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N-METHYL GLUCAMMONIUM SALICYLATE AND USES THEREFOR

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The present invention concerns a new and novel salicylate compound, the process for its preparation and the method of use to achieve an elevated blood level of salicylate ion. In particular, it is concerned with N-methyl glucammonium salicylate, the process for its preparation and the use of the said compound to achieve an elevated blood level of salicylate ion.

There is a well recognized therapeutic need for a salicylate compound which does not cause gastrointestinal distress or local mucosal erosion, as shown by colicky pain or blood in the stool. With the widespread use of the salicylates in the treatment of rheumatic disorders, problems for the administration of large quantities of this drug, are presented to the prescribing physician. Thus, the need for a more rapid absorption has been, in part, solved through the formation of water-soluble salts as, for example, sodium salicylate and potassium salicylate, but these salts have the inherent limitation of affecting the acid-base balance of the blood as well as the mineral ionic balance of the blood, when large quantities are ingested over prolonged periods of time, as is the case in the therapy of these chronic rheumatic diseases. Furthermore, the administration of sodium salicylate is particularly contraindicated for those patients wherein steroid therapy or concomitant cardiac disease mitigates against the administration of sodium-containing compounds.

A problem of the usage of the ammonium derivatives extends to the general class of amine salicylate compounds and, that is, its hydroscopic properties, which limit the formulation of these compounds into pharmaceutically acceptable dosage forms. The hygroscopic properties of salts of salicylic acid, in general, are such that special techniques must be employed in the preparation of solid dosage forms and, consequently, the free acid form is most often used. While free salicylic acid may not be readily administered because of its tissue corrosive properties, the acetylated form is utilized, but is unstable to aqueous media.

Absorption of the salicylate into the blood stream is a necessary factor to achieve the desired therapeutic effect. The more rapid the minimum effective therapeutic threshold blood level achieved, the more rapid will be the onset of the desired pharmacologic effect. Similarly, the higher the blood level obtained, the greater will be the analgetic action achieved. Thus, while salicylic acid is rather insoluble in water, the salts of salicylic acid are somewhat more soluble. This increased solubility in aqueous fluids is without much positive effect on influencing the blood level of salicylate ion since, for the conventional basic salts of salicylic acid, the acidity of the gastric pouch is sufficient to cause a decomposition of the salt, to reverse the salt formation. Thus, it becomes necessary to achieve a soluble salt of salicylic acid which is capable of passing through the gastric acidity and into the blood stream at a rapid rate, without decomposition and without irritation to the gastrointestinal mucosa.

The product of the present invention, N-methyl glucammonium salicylate, possesses such characteristics which make it especially suitable for therapy over prolonged periods. Its administration will result in the rapid elevation of the blood level of salicylate ion, causing a more

rapid onset of analgetic action. N-methyl glucammonium salicylate has important advantages over the numerous known salicylates which have been recommended for clinical use. It is more stable in aqueous solution than the commonly used acetylated salicylic acid (aspirin), and it does not cause the gastrointestinal disturbances which have been reported after the administration of aspirin and other conventional salicylate drugs. N-methyl glucammonium salicylate is rapidly absorbed into the blood stream and does not interfere with the acid-base balance of the blood nor does it contribute large quantities of sodium ion to affect the water retention of the tissues.

N-methyl glucammonium salicylate is a white crystalline solid, melting at 100° C. and is stable under the usual conditions of storage. It does not have the hygroscopic properties of other substituted salts of salicylic acid and, therefore, may be prepared in solid dosage forms, suitable for oral administration without special techniques or costly manufacturing handling procedures.

The tolerance to N-methyl glucammonium salicylate is excellent and the compound has a low order of acute toxicity. The cation moiety is tolerated practically without limit and causes none of the physiologic side reactions common to the older salicylate drugs. The pH of an aqueous solution of N-methyl glucammonium salicylate is approximately neutral and the pH of a 10 percent aqueous solution of the compound is pH 6.6, while that for the 1 percent aqueous solution is pH 6.47.

