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STABLE ANTI-HEMORRHAGIC POWDERS

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This invention relates to anti-hemorrhagic compositions, and more particularly it relates to dry, stable, substantially non-dusting powders containing water insoluble anti-hemorrhagic compounds.

A number of anti-hemorrhagic compounds of the vitamin K type have been found to be useful in the prevention and treatment of hypoprothrombinemia, hemorrhagic diathesis of the newly born, in the treatment of post operative bleeding, in jaundice, or in persons having prothrombin deficiencies.

In the past, these substances have been administered orally or parenterally in solutions of fixed oils such as olive oil, sesame oil, peanut oil, etc. Alternately, water soluble salts of these vitamin K compounds have been used for parenteral injection. The vitamin K type compounds are generally unstable to light. The oil solutions proposed in the past have not imparted to these compounds any substantial increased stability to light. Moreover, the rate of absorption of the vitamin K type compounds from oil solutions is retarded somewhat. The aqueous solutions of salts are somewhat more desirable than the oil solutions, but have the disadvantages that the salts are not always equivalent in activity to that of the parent substance, and furthermore, some of the anti-hemorrhagic compounds do not form water soluble salts. Moreover, as to the oil solutions, the oils are, of course, subject to becoming rancid, thus producing disagreeable odors. Of more importance in this regard is the fact that when the oils become rancid, they apparently contribute to the decomposition of the vitamin K type compounds. In spite of these disadvantages, the common products found on the market incorporating vitamin K type compounds are generally found in an oil solution. These oil solutions present several other problems. The more common vitamin K type compound, menadione, is soluble in most vegetable oils to the extent of only about 2% w./v. As a result of this a very large volume of the oil solution must be utilized in order to produce a composition in a dosage unit form that contains a sufficient quantity of menadione to adequately accomplish the purpose for which it is intended. Various other proposals have been set forth in an attempt to overcome these disadvantages, but up to the present time none have been proposed which adequately answer the problems presented. For whether the vitamin K type compound be used per se or in an oil solution, or in some other composition, none of these preparations have very good heat stability.

It has now been found that the various water-insoluble anti-hemorrhagic compounds can be dissolved in certain organic esters and absorbed on certain solid silica aerogel carriers to produce a dry, substantially white, substantially non-dusting, free-flowing powder, the anti-hemorrhagic activity of which is substantially greater per unit volume than any of the known preparations. Moreover, the water-insoluble anti-hemorrhagic compounds are substantially more stable to heat, light, air-oxidation, and decomposition in these powder compositions than in known preparations.

Suitable esters for preparing the powders of the present invention include the ethyl and butyl esters of certain dicarboxylic acids, namely, succinic and pimelic. Any of the water-insoluble substances possessing vitamin K activity can be used in this invention; these anti-hemorrhagic compounds include: 2-methyl-3-phytyl-1,4-naphthoquinone, 2-methyl-1,4-naphthoquinone, 2-methyl-3-hydroxy-1,4-naphthoquinone, 2-methyl - 1,4 - naphthohydroquinone, dimethoxynaphthalene, 2,3-dimethyl-1,4-naphthoquinone, 4-amino-2-methyl-1-naphthol, 2-methyl-1-naphthol, 2-methyl-1-naphthylamine, 2-methyl-1,4-naphthoquinone-2,3-oxide and esters of the same.

The first mentioned compound above is natural vitamin K and the remainder of the compounds, for the most part, are vitamin K analogs. One of the simplest members of this series of anti-hemorrhagic substances is menadione (2-methyl-1,4-naphthoquinone), it is the preferred substance for preparing the compositions of the present invention because of its outstanding anti-hemorrhagic action.

The silica aerogels of this invention are any of a number of commercially available aerogels produced either in the vapor phase or in the liquid phase. The most important characteristic of these aerogels is their extremely large surface area; this may run between 100 to 400 square meters/gram. These silica aerogels are dry, highly porous powders having a particle size of from about 5 millimicrons to about 5 microns. They contain somewhere between 85% and 98% silica, the remainder being made up of various organic and inorganic constituents. The silica may be present as silicon dioxide, silicic acid, or silicic acid salts such as calcium silicate. The silica is the only important constituent of the silica aerogel; as long as the other constituents are non-toxic, their identity is immaterial.

