

COMPOSITION FOR COMBATING MALARIA AND PROCESS OF MAKING SAME

John O. Barnett, Philadelphia, Pa., assignor, by mesne assignments, to American Home Products Corporation, New York, N. Y., a corporation of Delaware

No Drawing. Application November 14, 1952, Serial No. 320,624

12 Claims. (Cl. 167—65)

This invention relates to a new therapeutic composition which is effective in combating malaria. It is also concerned with a new and improved process by which the new antimalarial composition may be prepared.

In the treatment of malaria, particularly in regions where it is endemic, it is frequently difficult, and sometimes impossible, to administer compositions for combating the disease in the usual manner by supplying pills, capsules, tablets, etc. of a solid composition which is effective against the malarial organism for ingestion by persons who may be suffering with the disease.

In many cases persons who suffer with malaria have a definite aversion to taking medicinals of any sort which would help in combating their infection. While this aversion is sometimes more prevalent among persons of relatively more primitive culture, objections to the ingestion of therapeutic agents in the form of pills, tablets, capsules, other forms of solid medicament, etc., are often encountered even among more educated persons.

Even where objections to the taking of therapeutic agents by mouth are not experienced, there are frequently definite advantages in being able to administer medicaments incorporated on a foodstuff, condiment, or other article of diet, so that the active material may be taken orally along with other substances at meal times, no separate ingestion of therapeutic agents being required. This has previously been accomplished to some extent with some types of pharmaceutical preparations, but it has ordinarily not been successful where a relatively very small amount of a solid therapeutic agent is to be distributed throughout a much larger amount of a solid material of a powdered or granular character, such as table salt, sugar, rice, or similar solid carrier.

Among those solid materials of a food or condiment character which might be used as a base or carrier to support a therapeutic agent, such as an organic compound effective against malaria, so that the anti-malarial agent could be administered along with the dietary material, ordinary table salt would appear to be among the more promising. Salt is consumed as a part of the regular diet, both by those persons who are generally more receptive to taking medication by mouth, as well as by those of a more primitive culture who are frequently more difficult to convince as to the desirability of taking medication for malaria. Since malaria is endemic in many areas which are deficient in medical facilities and which are inhabited by native populations difficult to reach with medication, it is evident that the administration of an antimalarial compound along with the daily intake of salt would be advantageous from many points of view. Effective antimalarial agents, if homogeneously dispersed throughout the table salt, and if no objectionable taste or odor were imparted thereto by the additive, could be thus rendered more widely available, both to persons who are located in inaccessible places, reachable by medical officials only with difficulty, as well as to persons who are more fortunately situated with reference to medical facilities.

While compounds effective in the treatment of malaria are now available, some of them such as 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, and 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline being especially active, many of these compounds are effective in such relatively small dosages that the homogeneous dispersion of the small amount of antimalarial compound necessary throughout a much larger amount of a carrier material, such as ordinary table salt, is a very difficult operation.

The compound 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, known as Daraprim, is described in Patent No. 2,576,939.

The compound 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, known as Primaquine, is described in the Journal of the American Chemical Society, vol. 68, page 1525 (1946). The compound 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline, known as Chloroquine, is described in Patent No. 2,233,970. All three compounds, as well as their salts, are potent antimalarials. Whenever they are referred to herein, it is my intention that the named chemical compounds shall also denote the salts of the bases, since they are frequently administered in the form of their salts.

The homogeneous and uniform dispersion of the organic antimalarial compound is ordinarily essential, for it is very desirable that different samples of the table salt shall contain substantially the same proportion of the antimalarial compound distributed throughout the sample. Since an antimalarial compound, such as any one of the three compounds mentioned, is effective in proportions ranging from 1 part of the organic compound in 5,000 parts of table salt, to 1 part of the organic compound in 500 parts of table salt, based on the average daily consumption of salt, it is obviously not easy to secure uniform distribution of the organic compound in the salt in such relatively dilute concentrations.

When an antimalarial compound is coated directly on table salt, separation of the compound from the salt in the form of "fines" usually occurs when the coated product is subjected to even a moderate amount of vibration. This tendency of the smaller-sized particles to drop to the bottom of the container is common with powders which vary in particle size. If an effort is made to coat table salt directly with an antimalarial compound, such, for example, as 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, or 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline, the antimalarial being present only in minor amount on a relatively very much larger amount of salt, the resulting product is not satisfactory from the point of view of particle separation. This is true when a conventional coating method is used, such as deposition of the antimalarial compound on the salt by wetting the table salt with a solution of the antimalarial in an organic solvent, followed by drying the wetted salt. The active compound is so loosely held on the salt crystals, and is so dispersed throughout the mass of a very much larger volume of salt, that it is easily shaken loose therefrom to separate as an objectionable fine layer in the bottom of the container.

