polyol powder which also avoids the problem of starch peritonitis.

A chitin-derived, finely divided biodegradable powder is described in U.S. Patent No. 4,064,564 to Casey for use as a
20 lubricant on surgical gloves. Derivatized chitin, however, is believed to be expensive relative to modified starch and is difficult to obtain in commercial quantities.

Other medical lubricants are disclosed in U.S. Patent No. 4,773,902 to Lentz et al. which is directed to the use of
25 oxidized cellulose, and U.S. Patent No. 4,152,783 to Choski which is directed to a surgeon's glove provided with a sodium



bicarbonate powder.

It has now been discovered in accordance with the present invention that a new modified starch can be prepared which meets USP Standards for absorbable dusting powders while
5 avoiding many of the problems associated with prior art products. The starch is modified in two steps. First, it is treated with sodium hypochlorite to remove protein, oxidize some of the hydroxyl groups and whiten the product. Second, the hypochlorite treated starch is cross-linked with POCl_3 at a
10 low level to allow better assimilation while meeting USP Standards. The use of POCl_3 for cross-linking avoids any risk of residual chlorohydrins associated with the use of epichlorohydrin.

U.S. Patent No. 4,562,086 to Smolka et al. discloses a
15 modified starch for use in food applications which is prepared by etherification with an alkylene oxide followed by cross-linking. Phosphorus oxychloride is disclosed as a cross-linking agent. Treatment of corn starch with hypochlorite is disclosed in U.S. Patent No. 2,070,776 to Bochslandl, U.S.
20 Patent No. 2,951,776 to Scallet et al. and U.S. Patent No. 2,989,521 to Serti et al. The Serti et al. patent describes a process whereby starch is first cross-linked with epichlorohydrin followed by treatment with sodium hypochlorite. These patents do not disclose the processing conditions, or the
25 products of the present invention and none of them relate to the preparation of modified starches for medical uses.

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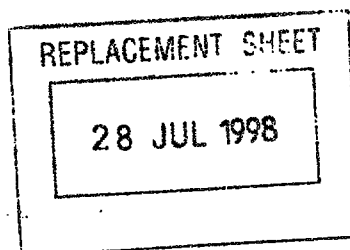
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The JP-B-7 106 377 discloses

a treatment method for modified starch characterized by the fact that starch in an aqueous suspension is treated with 0.1-1.0% of an oxidizing agent and 0.1-1.0%, based on the starch, of sodium trimetaphosphate in the presence of Na^+ ion as a catalyst and at a pH ranging from 8-12.

U.S. Patent No. 2,938,901 discloses a process for making an inert dusting powder which comprises treating starch with metaphosphates or polymetaphosphates in an amount of 0.01 to 3.0 percent based on starch..

A medical dusting powder comprising a partially etherified starch powder and 0.05 to 10 percent by weight of magnesium oxide is disclosed in U.S. Patent No. 2,626,257.



SUMMARY OF THE INVENTION

The absorbable dusting powder composition of the invention is made by modifying starch, preferably corn starch, in two steps. In the first step, the starch is treated with a hypochlorite to remove most of the protein and oxidize some of the hydroxyl groups. This step also causes whitening of the product. It has been found that protein from plant sources can cause allergenic response in humans. To reduce any possible allergenic reaction from the protein in starch, treatment, using hypochlorite, is important in the development of an absorbable dusting powder.

In the second step, the hypochlorite modified starch is partially cross-linked with POCl_3 to allow better assimilation while meeting USP Standards. A sufficiently low level of cross-linking with POCl_3 prevents gelatinization during heat-pressure based sterilization. The low levels of cross-linking also increase the opportunity for assimilation by normal physiological functions. The USP requires that sedimentation, a measure which depends on the degree of cross-linking, not exceed a value of 75 milliliters (which, for the product of the present invention, is approximately equivalent to bound phosphorus levels of about 400 parts per million (ppm) as explained later in this specification).

