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2,918,485

DIHYDROXY ALUMINUM SALICYLATES

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Analgesics are chemical substances which have the property of destroying or ameliorating low-level pain, such as common headache, mild rheumatism and the like. They do not ordinarily cure the pain in the sense of removing its cause, but rather prevent it from being appreciated. Of the many analgesics known, salicylates are the safest by a wide margin, in that they combine a high degree of effectiveness with a minimum of side-reactions, and are comparatively harmless even in very large overdoses. Many salicylic derivatives have been described, but only two account for the bulk of the very large annual consumption: salicylic acid itself, together with its salts, and acetylsalicylic acid, commonly known as aspirin.

While most persons can take salicylates by mouth, in therapeutic doses, without any perceptible side-effects whatever, there is an appreciable group in which they cause slight irritation of the stomach walls. This stimulates the secretion of hydrochloric acid by the gastric mucosa and produces the type of discomfort generally referred to as "acid indigestion." To prevent such after-effects sensitive individuals are advised to take with their salicylates some acid-counteractant; sodium bicarbonate, magnesium or calcium carbonate, magnesium or aluminum hydroxide are typical substances of this type. This procedure is in fact recommended to every user of salicylates, sensitive or not, as a routine precaution against complications.

Since it is often inconvenient to be required to take two different kinds of tablet, capsule, powder or liquid just to administer a simple remedy, particularly if the ingredients must be carried about on the person, attempts have been made to incorporate both components into a single dose. These have not been notably successful, mainly because aspirin, which is the salicylate usually chosen for maximum effectiveness, is incompatible with basic substances. Compounded with carbonates, bicarbonates or magnesium hydroxide, it is slowly decomposed with loss of the acetyl radical. The only antacid with which it may safely be mixed is aluminum hydroxide, and this, in the dry state, is comparatively ineffective for its intended purpose.

A further drawback to the use of mixtures in this application is the difficulty of insuring that each tablet or other subdivision of the bulk mixture is of the proper composition. Differences in density and particle size among the ingredients often cause a tendency of one or another to settle out as a lot is measured out into doses, with the result that uniformity of composition throughout the batch is not maintained.

Both the aforementioned difficulties may be overcome by the incorporation of the two requisite properties, namely, analgesic activity and the ability to neutralize strong acid, in a single chemical compound. Substances of this type include dihydroxy aluminum salicylate, dihydroxy aluminum acetylsalicylate, dihydroxy aluminum salicylsalicylate and dihydroxy aluminum salicyl ethyl carbonate. Members of this class are stable salt-

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like compounds in which the relative proportions of analgesic and antacid cannot be affected by handling.

While dihydroxy aluminum salicylates are stable in aqueous suspension in the ordinary pH range, they are decomposed at a pH below about 4. When such a preparation is swallowed, it breaks up on encountering the gastric contents at a pH near 1. Since salicylic acid is a weak acid, it is liberated from combination with the aluminum by the strong hydrochloric acid of the stomach, and can then be freely absorbed into the bloodstream. The inorganic moiety is converted to basic aluminum chloride, neutralizing one equivalent of strong acid in the process. Basic aluminum chloride is still capable of neutralizing a further two equivalents of strong acid, in the manner known to be characteristic of aluminum hydroxides.

In addition to the maintenance of a fixed composition, dihydroxy aluminum salicylates exhibit a further advantage over physical mixtures of dried aluminum hydroxide and salicylic acid or a derivative thereof. In combination as a basic salt, aluminum hydroxide retains its full effectiveness in neutralizing strong acids, whereas the unmodified hydroxide loses the greater part of its activity on drying.

Combinations of aluminum hydroxide with acetylsalicylic acid have previously been described, notably by Beekman in U.S. Pat. No. 2,698,332. The procedure outlined therein for their preparation, however, is impracticable on two counts. In the first place, the apparatus on which the process is dependent, a high speed rotary mixer of the design known as a "Waring Blendor," is a device suitable for laboratory-scale investigations of a few ounces of material; it is completely inapplicable to the commercial manufacture of pharmaceuticals in lots of several hundred pounds. Furthermore, the basic aluminum acetylsalicylates thus obtained are not pure compounds. Acetylsalicylic acid is not stable in the presence of water, particularly at elevated temperatures; when it is maintained in aqueous suspension near 60° C. for 30 to 60 minutes, as specified in the cited patent, appreciable hydrolysis to acetic and salicylic acids occurs. As a result, the organic moiety of the product is not pure acetylsalicylic acid but a mixture of this with salicylic acid containing 20 to 50% of the latter. Through our improved process, in contrast, it is possible to prepare combinations of aluminum hydroxide with even the most unstable acylated salicylic acid derivatives, of the highest purity and in any quantity, in simple, standard equipment.

In our method of producing dihydroxy aluminum acylated salicylates, an appropriate acylated salicylic acid derivative is treated at elevated temperatures with a dilute suspension of freshly-precipitated aluminum hydroxide in the presence of a water-miscible organic liquid which is a solvent for the acylated salicylic acid derivative. Any physiologically active acylated salicylic compound may be used, provided it contains a free carboxyl group to provide a point of linkage with the aluminum. Suitable reagents include acetylsalicylic acid, salicylsalicylic acid and salicyl ethyl carbonate. The optimum concentration for the initial aqueous aluminum hydroxide suspension is approximately 5% calculated as aluminum oxide. Somewhat greater dilutions may also be employed. It is of course possible to start with commercial gels of higher concentration, perhaps to 9% to 13% Al_2O_3 , but these should first be diluted to the 5% level in order to prevent coagulation on addition of organic solvent and to avoid too great a viscosity in the final slurry. Considerable latitude is permissible in the selection of the organic solvent, which must be miscible with water and not acidic, either directly or as a result of hydrolysis. Ethyl, n-propyl, isopropyl and t-butyl al-

cohols and 1,4-dioxane are all highly suitable. Methanol and acetone may also be used, but are less desirable on account of their low boiling points.