Moreover table salt is relatively hygroscopic in character, tending to cake when stored in a humid atmosphere. This tendency to cake, especially when stored under moist climatic conditions, renders the product less satisfactory from a dietary point of view. When a medicament is administered as a coating on a lumpy unattractive food seasoning, it is difficult to insure adequate medication by the ingestion of uniform and effective quantities of the antimalarial along with the salt.

I have now found that it is possible to disperse a very

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small amount of an antimalarial compound throughout a much larger amount of table salt in such a manner as to secure uniform and homogeneous dispersion thereof provided the salt crystals are first given a coating of a wax-like, water-soluble, non-hygroscopic solid, the organic compound active against malaria being then attached to this wax-like surface coating on the salt crystals. Moreover by first forming on the salt a primary coating of wax-like character, the organic antimalarial compound has been found to adhere more satisfactorily to the wax-coated salt, so that separation of fine particles from the mixture as a result of vibration is almost completely avoided. This is due to the "adhesiveness" of the wax-like solid, an inherent property which results in the medicinal firmly adhering to the wax-like, water-soluble, non-hygroscopic solid, and thence to the coated salt crystals or particles. When the salt crystals are provided with a protective primary layer of wax-like, non-hygroscopic material, the coated product containing the agent effective against malaria is more desirable as a table seasoning or condiment, as it is substantially non-hygroscopic and exhibits little or no tendency to cake, even upon storage under relatively moist conditions.

As the antimalarial compound with which the table salt is to be coated, and which compound adheres to and is substantially uniformly distributed on the primary coating of wax-like, water-soluble, non-hygroscopic solid which surrounds the salt crystals, one of the three organic antimalarials: 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine (Daraprim); 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline (Primaquine); or 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (Chloroquine), is employed.

The wax-like solid with which the salt crystals are first coated must be one that does not appreciably affect the taste of the resulting product, and which is devoid of any objectionable odor. While various water-soluble, wax-like solid products that are available might be utilized, I prefer first to coat the salt crystals with a commercially available product, which is chemically identified as polyethylene glycol having a molecular weight in excess of about 1,000. Wax-like polyethylene glycol products of this type, substantially devoid of odor and taste, and non-hygroscopic even when stored under humid conditions, are sold by Carbide & Carbon Chemicals Corporation as "Carbowax 6,000." Other polyethylene glycol solid products bearing different trade designations may also be used.

The amount of polyethylene glycol having a molecular weight in excess of 1,000 which should be applied as a primary coating to the salt will generally vary with the particular concentration of antimalarial which is desired on the coated salt product. For concentrations of 1 part by weight of the antimalarial compound in 1,000 parts by weight of salt, or less, I prefer to apply as the primary coating about 1.25 parts by weight of the polyethylene glycol solid wax-like, water-soluble, non-hygroscopic solid product for each 1,000 parts by weight of salt. If the antimalarial is to be present in a higher concentration, in excess of 1 part of organic antimalarial compound per 1,000 parts of salt, the amount of polyethylene glycol wax-like solid applied to the salt as the primary coating should be increased. When the antimalarial is present in amounts up to 0.2% by weight (2.0 milligrams per gram of salt), the amount of polyethylene glycol wax-like solid used to coat the salt in the primary coating may range up to 2.5 parts of polyethylene glycol per 1,000 parts of salt.

Coating the polyethylene glycol having a molecular weight in excess of about 1,000 on the salt crystals as a water-soluble, wax-like primary coating is best accomplished by applying to the salt a solution containing the desired amount of the wax-like solid dissolved in a suitable volatile solvent, such as an alcohol, one of the lower alkanols being preferred. This may advantageously be

carried out while the salt is retained in a revolving coating pan.

It is ordinarily advantageous to add the solution of wax-like, water-soluble, non-hygroscopic solid to the salt in the form of several small portions, rather than to add the entire solution all at once. The salt is then dried by the passage of a current of air over it while it is still in the revolving pan, followed by transference to a drying oven and evaporation off of residual solvent at a temperature of approximately 50° C. Alternatively, after being wet with the solution of the wax-like solid in a solvent such as ethyl alcohol, the sodium chloride may be transferred directly to a drying oven and the entire operation of drying carried out in the oven.