The general method of preparing N-methyl glucammonium salicylate is to react N-methyl glucamine or the carbonate or bicarbonate salts of N-methyl glucamine with salicylic acid, or an acid salt of N-methyl glucamine with a metallic salt of salicylic acid and isolating the resultant N-methyl glucammonium salicylate. The solvent for this reaction may be water or a liquid alkanol of from 1 thru 6 carbon atoms, or acetone-water mixtures, or mixtures of these.

A preferred method for obtaining N-methyl glucammonium salicylate in relatively pure state is to react stoichiometric equivalent quantities of N-methyl glucamine and salicylic acid in the presence of water or a lower alkanol containing from 1 thru 4 carbon atoms and utilizing gentle heat to facilitate the rate of compound formation. After a half-hour of warming, at temperatures not exceeding 60° C., the n-methyl glucammonium salicylate may be obtained in a high degree of purity by precipitation with isopropyl alcohol and chilling. The solid crystalline compound is filtered, washed with small portions of cold isopropyl alcohol and dried.

N-methyl glucammonium salicylate may also be prepared thru the inter-reaction of a salt of N-methyl glucamine as, for example, N-methyl glucamine carbonate, N-methyl glucamine bicarbonate, N-methyl glucamine hydrochloride, N-methyl glucamine hydrobromide, N-methyl glucamine hydroiodide, N-methyl glucamine sulfate and N-methyl glucamine nitrate, with a metallic salt of salicylic acid, as for example, sodium salicylate, potassium salicylate, calcium salicylate, magnesium salicylate, aluminum salicylate, lead salicylate, copper salicylate and silver salicylate.

When the reaction involves the use of an insoluble salicylate salt as, for example, lead salicylate, copper salicylate, aluminum salicylate and silver salicylate, then from 1 to 5 percent of sodium hydroxide, based upon the weight of metallic salicylate used, may be added to the reaction mixture.

The separation of the inorganic salt formed as a consequence of the double decomposition reaction employed, is achieved through the proper choice of eluting solvents. Thus, hot ethanol will preferentially dissolve the N-methyl glucamine salicylate in preference to the inorganic metallic salt formed. Furthermore, selective

solubilization of the inorganic salt may also be utilized to achieve a separation of the products of the reaction. Thus, for example, when N-methyl glucamine sulfate is reacted with calcium salicylate, calcium sulfate forms in addition to N-methyl glucammonium salicylate. A separation of these two compounds is obtained thru the use of water which dissolves the N-methyl glucammonium salicylate, but does not dissolve the calcium sulfate formed.

An alternate method for preparing N-methyl glucammonium salicylate is to react N-methyl glucamine carbonate or bicarbonate with salicylic acid in an aqueous media. The carbon dioxide formed volatilizes and the residue consist of pure N-methyl glucammonium salicylate.

When it is desired to utilize N-methyl glucammonium salicylate in therapy, then it may be administed in the form of tablets, capsules, granules or liquid preparations by the oral route or as suppositories by the rectal route, with a dosage range of from 0.2 gm. to 1.5 gm. per unit dosage form. Daily dosage levels of from 0.2 gm. to 12 gm. of N-methyl glucammonium salicylate, per day, may be utilized in therapy through the administration of multiples of the unit dosage form. It is recognized that the individual daily dosage will depend upon the particular clinical indication being treated, as well as the individual patient's needs.

The following examples illustrate the scope of this invention:

Example 1

In a glass reaction vessel containing 60 ml. of ethanol is placed 27.6 gm. of salicylic acid and 39.05 gm. of N-methyl glucamine. The mixture is warmed slightly while stirring until complete solution is achieved. The resulting solution is concentrated under vacuum and a viscous syrup is obtained, which is set aside to crystallize. Crystallization will be complete on standing for several days or may be accelerated by "seeding" with a crystal of N-methyl glucammonium salicylate and placing in an ice chest overnight. The resultant crystalline product is filtered and washed with a small quantity of cold ethanol and dried.