Magnesium oxide (MgO) can be added to the hypochlorite-modified cross-linked starch if desired. Magnesium oxide is

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commonly used to increase the flowability of dry starch products. When the starch materials formulated with MgO are placed in water, the MgO becomes magnesium hydroxide, an alkaline substance. The USP has limits on the maximum quantities of magnesium oxide that can be used as well as a maximum pH specification that would be indicative of the generation of magnesium hydroxide in solution.

DETAILED DESCRIPTION OF THE INVENTION

The starting material starch used in accordance with the present invention can be derived from various cereal and root materials including corn, milo, wheat, rice, arrowroot, beet, potato, tapioca, waxy corn and waxy milo. Granular corn starch which is made in the corn wet-milling process is preferred because it is readily available, inexpensive and relatively pure as it is produced so that it does not have to be heavily refined after it comes from a corn-wet milling plant.

Corn starch is a carbohydrate polymer derived from corn of various types and composed of about 25% amylose and about 75% amylopectin. It is generally in the form of a fine white powder having a granule size from about 5 to about 25 microns with the average granule size being about 13.9 microns. Bulk density ranges from about 0.61 to 0.75 g/cm³ (38 to 47 pounds per cubic foot) depending on the drying technique used. Flash dried and spray dried starches have bulk densities at the low end of the range and belt dried starches have bulk densities at the high end. Moisture content of corn starch is generally about 12%, but

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varies with ambient relative humidity. The gelatinization temperature, as defined by the loss of birefringence, is from about 68 to 72° C.

5 The starting material starch can be unmodified or modified. Suitable modified starches include oxidized starches such as those prepared with hypochlorite or peroxide.

The hypochlorite used in accordance with the invention may be a hypochlorite of sodium, potassium, calcium or magnesium. Sodium hypochlorite (NaOCl) is preferred because it is more
10 readily commercially available.

The phosphorus oxychloride (POCl₃) used in accordance with the invention is a technical grade compound which generally has a specification of 99.5% purity. Phosphorus oxychloride, which is also known as phosphorus oxytrichloride or phosphoryl
15 chloride, is a colorless to pale yellow fuming liquid. It reacts exothermically with water to produce phosphoric and hydrochloric acids.

If magnesium oxide is used in accordance with the invention, it should meet the requirements of USP Standards.

20 The process of the invention can be carried out in a continuous or batchwise manner. The first process step comprises treating a slurried starting material starch with a hypochlorite to remove most of the protein and oxidize some of the hydroxyl groups. The slurried starting material starch
25 should have a dry substance (d.s.) from 10% to 45%.

The hypochlorite used can have a concentration from

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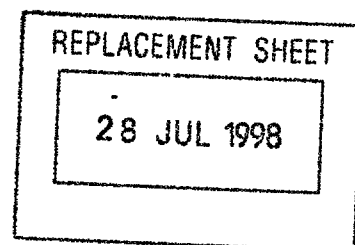
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5% to 25% by weight (w/w) chlorine. If necessary, an acid or alkali is added with the hypochlorite to maintain the pH of the reaction mixture at from 5 to 10.

Suitable reagents for this purpose are hydrochloric acid, sulfuric acid, phosphoric acid, sodium hydroxide and potassium hydroxide.

The starch is preferably reacted with hypochlorite at a temperature from about 38°C (100°F) to about 66°C (150°F) for a period of time sufficient to remove the protein to a level of less than about 0.15% w/w, with levels of about 0.05% w/w or less being particularly preferred, and oxidize from 0.5% w/w to 0.05% w/w of the hydroxyl groups. Typical reaction times are from 15 minutes to 2 hours. The degree of oxidation is determined by measuring the carboxyl content of the starch using standard analytical methods such as those set forth in Whistler et al., STARCH: Chemistry and Technology, Vol II (Academic Press 1967) Chapter XXV entitled "Characterization and Analysis of Starches" pp. 620-621; and Bernetti et al., Modern Methods of Analysis of Food Starches, Cereal Foods World, Vol. 35, No. 11, November 1990 (American Association of Cereal Chemists Inc. 1990) p. 1102.