The anti-hemorrhagic compounds are sufficiently soluble in the esters herein utilized to produce a composition containing 4 to 5 times as much of these compounds on an activity basis as those known in the prior art; for example, menadione (2-methyl-1,4-naphthoquinone) has a solubility in diethyl succinate of about 12% w./v., whereas in oils its solubility is about 2% w./v. When compared with other known preparations containing vitamin K type compounds, the powder compositions of this invention exhibit other substantial advantages. Powders of menadione per se and the other vitamin K type compounds are extremely dusty powders which are very irritating to the skin and mucous membranes, particularly the tissues of and surrounding the eye, nose, mouth and respiratory passages. When the vitamin K type compounds are compounded with the esters and the silica aerogels of this invention, this problem is substantially overcome. Therefore, the powder compositions of this invention permit safer and more expeditious handling in production operations. The compositions of this invention are white free-flowing powders compared to the yellow color of menadione powder per se. In many pharmaceutical preparations a white powder is preferred. The vitamin K type compounds are decomposed by sunlight and are destroyed by alkalies and reducing agents. The compositions of this invention afford these vitamin K type compounds a greater degree of stability in the presence of the decomposing conditions described above. Furthermore, the components of the compositions of the invention afford protective action in minimizing reaction of the vitamin K type compounds with other materials with which they may be compounded, for example, those in a multi-vitamin preparation. Moreover, in general, preparations of vitamin K type compounds do not have long term stability, particularly in the presence of heat. However, it will be shown below that when a solution of one of the vitamin K type compounds is absorbed on

one of the silica aerogels of this invention, improved heat stability results. Other advantages of the compositions of this invention over those of the prior art will be apparent from the examples and tables that follow.

In preparing the compositions of this invention, it is essential that the menadione or other vitamin K type compound be uniformly distributed throughout the silica aerogel. The simplest method by which this end can be obtained is to dissolve the menadione or other vitamin K type compound in one of the above described esters and then mix the solution of the vitamin K type compound dissolved in the ester with the desired quantity of the silica aerogel. Alternately, one can mix the proper proportions of all three components simultaneously and by careful and thorough mixing achieve the uniformly dispersed condition desired.

As indicated above, menadione has a solubility of about 12% w./v. in diethyl succinate (10 to 11% w./w.). This, therefore, is the upper limit of the amount of menadione it is possible to incorporate into the compositions of this invention. There is no theoretical lower limit, only one of practicality. This solution of menadione, or other similar solutions of vitamin K type compounds of the same concentration, or of lesser concentrations, is then mixed with a quantity of the silica aerogel. The upper limit of the amount of the solution of the vitamin K type compound utilized is about 4 parts by weight of the vitamin K type compound solution to 1 part by weight of the silica aerogel. Obviously, any ratio smaller than this can be used as the 4:1 ratio described above produces a dry, free-flowing powder. As a matter of fact, a ratio of 2:1 is preferred for the purposes of this invention. If the amount of the solution is increased substantially beyond 4 parts by weight to 1 part by weight of the silica aerogel, the composition, on standing, will not remain a free-flowing powder. On the contrary, it will become sticky and tend to agglomerate.

The following examples are set forth in an illustrative sense only, in no way to be considered as limiting, the scope of the invention being limited by the scope of the appended claims.

EXAMPLE 1

The following solutions of menadione and diethyl succinate were formulated (*a*) 11 grams of menadione in 89 grams of diethyl succinate, (*b*) 8 grams of menadione in 92 grams of diethyl succinate, (*c*) 6 grams of menadione in 94 grams of diethyl succinate. A 20 g. portion of each of the above solutions was mixed with thorough agitation with a 10 g. portion of each of the following silica aerogels: (1) a silica aerogel having a particle of from about 3 to about 5 microns and a surface area of approximately 110 to about 150 square meters/gram, (2) a silica aerogel having a particle size of from about 15 to about 20 millimicrons and a surface area of from about 175 to about 200 square meters/gram, (3) a silica aerogel having a particle size of from about 50 to about 100 millimicrons and a surface area of about 200 square meters/gram, (4) a silica aerogel having a particle size of about 100 millimicrons and a surface area of about 200 square meters/gram (silica as calcium silicate), (5) a silica aerogel having a particle size of from about 8 to about 10 millimicrons and a surface area of from about 285 to about 335 square meters/gram. Each of the above mixtures of the respective menadione-diethyl succinate solutions with their respective silica aerogels forms a substantially white, substantially dry, free-flowing, substantially non-dusting powder which contains approximately 7% w./w. of menadione.