The crystalline product obtained is N-methyl glucammonium salicylate and melts at 100° C. It is soluble in water, methanol, hot ethanol and hot isopropanol. It is insoluble in cold, absolute ethanol, cold isopropanol and acetone. N-methyl glucammonium salicylate has the empirical formula, $C_{14}H_{23}O_8N$ with a molecular weight of 333.33. On analysis for carbon, hydrogen and nitrogen, there was good agreement with the calculated theoretical values:

Theory: carbon—50.44%; hydrogen—6.96%; nitrogen—4.20%. Found: carbon—50.64%; hydrogen—7.09%; nitrogen—4.16%.

The N-methyl glucammonium salicylate thus obtained is suitable for use in the preparation of tablets, granules, capsules, liquid and suppository preparations.

Example 2

To 55.2 gm. of salicylic acid, dissolved in 180 ml. of ethanol, is added 80.5 gm. of N-methyl glucamine bicarbonate, in small increments. The mixture is stirred throughout the entire period of the reaction and warmed to remove the formed carbon dioxide from the solvent. When complete solution has been achieved, and no further ebulition of gas occurs, the mixture is cooled in an ice chest and "seeded" with a crystal of N-methyl glucammonium salicylate and the whole set aside to crystallize for a period of 14 to 16 hours. The mixture is then filtered and the solid material washed with a small quantity of cold ethanol and the solid portion dried. The dried crystalline salt is N-methyl glucammonium salicylate, corresponding in every way to that obtained as a result of Example 1, above.

Example 3

To 160.1 gm. of sodium salicylate, dissolved in 1 liter of water is added, in small quantities, a solution of 231.7 gm. of N-methyl glucamine hydrochloride, dissolved in 2 liters of water. When all of the N-methyl glucamine hydrochloride has been added, the mixture is stirred and then carefully evaporated to dryness under reduced pressure. The solid material consists of N-methyl glucammonium salicylate and sodium chloride. A separation of the N-methyl glucammonium salicylate is achieved by extracting the solid residue with hot anydrous isopropanol. On cooling of the isopropanol extract, a crystallization of N-methyl glucammonium salicylate occurs, which is substantially pure and conforms, in every way, to that obtained as a result of Example 1, above.

Example 4

In place of the ethanol or isopropanol or water used in Examples 1 thru 3 above, there may be substituted, in equivalent quantities, a member of the class of alkanols of from 1 thru 6 carbons, or water, or mixtures of these.

Example 5

In place of the sodium salicylate described in Example 3, above, there may be substituted, in stoichiometric equivalent quantities, a metal salt of salicylic acid selected from the groups consisting of potassium salicylate, calcium salicylate, magnesium salicylate, aluminum salicylate, lead salicylate, copper salicylate and silver salicylate. The remainder of the steps being the same and the product obtained is N-methyl glucammonium salicylate, conforming in every way to that obtained as a result of Example 1, above.

Example 6

In place of the N-methyl glucamine hydrochloride described in Example 3, above, there may be substituted, in stoichiometric equivalent quantities, a compound selected from the group consisting of N-methyl glucamine carbonate, N-methyl glucamine bicarbonate, N-methyl glucamine sulfate, N-methyl glucamine hydrobromide, N-methyl glucamine hydroiodide and N-methyl glucamine nitrate. The remainder of the steps being the same and the product isolated is N-methyl glucammonium salicylate, conforming, in every respect, to that obtained as a result of Example 1, above.

Example 7

When it is desired to achieve a therapeutic effect with N-methyl glucammonium salicylate, then either tablets, capsules, granules or a liquid preparation may be administered by the oral route. If oral administration is not available, because of individual patient requirements, then the compound may be administered by the rectal route.