Following the reaction with hypochlorite, any free chlorine present in the reaction slurry should be neutralized; otherwise the reaction can continue, even in the dry form, although at a reduced rate. Neutralization, if needed, can be accomplished by admixing a neutralizing compound such as sodium

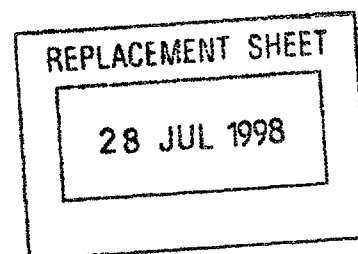


bisulfite, sodium sulfite, potassium bisulfite, potassium sulfite or sulfur dioxide gas in a sufficient quantity to achieve a value of no detectable chlorine as determined by suitable analytical methods for residual oxidants such as that set forth in the USP Standards for starch, page 1986 [9005-25-8] under "Oxidizing Substances".

At this stage, the reaction slurry can either be directed to the next reaction step, or dewatered and the hypochlorite treated starch can be dried by conventional means and saved for subsequent processing. If the material is to be saved, reaction slurry pH is adjusted to from 5 to 8 before dewatering and drying. Suitable pH adjustment agents include sodium hydroxide, potassium hydroxide; hydrochloric, sulfuric or phosphoric acid; or any other acid or base that will yield non-toxic soluble salts. Suitable dewatering techniques include centrifugation and filtration. Drying can be carried out in a flash dryer, ring dryer, spray dryer, belt dryer or the like.

The reaction slurry from the hypochlorite treatment stage is adjusted by the addition or removal of water, if necessary, to a d.s. from 10% to 45%. If dried hypochlorite treated starch is used, it is reslurried with the addition of water to a d.s. within the same range and mixed to prepare a uniform dispersion. Slurry temperature at this stage is preferably maintained at from 38°C (100°F) to 66°C (150°F).

A salt can be added at a level from 1% to 5%.



dry basis (d.b.) to the slurry as a gelation suppressant to reduce the tendency of starch granules to swell in the presence of base or alkali and to retard hydrolysis of the POCl_3 reagent. Commonly used salts include sodium chloride and sodium sulfate. Then the pH is adjusted by adding caustic to attain a slurry pH from about 11.5 to about 12.5. Suitable caustic agents include sodium hydroxide and potassium hydroxide. Phosphorus oxychloride is then added at a concentration from about 0.05% to about 1.1% w/w, preferably from about 0.5% to about 1.0% w/w, based on dry substance, to cross-link the starch. Typical reaction times are from about 15 to about 45 minutes. At higher slurry temperatures shorter times might be used and longer times may be suitable for lower slurry temperatures. Higher concentrations will result in more cross-linking and lower concentrations will result in less cross-linking.

The degree of cross-linking of the product of the invention can be expressed as that which will yield a USP

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sedimentation value in milliliters (ml.) of 45 to -
95, preferably 70-95, and most preferably from 70-
75. (The most preferred range is based on present USP
standards. However, compositions having higher sedimentation
5 values may be more desirable since they are more easily
assimilated by the body.) Excessive cross-linking, yielding a
sedimentation value of less than about 45 ml. is detrimental to
physiological assimilation which becomes difficult or reduced
at such levels.

10 The cross-linked product is then washed and neutralized.
Washing can be carried out either before or after neutralizing,
but it is preferred to neutralize first because it reduces the
presence of ash before washing. (Neutralization is necessary
because it converts hydroxides to salts and salts are easier to
15 remove.) Neutralization is accomplished by adding acid to
bring the slurry to a pH of from 6 to 8. Suitable
neutralizing acids include hydrochloric, sulfuric and
phosphoric acids. Hydrochloric acid is preferred because it is
readily available and essentially all of the resulting salts
20 are soluble.