EXAMPLE 2

Fifteen multi-vitamin preparations were formulated incorporating the following quantities of the various vitamins and a 2.5 mg. quantity of menadione from each of the 15 menadione powders prepared in Example 1. Each of these 15 multi-vitamin preparations contains the following vitamins in the amount indicated:

Thiamine mononitrate (B_1)	mg..	10
Riboflavin (B_2)	mg..	10
Niacinamide	mg..	100
Ascorbic acid	mg..	300
Pyridoxine HCl (B_6)	mg..	2
Vitamin B_{12}	mcg..	4
Folic acid	mg..	1.5
Calcium pantothenate	mg..	20
Vitamin K as menadione	mg..	2.5

Each of these 15 preparations was filled in soft shell gelatin capsules. Satisfactory capsules were obtained in each instance, i.e. they were of the desired elliptical shape; they sealed properly; they were not discolored; they had no unpleasant odor, and they were of the desired potency. After storage, they exhibited the required potency; there was no gas or odor formation, bacterial growth, or shell destruction or distortion.

EXAMPLE 3

The procedure of Example 1 was repeated utilizing the same solutions of menadione in the quantities indicated in Example 1, however, di-n-butyl succinate was substituted for diethyl succinate. The identity and quantity of the silica aerogels utilized in the procedure of this example was the same as in Example 1. Results were obtained herein which were substantially identical to those obtained in Example 1.

EXAMPLE 4

The procedure of Example 1 was repeated utilizing menadione and diethyl succinate in the same quantities as in Example 1. 20 g. of each of the 3 solutions thereby produced was mixed with thorough agitation with 5 g. of each of the 5 silica aerogels of Example 1. Each of the 15 powders thereby produced was substantially white, dry, free-flowing, and substantially non-dusting.

EXAMPLE 5

The procedure of Example 1 was repeated utilizing the same quantities of menadione and the ester; however, diethyl pimelate was substituted for the diethyl succinate of Example 1. The same quantities of each of the resulting solutions were formulated with the same silica aerogels in the same quantities as in Example 1. A substantially white, dry, substantially non-dusting, free-flowing powder resulted in each instance.

EXAMPLE 6

The procedure of Example 1 was repeated utilizing the same quantities of menadione and the ester; however, di-n-butyl pimelate was substituted for the diethyl succinate of Example 1. The same quantities of each of the resulting solutions were formulated with the same silica aerogel in the same quantities as in Example 1. A substantially white, substantially non-dusting, free-flowing dry powder resulted in each instance.

EXAMPLE 7

The procedure of Example 1 was repeated utilizing the same ester and silica aerogel in the same quantities. However, 2-methyl-1,4-naphthohydroquinone was substituted for the menadione in the same quantity as found in Example 1. Each of the fifteen powders thereby produced was dry and free-flowing, and substantially white and non-dusting.

EXAMPLE 8

The procedure of Example 1 was repeated utilizing the same ester and silica aerogel in the same quantities. However, 2-methyl-1,4-naphthoquinone-2,3-oxide was substituted for the menadione in the same quantities as found in Example 1. Each of the fifteen powders thereby produced was dry and free-flowing and substantially white and non-dusting.

EXAMPLE 9

Chick bioassays were run utilizing a capillary tube-whole blood clotting time method patterned after the procedure found at pages 156 through 158 of "Vitamin Methods," volume II (1951), by P. Gyorgy, published by Academic Press. These bioassays compare the efficacy of the menadione-diethylsuccinate-silica aerogel of Example 1 [(*a*) and (1)] with other preparations of vitamin K type compounds in the multi-vitamin preparation of Example 2. The results of these bioassay determinations are set forth in the following table.