The following examples will serve to illustrate typical procedures for these useful substances:

Example 1.—To 1020 parts by weight of a freshly precipitated suspension of aluminum hydroxide containing 5% by weight of Al_2O_3 is added, with vigorous stirring, about an equal volume of ethyl or isopropyl alcohol. One hundred thirty eight parts by weight of USP salicylic acid is next introduced, and, without interrupting the stirring, heat is applied to the mixture. Shortly after the liquid reaches the boiling point the slurry begins to thicken, and after it has boiled for half an hour or so it reaches its maximum viscosity. Should the mix at any point become too thick for effective stirring, it is further diluted with a little additional water and/or alcohol. At completion of the reaction the slurry is cooled and transferred to a vacuum filter or a centrifuge where the mother liquor is removed as completely as possible for recovery of the alcohol. The cake may be dried in a hot air oven below 150°C ., or it may be resuspended in pure water and pumped through a spray drier. The product in either case amounts to 198 parts by weight of a white, tasteless, fluffy powder, very slightly soluble in water and containing 13.6% of aluminum, which corresponds to the formula $(\text{OH})_2\text{AlC}_7\text{H}_5\text{O}_3$.

Example 2.—The procedure of Example 1 is followed precisely except that the salicylic acid is replaced by 180 parts by weight of USP acetylsalicylic acid. The product is similar in its properties, but amounts to 240 parts by weight and contains 11.2% of aluminum, corresponding to the formula $(\text{OH})_2\text{AlC}_9\text{H}_7\text{O}_4$.

In the above examples ethyl alcohol or isopropyl alcohol have been specified as the organic solvent. It will be understood, however, that tertiary butyl alcohol and 1,4-dioxane may be substituted for the alcohols specified for the same relative volumes as given in the examples. Likewise, either methanol or acetone may be used in place of the organic solvents specified in the examples. It is intended that these substitutions of organic solvents should be considered as defining separate examples in which the remaining portions of Example 1 would be repeated. Repetition of the example has been avoided in order to avoid undue extension of this specification.

In addition to the lower aliphatic alcohol or alicyclic ether, or acetone, the process of the present invention may be practised by substituting for these organic solvents a water-miscible aliphatic ether selected from the ethers of ethylene glycol, propylene glycol, polyethylene glycol and polypropylene glycol. Specific examples of suitable water miscible ethers are ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, diethylene glycol diethyl ether, ethylene glycol monobutyl ether and diethylene glycol monobutyl ether.

Having thus described our invention, we claim:

1. The process of producing basic aluminum acylated salicylates by means of boiling a physiologically active acylated salicylic compound containing a free carboxyl group selected from the group consisting of acetylsalicylic acid, salicylsalicylic acid and salicyl ethyl carbonate with a dilute suspension of precipitated aluminum hydroxide and about an equal volume of a water miscible organic liquid selected from the group consisting of lower aliphatic alcohols, aliphatic ethers, 1,4-dioxane and acetone.

2. The process of producing dihydroxy aluminum

acetylsalicylate comprising the step of boiling acetylsalicylic acid with a dilute suspension of precipitated aluminum hydroxide and about an equal volume of a water miscible organic liquid selected from the group consisting of lower aliphatic alcohols, aliphatic ethers, 1,4-dioxane and acetone.

3. The process of producing dihydroxy aluminum salicylsalicylate comprising the step of boiling salicylsalicylic acid with a dilute suspension of precipitated aluminum hydroxide and about an equal volume of a water miscible organic liquid selected from the group consisting of lower aliphatic alcohols, aliphatic ethers, 1,4-dioxane and acetone.

4. The process of producing dihydroxy aluminum salicylate ethyl carbonate comprising the step of boiling salicyl ethyl carbonate with a dilute suspension of precipitated aluminum hydroxide and about an equal volume of a water miscible organic liquid selected from the group consisting of lower aliphatic alcohols, aliphatic ethers, 1,4-dioxane and acetone.

5. The process of producing basic aluminum salicylates comprising the step of boiling a physiologically active acylated salicylic compound containing a free carboxyl group selected from the group consisting of acetylsalicylic acid, salicylsalicylic acid and salicyl ethyl carbonate with a dilute suspension of precipitated aluminum hydroxide and about an equal volume of a liquid, water miscible organic solvent consisting of a monohydric alcohol containing from one to four carbon atoms.

6. A process of producing basic aluminum salicylates comprising boiling a physiologically active acylated salicylic compound containing a free carboxyl group selected from the group consisting of acetylsalicylic acid, salicylsalicylic acid and salicyl ethyl carbonate with a dilute suspension of freshly precipitated aluminum hydroxide and about an equal volume of ethyl alcohol.

7. In a process for producing basic aluminum salicylates, the steps comprising adding a water miscible organic liquid selected from the group comprising the lower aliphatic alcohols, aliphatic ethers, 1,4-dioxane and acetone to about an equal volume of a suspension of aluminum hydroxide, adding a physiologically active acylated salicylic compound containing a free carboxyl group selected from the group consisting of acetylsalicylic acid, salicylsalicylic acid and salicyl ethyl carbonate to said mixture, boiling the mixture thus obtained until a slurry is formed, cooling the slurry and removing the mother liquor and recovering the desired product from the residue.

8. The process of producing dihydroxy aluminum acetylsalicylate comprising the step of boiling acetylsalicylic acid with a dilute suspension of precipitated aluminum hydroxide and about an equal volume of ethyl alcohol.

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