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ENTERIC COATING

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The invention relates to compositions for use in coating medicaments and like materials for oral ingestion with a layer or film which is substantially soluble in, or disintegrated by, the intestinal secretions but which is substantially insoluble in the acid secretions of the stomach.

Numerous substances have been proposed for the purpose of applying and drying an enteric coating or film onto medicaments, powders, tablets and the like. However, none of them combine all the advantages of resisting penetration of the coating by the stomach secretions during the period of time in which the coated products are normally in contact with such secretions, while at the same time breaking up and releasing medicament with sufficient rapidity in the intestinal tract, and having the property in the liquid state that the coating can be rapidly and efficiently applied in commercial practice.

This invention has for its object to provide an enteric coating which does not break down in the stomach, but which disintegrates and completely releases the imprisoned powder or pill or the like when it reaches the intestines and which possesses the unique property when in the liquid state, prior to its application and subsequent drying, that it can be rapidly and efficiently applied and will quickly dry to give a coating consisting of a very large content of solid material, thereby greatly decreasing the number of times that the liquid preparation must be applied in order to obtain a satisfactory final coating upon drying.

Another object of the invention is to provide a liquid enteric coating compound which is exceptionally valuable and efficient in the process of applying a coating to a medicament and which works well in the rotating pans ordinarily used for this purpose.

Heretofore it has been proposed to use cellulose esters and cellulose ethers containing free carboxyl groups. I have found that such esters or mixtures of esters and ethers, when made up in organic solvent and poured, or sprayed, or otherwise coated onto medicaments, result in enteric coatings which are to a certain extent satisfactory from the standpoint that they may pass through the stomach without disintegrating and will break up upon reaching the intestines. However, I have found that they are totally unsatisfactory for a commercial coating process, due to the fact that they must be highly diluted by solvent in order to give preparations which can be quickly and uniformly applied in the usual large scale commercial coating methods. These known liquid cellulose derivative compositions require a

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great many separate applications to the medicament in order to build up a satisfactory dry coating of sufficient thickness. It is quite important that the liquid be applied a sufficient number of times, with adequate drying between coats, since the final dry enteric coating must be of such thickness that the stomach secretions do not penetrate the same during the considerable period of time in which the coated tablet or pill normally remains in the stomach.

I have now found that cellulose esters of polycarboxylic acids containing free unesterified carboxylic acid groups can be combined in certain proportions with a lac, or resinous plant or insect exudate, of the type of shellac and the combination dissolved or taken up in a common solvent to give liquid preparations of exceptional value in the process of applying a coating quickly and effectively to medicaments and other products intended for oral ingestion.

I have further found that the dry coatings obtained from such liquid preparations dissolve with satisfactory rapidity in the intestines, in spite of the presence of large quantities of lac in such dry coatings. For example, it is known that enteric coatings consisting of shellac, when made thick enough to stand up in the stomach, do not dissolve as rapidly or as completely in the intestines as they ought to for the proper release of medicament. My new coatings are definitely superior to straight shellac coatings in this respect.

In carrying out my invention, I may use, as cellulose derivatives containing free carboxyl groups, any of those made by known methods of preparation, such as those disclosed in United States Patents Nos. 2,093,462 and 2,093,464 and also 2,126,460. For example, cellulose or its derivative containing free hydroxyls can be reacted with a polycarboxylic acid acylating agent, such as an anhydride of the polycarboxylic acid in the presence of a base, or in the presence of a solvent and in the absence of an organic base. The esters of cellulose may be simple esters of polycarboxylic acids or may be mixed esters wherein more than one kind of polycarboxylic acid group is present. They may be also esters of such acids which also contain cellulose ether groups of the mixed ether-ester type.

I may use the reaction products of polycarboxylic acid anhydrides with cellulose or its esters or ethers or ether-esters containing free hydroxyls capable of combining with the acid anhydride to form an ester linkage and also leaving free carboxylic acid groups present. Such anhydrides

are, for example, phthalic, succinic and maleic anhydrides. Examples of cellulose derivatives which may be acylated are cellulose acetate, propionate, acetate-propionate, acetate-butyrate, and ethers of cellulose such as ethyl cellulose, benzyl cellulose, etc., containing free hydroxyls in the cellulose part of the ester.

I prefer to use non-toxic mixed cellulose esters of lower monobasic fatty acids and a polybasic acid, such as phthalic acid, with at least one free unesterified carboxylic acid group, e. g., cellulose-acetate-propionate-phthalate and the like. Free carboxyl need not be present in molecular proportions but the ester, including the ether-esters, may have any free carboxyl content from only a few percent up to about 25%. A free carboxyl content between about 10 and 15% has been found to be the most preferable.