Washing is necessary to remove residual inorganic and
organic components and is accomplished by dewatering and
reslurrying in one or more cycles until acceptable levels
(preferably the lowest possible levels) of such residual
25 components are reached. Dewatering can be carried out by means
of a filter or centrifuge. Reslurrying following dewatering

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should be to 10 to about 20% w/w solids. Slurry washing can also be accomplished using successive stages of hydroclones.

5 The washed, neutralized slurry is then dried to a moisture content from 8% to 14% using a spray dryer, flash dryer, ring dryer, belt dryer or the like.

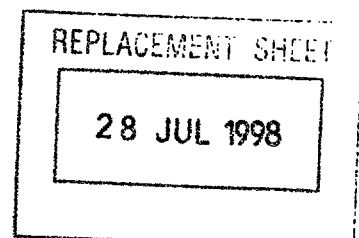
The dried modified starch product is a free flowing white powder and is characterized by a protein content of less than about 0.15%, preferably about 0.05% or less, hydroxyl groups
10 oxidized to a level of from 0.05% w/w to 0.5% w/w and a degree of cross-linking of hydroxyl groups characterized by bound phosphorus levels from about 200 to about 1200 ppm.

The modified starch composition can be used as a medical dusting powder for various applications including surgical
15 gloves, catheters, tubing, drains and the like. It can be admixed with magnesium oxide if desired or if necessary to meet regulatory standards. The magnesium oxide can be added in an amount less than about 2% w/w dry substance and preferably from about 0.5% to 2% w/w dry substance, with the maximum
20 being based on USP specifications. When magnesium oxide is added, the objective is to obtain an end product having USP sedimentation values within the range of 45 to 95 ml., preferably 70-95 ml. and most preferably 70-75 ml.

25

EXAMPLES

Six samples of absorbable dusting powder were prepared.



The final processing steps were conducted in a batch process using a 378 l (100 gallon) tank provided with an agitator. A high

level of agitation was attained by adjusting a portable mixer so that the impeller was near the liquid surface. Agitation was continuous during all of the process steps from preparation of the starch slurry through completion of the cross-linking reaction. Each batch was made in the same way except for variations in concentrations and quantities as indicated below.

Reaction Sequence

10 45kg (One hundred pounds) of BUFFALO (registered trademark) food grade granular starch available from Corn Products, Box 345, Summit-Argo, Illinois 60501 USA, is treated with sodium hypochlorite in a continuous process. The starch is slurried at 41% d.s. and combined with sodium hypochlorite having a concentration of 15% w/w chlorine and 31% w/w hydrochloric acid. The starch slurry is added to a reaction hold tank at a rate of 10.2 liters per minute, sodium hypochlorite is added at a rate of 14.5 liters per hour and hydrochloric acid is added at a rate of 0.69 liters per hour. The reaction mixture in the reaction hold tank is maintained at a temperature of 47°C. (117°F.) and a pH of 6.4 ± 0.3 . Residence time in the reaction hold tank is 30 minutes.

Sodium bisulfite (having a concentration of 15% w/w) is admixed with the product leaving the reaction hold tank to neutralize free chlorine. The addition takes place in a neutralization pipeline on the way into a neutralization tank. The flow of sodium bisulfite is adjusted as necessary to

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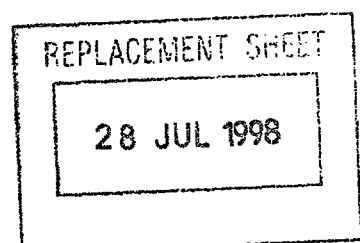
achieve no detectable free chlorine.

Soda ash (having a concentration of 5% w/w) is added to the product leaving the neutralization tank. The addition takes place in a neutralization pipeline on the way to a basket centrifuge for dewatering. The flow rate of soda ash is adjusted as necessary to achieve a slurry pH of 5.0-5.5.