Table I

Menadione Composition	Initial Concentration of Menadione in Multivitamin Mix	Menadione Potency Found by Chick Bioassay after 5 Weeks	
		At 20° C.	At 42° C.
Menadione Powder	2.5 mg./550 mg. Mix	2.50 mg./550 mg.	2.25 mg./550 mg.
Menadione Power and Silica Aerogel [1]	2.5 mg./cap	Less than 1.25 mg./cap.	1.79 mg./cap.
Menadione 2,3-Oxide Powder	2.7 mg./550 mg. Mix equivalent to 2.5 mg. Menadione.	1.5 mg./550 mg.	Less than 1.25 mg./550 mg.
Menadione in 11% w./w. Ethyl Succinate	2.5 mg./570 mg. Mix	2.06 mg./570 mg.	Less than 1.25 mg./570 mg.
Menadione in Ethyl Succinate Absorbed on Santocel.	2.5 mg./550 mg. Mix	2.5 mg./550 mg.	2.45 mg./550 mg.

[1] A composition of the following w./w. percentage composition:

	Percent
Menadione	16.67
Silica Aerogel of Example 1 (1)	33.33
Algin	1.00
Glycerine	0.05
Ethanol	2.00
Sodium benzoate	0.05
Distilled water	46.90

The data in the foregoing table indicate that, of the preparations tested, only the compositions of this invention are heat stable after storage for 5 weeks at elevated temperatures. They indicate further that only the compositions of this invention and menadione powder per se are stable after storage for 5 weeks at room temperature (20° C.). Of particular interest are the data showing that neither the combination of menadione and the silica aerogel nor the combination of menadione and the ester are stable at either 20° C. or 42° C., whereas unexpectedly the combination of menadione, the ester and the silica aerogel are stable at both of these temperatures.

The foregoing examples illustrate one use of the compositions of this invention, i.e. oral multi-vitamin preparations. Obviously, the compositions of this invention have many other uses which will be apparent to those skilled in the art, e.g. oral and parenteral administration of menadione in and of itself, and in combination with other substances, i.e. medicaments, vitamins, nutrients and nutritional factors.

We claim:

1. A dry, free-flowing, substantially non-dusting powder comprising a water-insoluble anti-hemorrhagic compound having vitamin K activity, an ester selected from the group consisting of diethyl succinate, di-n-butyl succinate, diethyl pimelate, and di-n-butyl pimelate, and a silica aerogel having a surface area of from about 100 to about 400 square meters/gram, said water insoluble anti-hemorrhagic compound being in solution in said ester and uniformly distributed in and throughout said silica aerogel.

2. The powder of claim 1 wherein the particle size of said silica aerogel is between about 5 millimicrons and about 5 microns.

3. The powder of claim 2 wherein said anti-hemorrhagic compound is 2-methyl-1,4-naphthoquinone and said ester is diethyl succinate.

4. The powder of claim 3 wherein said silica aerogel has a particle size of from about 3 to about 5 microns and a surface area of from about 110 to about 150 square meters/gram.

5. The powder of claim 3 wherein said silica aerogel has a particle size of about 100 millimicrons and a surface area of about 200 square meters/gram.

6. The powder of claim 2 wherein said anti-hemorrhagic compound is 2-methyl-1,4-naphthohydroquinone.

7. The powder of claim 2 wherein said anti-hemorrhagic compound is 2-methyl-1,4-naphthoquinone-2,3-oxide.

8. The powder of claim 2 wherein said ester is di-n-butyl succinate.

9. The powder of claim 2 wherein said ester is diethyl pimelate.

10. The powder of claim 2 wherein said ester is di-n-butyl pimelate.

11. The powder of claim 2 wherein said silica aerogel has a particle size of from about 15 to about 20 millimicrons and a surface area of from about 175 to about 200 square meters/gram.

12. The powder of claim 2 wherein said silica aerogel has a particle size of from about 50 to about 100 millimicrons and a surface area of about 200 square meters/gram.

13. The powder of claim 2 wherein said silica aerogel has a particle size of from about 8 to 10 millimicrons and a surface area of from about 285 to about 335 square meters/gram.

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