As solvents for the cellulose esters containing free carboxyl groups, any of the known inert organic solvents for such esters may be used, providing the solution of ester will also hold in solution considerable quantities of lac of shellac. I may use acetone, methyl ethyl ketone, isopropyl alcohol, combinations of these such as acetone with ethyl alcohol and, in general, any suitable volatile common solvent or solvent combination for the lac or resin and the cellulose derivatives. Suitable solvents can readily be ascertained by simple experiment. For example, the cellulose ester is thoroughly mixed with the solvent, either with or without heating, until it is dissolved. The plant lac or resin is then worked or triturated gradually in its solid form into the solution of ester. Alternatively, a solution of the lac in the same or a similar solvent may be mixed with the solution of ester. By varying the proportions of solvents and dissolved materials, any combinations having a tendency to throw out ester or lac, or both can be noted. Thereby, one can readily determine the safe limits of concentration to be used with a given combination of solvent, resin and cellulose derivative. However, the solvent should always be sufficiently volatile that drying of each application of the coating liquid is finished before the coating becomes too tacky and begins to lose its uniformity. On the other hand, the solvent should not be too volatile, since the period of fluidity of the mixture would be shortened so that the coating would not then be uniformly distributed over each tablet before the solvent has evaporated.

The resins, lacs or gums which I use in my preparations are referred to herein and in the appended claims as "resinous carriers" for the cellulose derivatives and may be any of the known compositions of this type, of natural or synthetic origin, which are therapeutically innocuous and insoluble in acid but soluble in the alkaline medium of the intestines.

Examples of these resinous carriers for the cellulose derivatives which I use are elemi, mastic and sandarac gums, damar, tolu and shellac, resins, rosin, hydrogenated rosins, soluble Bakelite resins (phenol-formaldehyde type resin) and other synthetic resinous condensates and polymers soluble in the volatile organic solvents mentioned above.

The proportions of resinous carrier and cellulose derivative will vary according to the combination used. For example, when using shellac with cellulose acetate-phthalate containing about 20% acetyl and about 33% phthalyl, I have found that ranges of about 50% to 90% shellac and

10% to 50% of the acetate-phthalate are satisfactory.

The invention can be illustrated by the following examples:

Example 1

10 lbs. of bleached shellac are dissolved in 2½ gallons of denatured 95% ethyl alcohol (U. S. Government formula 3A). Another solution is made by dissolving 5 lbs. of cellulose acetate-phthalate in 3 gallons of acetone. The two solutions are then mixed together slowly with stirring. The resulting liquid preparation is excellently suited to use in coating medicaments, such as tablets, because it is of a mucilaginous character, pours somewhat like castor oil and is sufficiently fluid that it spreads over the tablets and coats them uniformly. It has a viscosity of 250 Saybolt seconds at 30° C.

Example 2

The liquid preparation of Example 1 is poured over 2 grain compressed tablets containing 1 grain of desiccated thyroid gland and having been previously given a thin sub-coat of acacia mucilage and then dusted with calcium carbonate or talc. During the pouring of the coating liquid, the tablets are rolled about and agitated in the customary manner in a rotating drum-like pan provided with a drying-air duct. For example, about 100,000 of these 2 grain tablets can be given a single dose coating by pouring onto them during agitation 1½ to 2 pints of the liquid preparation. The liquid can be applied in a few seconds and the tablets are uniformly coated and begin to get tacky in only one minute or even less. At this time talc or similar dusting powder is added in sufficient quantity to prevent the tablets from sticking to each other or to the pan.

The dusted tablets need only ½ hour of further rolling and drying in the pan until they are ready for another coating which is applied in the same manner.

By repeating the coatings until a total of four or five coats have been applied, one obtains enteric coated tablets of thyroid gland which do not break up in the stomach but which disintegrate readily and completely in the intestines. Approximately two hours is all the time needed to get these final enteric coated thyroid tablets when using my new liquid preparations. On the other hand, when using this kind of alcohol-acetone solution of cellulose acetate-phthalate in the absence of any resinous carrier such as shellac, the total time required to get a satisfactory enteric coating is upwards of 12 hours and much more labor is needed, since 20 or 30 separate applications, with intermediate drying periods, must be put on the tablets. Moreover, a coating which does not contain the resinous carrier very frequently ruins the entire batch of tablets, because irregularities form on the inner lining of the pan during drying and these bring about formation of so-called "crumbs," bumps and like irregularities in the surface of the individual tablets. Such irregularities destroy the effectiveness of the coating and render the tablets unsightly and unmarketable.