The slurry is dewatered in the basket centrifuge and the dewatered hypochlorite-treated starch is dried in a flash dryer to a moisture content of 12% w/w.

Alternatively, 45kg (one hundred pounds) oxidized starch having a protein content of about 0.15% d.s. is treated with hypochlorite in the same manner as set forth above except that sodium hypochlorite containing about 4% w/w free sodium hydroxide is added at a comparable rate and no hydrochloric acid is added.

For each reaction batch, 170 l (45 gallons) of water were added to a 378 l (100 gallon) tank and heated to a temperature of about 110°F. (43°C.) For each of five samples, 136 kg (300 pounds) of BUFFALO starch (not hypochlorite-treated) was added to prepare starch slurries having 40% starch solids while maintaining the temperature at about 43°C (110°C). For the sixth sample, 45kg (100 pounds) of the hypochlorite-treated BUFFALO starch was added to 114 l (30 gallons) of water to prepare a starch slurry having 20% starch solids. There was no other adjustment or control of temperature during subsequent processing steps. Each starch slurry was mixed for from 15 to 30 minutes before further processing. The



objective of the mixing was to prepare a uniform dispersion.

Sodium chloride (NaCl) was added to each starch slurry as a dry solid at a level of 3% based on starch dry substance. About 15 minutes after NaCl addition, sodium hydroxide (NaOH) was added as a 4% by weight solution. (The 4% NaOH solution was prepared by adding 50% by weight NaOH to dilution water.) NaOH addition was gradual over a period of about 20 minutes until a concentration of 2.05% by weight NaOH based on starch dry substance was attained. The NaOH addition point was into an area of high agitation on the liquid surface in the reaction tank. Slurry pH after NaOH addition was from about 12.0 to about 12.4.

About 10 minutes after NaOH addition was completed, POCl_3 was measured in a graduated cylinder before addition. Of the six samples prepared, two were at a POCl_3 concentration of 0.6% by weight based on starch dry substance, two at 0.8% and two at 1.0%. The concentrations were varied to achieve different levels of cross-linking. POCl_3 was added gradually over a period of 30-60 seconds. Vapors were controlled with a vat hose connected to an exhaust fan. The cross-linking reaction was considered completed 10 minutes after POCl_3 addition. Reaction slurry pH following cross-linking was from 11.3 to 11.9.

Washing and Neutralization

Some of the reaction slurries were separated into two fractions with about one-third being neutralized before

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washing. The remaining two-thirds were neutralized after washing. Neutralization was accomplished by adding 1% w/w hydrochloric acid to the slurries to bring the pH to about 7.

The cross-linked reaction product was washed in three steps using a 91cm (36 inch) diameter gravity nutsche filter. (A nutsche filter is a tank equipped with a false bottom, perforated or porous, that may support a filter medium or may itself act as the septum.) Two different tightly woven filter cloths were used in separate trials. One was a white polyamide-nylon fabric made from a monofilament source having a mesh of -3-53/21 xx and a width of 40-42 inches. This cloth is sold under the trademark MITEX by Tetko Incorporated, 333 S. Highland Avenue, Briarcliff Manor, New York 10523 USA. The other was a gray cotton fabric made from a twisted multifilament thread and sold under the Style Number EMPH 101 by TestFabrics Inc., 200 Blackford Avenue, Middlesex, NJ 08846 USA. Both filter cloths gave satisfactory results. A vacuum generated by a vacuum pump at a level of 380 mm (15 inches) mercury (Hg) was used. Each filtration cycle was conducted for 5-15 minutes resulting in filter cakes 2.5-7.5 cm (1-3 inches) thick having a moisture content of about 50%. The filter cakes were reslurried to 35-40% by weight solids between each step and after the last filtration step.