Among alcohols in which polyethylene glycol having a molecular weight in excess of about 1,000 is soluble, good results have been secured both with ethyl alcohol and isopropyl alcohol. Heating may be advantageous in order to bring the polyethylene glycol into solution in the alcohol. However, the solution should ordinarily be cooled to a temperature within the range 25-30° C. before it is applied to the salt.

After the table salt has been coated with the primary layer of wax-like solid, it is preferably returned to the coating pan for treatment with a solution of the organic antimalarial compound, the purpose being to attach the antimalarial compound directly on the wax-like layer. It is usually first desirable to pass the salt with its primary coating through a sieve, as for example through one of standard No. 16 mesh, in order to eliminate undesirable large particles.

The application of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine (Daraprim) to table salt may be considered as a typical procedure, as exactly the same procedure, would be used if one of the other antimalarial compounds, i. e. 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline (Primaquine); or 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (Chloroquine) were coated on the salt.

It is desirable that the required amount of the antimalarial agent, 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine in the procedure herein given as typical, be weighed out, based on the weight of salt to be coated, and the antimalarial then dissolved in a volatile solvent such as acetone. Other organic solvents may also be used. The solution of "Daraprim" is added to the salt, preferably while the latter is retained in a revolving pan, and the solution is best applied to the coated salt in successive small amounts not all at once. The salt may then be dried by the passage of air over it while it is on the revolving pan, followed by transference to a drying oven where drying may be continued at a temperature of approximately 40° C. to eliminate the last traces of the volatile solvent. If desired, the entire drying operation may be carried out in a heated oven at a moderately elevated temperature, a temperature of about 40° C. having been found very satisfactory.

The dried salt is then sieved to remove large particles, as by passing it through a standard screen of No. 16 mesh. It is then packaged, and is available for use to supply therapeutically-effective blood levels of the antimalarial compound to persons who ingest the salt as seasoning on their daily supply of food, or who may consume salt for any other purpose.

As illustrative of the production of my new therapeutic composition, in accordance with my invention, the following detailed procedure, setting forth the amounts employed, may be given.

Example

To 1,000 grams of table salt on a revolving pan type of coating machine, there was added a solution containing 1.25 grams of Carbowax 6,000 dissolved in 25 milliliters of ethyl alcohol. Carbowax 6,000 is a trade designation for polyethylene glycol having a molecular weight

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in excess of 1,000. The solution was added to the salt in several successive divided applications, and not all at once.

The sodium chloride, wet with the solution of polyethylene glycol, was then partially dried with a current of air while still in motion on the revolving coating pan. It was then transferred to trays and dried at a temperature of 50° C. in a drying oven. It was cooled, and sieved to pass through a standard No. 16 mesh sieve.

The dried table salt, the individual crystals of which were coated with the white wax-like coating, were then returned to the coating pan for application of the antimalarial compound. 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine in the amount of 1 gram was then dissolved in 300 milliliters of acetone. The solution was added in incremental amounts of 20 milliliters each time to the salt, which was rotated on the pan and dried by means of a current of air passing over it after each application of the solution.

After all of the acetone solution of Daraprim had been added, and the salt subjected to preliminary drying by means of a current of air, the coated salt was spread on trays and dried in a drying oven at a temperature of 40° C. The completely dry product was then sieved to pass through a standard No. 16 sieve, and packaged.

The resulting product was a non-caking, white, odorless product wherein the individual salt crystals were surrounded and protected by a white wax-like coating. The antimalarial compound, i. e. 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, was securely retained on the salt crystals, being bonded to them by means of the wax-like primary coating. When placed in the mouth, the product tasted like ordinary table salt, and was free of any foreign taste.

When the product was stored under moist conditions, no appreciable amount of cake was apparent. It showed no tendency to separate into particles of varying particle size when the packaged product was subjected to vibration.

The antimalarial compound, in the amount of 0.1% by weight, was evenly distributed throughout the entire mass of salt, being supported by the individual salt crystals.

By following a similar procedure, it is possible to prepare coated sodium chloride products containing any desired level of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine ranging from 0.1 part of antimalarial compound per 1,000 grams of salt to 2 parts of antimalarial compound per 1,000 grams of salt, these ratios being by weight. The other antimalarials, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, or 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline, are applied in the same manner to the salt coated with the primary wax-like coating, the proportions of antimalarial to salt falling within the range specified.

Since various changes and modifications may be made in my invention as disclosed herein without departing from the scope thereof, it is my intention that such changes and modifications as may be within the scope of the appended claims will be regarded as part of my invention.