Example 3

10 lbs. of balsam tolu are dissolved in 10 pints of acetone. Another solution is made up by dissolving 4 lbs. of cellulose acetate-phthalate in 2½ gallons of isopropyl alcohol. The two solu-

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tions are slowly mixed. The coating liquid so obtained is applied as described in Example 2 to tablets of desiccated ovarian tissue. The liquid goes onto the tablets readily and uniformly and the dry coated tablets carry an efficient enteric coating.

Example 4

5 lbs. of cellulose acetate-phthalate and 10 lbs. of bleached shellac are dissolved in 2½ gallons of "Cellosolve" (ethylene glycol monoethyl ether). This liquid combination can be applied to gland tablets, in the manner already described or by any of the known coating methods.

Example 5

25 lbs. of cellulose propionate-phthalate and 50 lbs. of hydrogenated rosin are dissolved in 15 gallons of dioxane to give a liquid preparation suitable for application as an enteric coating to powdered gland products, crystalline substances such as ammonium chloride, sodium iodide, salicylate salts, etc.

Example 6

12 lbs. of gum sandarac are dissolved in 3 gallons of isopropanol. A second solution of 2½ lbs. of ethyl cellulose phthalate or succinate in 10 pints of methyl ethyl ketone is prepared and carefully mixed with the sandarac solution. This provides a coating liquid which applies to solid materials easily and quickly and dries to an enteric coating that functions ideally in the alimentary tract. For example, this liquid can be applied to medicaments encapsulated within the ordinary telescoping gelatin capsules as well as to pills and tablets.

The above examples are intended for illustration and the invention is not to be limited to the specific compositions, materials and conditions specified therein. Numerous equivalents and variations, over and above what is shown in the examples, are possible within the scope of the invention.

In general, I prefer combinations of cellulose ester compound, physiologically relatively inactive resinous carrier and solvent which have a viscosity between about 200 Saybolt seconds and about 500 Saybolt seconds at room temperature. When using shellac as the resinous carrier, it is preferred to use more shellac than cellulose ester because such proportions give the best combination of properties for the coating solutions.

What I claim as my invention is:

1. An enteric coated substance for use by oral ingestion, said substance being surrounded by an enteric film of a cellulose ester derivative containing free carboxyl groups incorporated in a resinous carrier for said derivative and which film is insoluble in the stomach but soluble in the intestines.

2. A solution for the application of enteric coatings consisting of a cellulose ester derivative containing free carboxyl groups and a resinous carrier therefor in solution in an inert volatile common organic solvent for said ester derivative and carrier.

3. An enteric coated substance for use by oral ingestion, said substance being surrounded by an enteric film of a cellulose ester derivative containing free carboxyl groups incorporated in shellac and which film is insoluble in the stomach but soluble in the intestines.

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4. A solution for the application of enteric coatings consisting of a cellulose ester derivative containing free carboxyl groups and shellac in solution in an inert volatile common organic solvent for said ester derivative and shellac.

5. A solution for the application of enteric coatings consisting of a cellulose ester derivative containing free carboxyl groups and shellac in solution in a mixture of acetone and alcohol having a viscosity at room temperature between about 200 Saybolt seconds and 500 Saybolt seconds.

6. A solution for the application of enteric coatings consisting of cellulose acetate-phthalate containing free carboxyl groups and shellac in an inert volatile common organic solvent for said acetate-phthalate and shellac.

7. A solution for the application of enteric coatings consisting of a lower fatty acid-partial phthalic acid mixed ester of cellulose, containing free carboxyl, and shellac in solution in an inert volatile common organic solvent for said mixed ester and shellac, having a viscosity at room temperature between about 200 Saybolt seconds and 500 Saybolt seconds.

8. A solution for the application of enteric coatings consisting of cellulose acetate-phthalate, containing about 33% phthalyl, and shellac in solution in an inert volatile common organic solvent, said acetate-phthalate and shellac being present in proportions within the ranges of about 10 to 50% acetate-phthalate and 50-90% shellac, said solution having a viscosity between about 200 Saybolt seconds and 500 Saybolt seconds.

9. An enteric coated substance for use by oral ingestion, said substance being surrounded by an enteric film of a lower fatty acid-partial phthalic acid mixed ester of cellulose containing free carboxyl groups incorporated in a resinous carrier for said ester and which film is insoluble in the stomach but soluble in the intestines.

10. An enteric coated substance for use by oral ingestion, said substance being surrounded by an enteric film of a lower fatty acid-partial phthalic acid mixed ester of cellulose containing free carboxyl groups incorporated in shellac, said film being insoluble in the stomach but soluble in the intestines.

11. An enteric coated substance for use by oral ingestion, said substance being surrounded by an enteric film of shellac and cellulose-acetate-phthalate, containing about 33% phthalyl, said acetate-phthalate and shellac being present in proportions within the ranges of about 10-50% cellulose acetate-phthalate and 50-90% shellac.

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