Drying

The washed, neutralized slurries were each separately spray dried in a DeLaval spray dryer (DeLaval, Inc.,

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Lawrenceville, New Jersey USA). Dryer inlet air at a temperature of 153°C (300°F) 10°C (50°F) wetbulb) was obtained from a gas furnace. Supply slurry was atomized through a high pressure nozzle at 18,000 kN/m² gauge (2600 p.s.i.g.) at a rate of 56.8 l/h (15 gallons/hour). Outlet
 5 air temperature was controlled at about 66°C (150°F). for a target product moisture of 10%. The drying rate was about 23 kg (50 pounds) of product per hour.

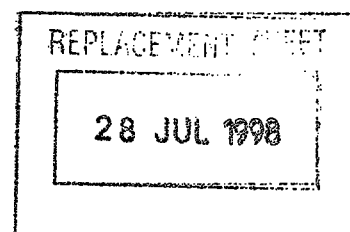
The spray dried product was free flowing with low dust generation when handled and had a somewhat granular texture.
 10 Microscopic examination revealed roughly spherical agglomerates ranging in size from a few to several hundred individual starch granules. In the presence of water, the agglomerates immediately and totally dispersed.

Product Analyses

15 Analytical results are summarized in Tables I and II below.

TABLE I

	Sample	POCl ₃ dose	% moist.	pH	Ash, 1 % d.b.	Sedi- mentation 2
20	1A	0.6	6.7	8.9	1.6	52
	1B	0.6	6.8	9.3	1.0	51
	2A	0.8	7.7	9.2	1.8	47
	2G	0.8	9.9	9.3	0.7	59
25	3A ³	1.0	8.3	8.8	1.5	45
	3B	1.0	10.0	9.3	1.1	50



1 % d.b. means % dry basis. Dry basis is calculated by
multiplying the sample weight by the dry substance (d.s.)
Dry substance is calculated by dividing the dried weight
5 (without moisture) of a sample by the total weight (with
moisture) of the sample before drying.

2 USP Sedimentation in milliliters based on the method
associated with the USP specifications.

3 This sample was tested for heavy metals as
10 representative of the others and 1 ppm heavy metals was
detected.

The POCl_3 dose was a percentage based on total starch, dry
substance.

15 The "A" samples and the "G" sample were washed before the
neutralization step and the "B" samples were washed after
neutralization. The "A" and "B" samples were made using the
BUFFALO starch starting material and the "G" sample was made
using the hypochlorite-treated BUFFALO starch starting
material.

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TABLE II

	<u>Sample</u>	<u>Na, ppm d.b.</u>	<u>Protein, % d.b.</u>	<u>Solubles, % d.b.</u>	<u>Bact.</u>	<u>Mold/ Yeast</u>
5	1A	6900	0.21	1.6	3500	5
	1B	2700	0.34	1.0	5200	180
	2A	7000	0.20	1.9	4800	70
	2G	2800	0.05	1.3	7800	40
	3A	4300	0.26	1.2	350	10
10	3B	1500	0.29	0.9	--	--

Microbial analytical values for bacteria (Bact.) and mold and yeast are in colony forming units per gram (cfu/g).

15 Sample Formulation With MgO

Each of the six samples was formulated in the laboratory with 0.25, 0.50 and 0.75 percent magnesium oxide to determine the effect on pH and sedimentation volume shown in Table III. A magnesium level of about 0.5% was enough to reach the minimum
 20 10.0 pH for all of the samples and still be within the sedimentation specification.

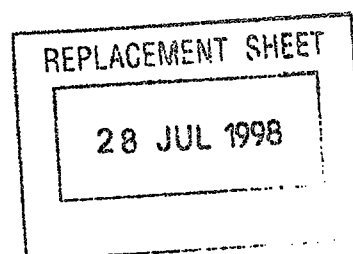
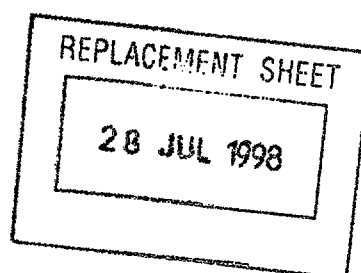