Tablets, granules and capsules of N-methyl glucammonium salicylate are prepared by the appropriate treatment of a granulation mixture by compounding into the selected final dosage form. The granulation mixture is prepared by mixing 1 part of N-methyl glucammonium salicylate with an equal part of a neutral inert diluent as, for example corn starch, sucrose or lactose, and 0.1 part of kaolin. After intimate mixing, the powder is granulated with the aid of a granulating solution as, for example, 1 percent acacia solution or 1 percent gum tragacanth solution and passed thru a No. 20 mesh screen, and dried.

If it is desired to utilize tablets as the mode of administration of the compound, then 0.05 part of magnesium stearate are added to the granulation mixture and the whole tableted by compression, utilizing punches and dies of the proper size and shape, so that each tablet contains from 200 to 1500 mg. of N-methyl glucammonium salicylate, with a preferred unit dosage concentration of N-methyl glucammonium salicylate of 500 mg. per tablet.

Should it be desired to administer the compound in the form of capsules, then the granulation mixture prepared above, is filled directly into gelatin capsules of suitable size and shape so that each capsule contains an amount of the compound ranging in unit dosage of N-methyl glucammonium salicylate of from 200 mg. to 1500 mg. per capsule.

Should it be desired to utilize granules as the dosage form for the administration of the compound, then the granulation mixture, prepared above, is mixed with 1 part of sucrose and 0.05 part of saccharin and the whole wetted with a mixture of 50 percent ethanol-water solution and granulated by passing thru a No. 8 mesh sieve and air dried. The resultant granules are administered in a unit dosage ranging from 1 gram to 5 grams of granules, with a concentration of N-methyl glucammonium salicylate of from 0.2 gm. to 1.5 gm.

Should it be desired to administer N-methyl glucammonium salicylate in the form of a liquid preparation, then the range of concentration of N-methyl glucammonium salicylate is from 0.2 gm. to 1.5 gm. of the compound, per 5 cc. of solution. A solution may be prepared by dissolving the calculated quantity of N-methyl glucammonium salicylate in the appropriate quantity of the solvent or by forming the active compound directly in the vehicle. The latter method is carried out as follows:

In a glass reaction vessel is placed 91.2 gm. of N-methyl glucammonium salicylate and 64.68 gm. of salicylic acid and to this is added 200 cc. of water and 125 cc. of 70 percent d-sorbitol solution. This mixture is stirred until all of the solid reagents have gone into solution and then 100 ml. of simple syrup is added. The mixture is stirred, and to this is added 500 mg. of methyl and propyl parabens and up to 1 gm. of a mixture of 1 part sodium saccharin and 10 parts of calcium cyclamate. The amount of saccharin and cyclamate mixture to be added will depend upon the degree of sweetening preferred and will be found to be within the optimal range of between 750 mg. and 1 gm. of the mixture described. The entire mixture is now warmed to 60° C. and stirred for one-half hour, after which time it is cooled to room temperature, filtered and then brought up to a volume of 500 cc. with distilled water. Should it be desired to color the solution, then appropriate quantities of pharmaceutically acceptable inert coloring agents may be used. The resultant solution contains 1.5 gm. of N-methyl glucammonium salicylate per unit does of 5 cc. (one teaspoonful).

Suppositories of N-methyl glucammonium salicylate may be prepared by mixing 500 mg. of N-methyl glucammonium salicylate with a suitable quantity of pharmaceutically acceptable suppository base as, for example, cocoa butter and the solid polyoxyethylene glycols which are known in the trade as "Carbowaxes," or mixtures of these, so that from 10 to 50 percent concentration of active ingredient in the suppository base, results. After intimate mixing, the suppositories are formed through the use of appropriate suppository molds so that each suppository shall range in weight of from 2 to 3 gm. and contain from 200 mg. to 1500 mg. of N-methyl glucammonium salicylate per unit dose.