I claim:

1. The process of preparing a therapeutic composition effective against malaria, which comprises coating sodium chloride salt particles with polyethylene glycol having a molecular weight in excess of about 1,000 to provide an adherent coating of wax-like material thereon, and then uniformly applying to said coated salt a solid compound possessing activity against malaria so that said compound is uniformly dispersed on said wax-like coating and thereby retained on said salt.

2. The process of preparing a therapeutic composition effective against malaria which comprises coating sodium chloride salt particles with polyethylene glycol hav-

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ing a molecular weight in excess of about 1,000 to provide an adherent primary coating of a wax-like material on said salt, and then uniformly applying to said coated salt an antimalarial selected from the group which consists of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, and 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

3. The process of preparing a therapeutic composition effective against malaria which comprises coating sodium chloride salt particles with polyethylene glycol having a molecular weight in excess of about 1,000 to provide an adherent primary coating of a wax-like material on said salt, and then uniformly applying to said coated salt 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine so that said compound is uniformly dispersed on said wax-like coating and thereby retained on said salt.

4. The process of preparing a therapeutic composition effective against malaria which comprises coating sodium chloride salt particles with polyethylene glycol having a molecular weight in excess of about 1,000 to provide an adherent primary coating of a wax-like material on said salt, and then uniformly applying to said coated salt 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline so that said compound is uniformly dispersed on said wax-like coating and thereby retained on said salt.

5. The process of preparing a therapeutic composition effective against malaria which comprises coating sodium chloride salt particles with polyethylene glycol having a molecular weight in excess of about 1,000 to provide an adherent primary coating of a wax-like material on said salt, and then uniformly applying to said coated salt 7-chloro-4-(diethylamino-1-methylbutylamino)quinoline so that said compound is uniformly dispersed on said wax-like coating and thereby retained on said salt.

6. Sodium chloride particles coated with an adherent primary coating of polyethylene glycol having a molecular weight in excess of about 1,000, and a layer of a solid compound possessing activity against malaria positioned on said coated particles and adhering to said polyethylene glycol layer thereon.

7. Particles comprising sodium chloride crystals coated with a primary coating of polyethylene glycol having a molecular weight in excess of about 1,000 and a secondary coating of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine adhering to said polyethylene glycol layer on said particles.

8. Particles comprising sodium chloride crystals coated with a primary coating of polyethylene glycol having a molecular weight in excess of about 1,000 and a secondary coating of 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline adhering to said polyethylene glycol layer on said particles.

9. Particles comprising sodium chloride crystals coated with a primary coating of polyethylene glycol having a molecular weight in excess of about 1,000 and a secondary coating of 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline adhering to said polyethylene glycol layer on said particles.

10. The process of preparing a therapeutic composition effective against malaria which comprises coating sodium chloride salt particles with polyethylene glycol having a molecular weight in excess of about 1,000 while said salt is retained on a revolving surface, thereby providing an adherent primary coating of a wax-like material on said salt, and then uniformly applying to said coated salt an anti-malarial selected from the group which consists of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, and 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline while said salt provided with said primary coating is retained on a revolving surface.

11. The process of preparing a therapeutic composition effective against malaria which comprises coating sodium chloride salt particles by applying thereto a solution of

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polyethylene glycol having a molecular weight in excess of about 1,000 in a volatile organic solvent while said salt is positioned on a revolving surface, drying said salt in order to remove said volatile organic solvent therefrom by passing a current of air thereover while said salt is on said revolving surface, uniformly applying to said salt coated with an adherent primary coating of said polyethylene glycol thereon a solution of an antimalarial selected from the group which consists of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, 8-(4 - amino-1-methylbutylamino)-6-methoxyquinoline, and 7 - chloro-4-(4-diethylamino-1-methylbutylamino)quinoline while said salt is on the revolving surface, and drying said salt by passing a current of air thereover while said salt is on said revolving surface in order to remove excess solvent therefrom, whereby salt particles wherein said antimalarial is firmly attached to said polyethylene glycol coating, and said polyethylene glycol coating is firmly attached to said salt, are secured.

12. Sodium chloride particles coated with an adherent primary coating of polyethylene glycol having a molecular weight in excess of about 1,000, and a layer of a compound possessing activity against malaria positioned on said coated particles and adhering to said polyethylene glycol layer thereon, said compound being one selected

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from the group which consists of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine, 8-(4 - amino - 1 - methylbutylamino)-6-methoxyquinoline, and 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

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