TABLE III

	<u>Sample</u>	<u>MgO, % on d.s.</u>	<u>pH</u>	<u>U.S.P. Sedi- mentation, ml</u>
5	1A	0	8.9	52
		0.25	9.65	68
		0.50	9.95	70
		0.75	10.0	70
	1B	0	9.3	51
		0.25	9.9	58
		0.50	10.05	62
		0.75	10.1	65
10	2A	0	9.2	47
		0.25	9.9	60
		0.50	10.05	63
		0.75	10.2	70
	2G	0	9.3	59
		0.25	10.2	73
		0.50	10.25	74
		0.75	10.35	76
15	3A	0	8.8	45
		0.25	10.05	60
		0.50	10.2	62
		0.75	10.3	64
	3B	0	9.3	50
		0.25	10.05	64
		0.50	10.25	66
		0.75	10.3	68





WE CLAIM:

1. A modified starch composition comprising a protein content of less than about 0.15% by weight, from 0.5 to 0.05% by weight carboxyl groups, obtainable by crosslinking with 0.05% to 1.1% w/w POCl_3 and having a USP sedimentation value ("USP XXII, NF XVII, The United States Pharmacopeia, The National Formulary") from 45 to 95 milliliters.
2. The composition of claim 1 further comprising magnesium oxide in an amount less than about 2% by weight dry substance.
3. The use of the composition of claim 1 as a medical lubricant.
4. A process for preparing a modified starch composition comprising treating a starch with a hypochlorite to remove protein to a level less than about 0.15% by weight and oxidize from 0.5 to 0.05% by weight of the hydroxyl groups, if present, neutralizing any free chlorine by admixing a chlorine neutralizing compound in a sufficient quantity, and then partially cross-linking the hypochlorite treated

REPLACEMENT SHEET

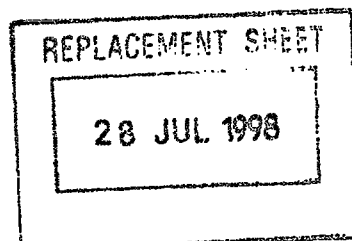
28 JUL 1998



starch with 0.05% to 1.1% w/w phosphorous oxychloride to obtain a composition having a USP sedimentation value ("USP XXII, NF XVII, The United States Pharmacopeia, The National Formulary") from 45 to 95 milliliters.

5. The process of claim 4 wherein the hypochlorite is sodium hypochlorite.

6. The process of claim 4 wherein a starch slurry having a dry substance from 10% to 45% is first reacted with a hypochlorite at a pH from 5 to 10 and a temperature from 38 (100) to 66°C (150°F) for a period of time sufficient to reduce the protein content of the starch to a level of less than about 0.15% by weight and oxidize from 0.5 to 0.05% by weight of the hydroxyl groups, followed by, if present, neutralizing any free chlorine by admixing a chlorine neutralizing compound in a sufficient quantity and followed by reacting with 0.05% to 1.1% w/w phosphorus oxychloride at a pH from 11.5 to 12.5 and a temperature from 38 (100) to 66°C (150°F) for a period of time sufficient to obtain a composition having a USP sedimentation value ("USP XXII, NF XVII, The United States Pharmacopeia, The National Formulary") from 45 to 95 milliliters.



ABSORBABLE DUSTING POWDER DERIVED FROM STARCH

ABSTRACT

5 Absorbable dusting powders suitable for medical
applications such as lubricating surgical gloves are prepared
by treating starch with a hypochlorite to remove protein and
oxidize some of the hydroxyl groups, and partially cross-
linking the hypochlorite-treated starch with phosphorus
10 oxychloride. The modified starch dusting powders are free
flowing and are characterized by a protein content of less than
about 0.15% by weight, hydroxyl groups oxidized to a level of
from about 0.5 to about 0.05% by weight and a degree of cross-
linking of other hydroxyl groups characterized by bound
15 phosphorus levels of from about 200 to about 1200 ppm.

11/21/90