Example 8

Under certain conditions, it may be desirable to administer N-methyl glucammonium salicylate in liquid form by either intramuscular or intravenous injection. This may be accomplished by preparing the solution of N-methyl glucammonium salicylate by an aseptic technique and packaging in a special glass ampule container to insure sterility.

When it is desired to accomplish this, then 160.1 gm. of sodium salicylate are dissolved in 2 liters of water-for-injection, and to this is added 231.7 gm. of N-methyl glucamine hydrochloride. The mixture is stirred and warmed below 60° C. until complete solution is achieved. When all of the solid material has gone into solution, the solution is cooled to room temperature and filtered. The volume is then adjusted to exactly 3333 ml. to result in a 10 percent solution of N-methyl glucammonium salicylate. The formed by-product, sodium chloride, remains in solution as an inert substance without physiologic effect. The resultant solution is then filtered through sterile, porcelain, bacterial filters and filled into 2 cc. ampules of type I glass. The sealed ampules may be sterilized by any of the conventional means as, for example, Tyndalization or autoclaving at 15 pounds pressure for one hour.

An alternate method of preparation of the ampule solution is to dissolve sufficient N-methyl glucammonium salicylate in water-for-injection to form a 10 percent solution utilizing an aseptic technique. The remainder of the steps of filtering, sterilizing and packaging remain the same.

The sterile solution for injection may then be utilized by parenteral administration of sufficient solution to achieve a total daily dosage of from 0.2 gm. to 12 gm. per day. The range in concentration of N-methyl glucammonium salicylate, in the solution for injection, is from 0.2 gm. to 1.5 gm. of N-methyl glucammonium salicylate per 2 cc. of solution.

Example 9

When it is desired to elevate the blood level of salicylate ion, then either the tablet, capsule, granule or liquid dosage form of N-methyl glucammonium salicylate may be administered in a daily dosage of from 0.2 gm. to 12 gm. of the active compound, per day. This may be readily accomplished thru the administration of multiples of the unit dosage containing from 0.2 to 1.5 gm. of N-methyl glucammonium salicylate per unit dose, several times per day. The compound will be found to be readily absorbed from the gastrointestinal tract and will not cause local gastrointestinal distress. Therapy with this compound may be maintained over prolonged periods depending upon the individual patient needs without the tolerance to the compounds being effected.

What is claimed is:

1. N-methyl glucammonium salicylate.

2. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically sufficient amount of N-methyl glucammonium salicylate.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and from 0.2 gm. to 1.5 gm. per unit does of N-methyl glucammonium salicylate.

4. A pharmaceutical preparation comprising a pharmaceutical carrier in the form of a tablet including a therapeutically sufficient amount of N-methyl glucammonium salicylate.

5. A pharmaceutical preparation as described in claim 4, the concentration of said N-methyl glucammonium salicylate being from 0.2 gm. to 1.5 gm. per tablet.

6. A capsule containing from 0.2 gm. to 1.5 gm. of N-methyl glucammonium salicylate.

7. A capsule of N-methyl glucammonium salicylate containing a pharmaceutically acceptable carrier and from 0.2 gm. to 1.5 gm. of N-methyl glucammonium salicylate.

8. A granule comprising a pharmaceutically acceptable diluent, a pharmaceutical binder and a therapeutically sufficient amount of N-methyl glucammonium salicylate.

9. A granule comprising a pharmaceutically acceptable diluent, a pharmaceutical binder and from 0.2 gm. to 1.5 gm. of N-methyl glucammonium salicylate per unit dose.

10 A liquid preparation comprising a pharmaceutical liquid vehicle and N-methyl glucammonium salicylate in a concentration of from 0.2 gm. to 1.5 gm. per unit dose of 5 cc. of liquid preparation.

11. A suppository medication comprising a pharmaceutically acceptable suppository base and a dispersion therein of from 0.2 gm. to 1.5 gm. of N-methyl glucammonium salicylate per suppository.

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