PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Novel Vitamin-containing Compositions

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel vitamin-containing compositions. More particularly, the invention is concerned with novel high-potency vitamin-containing compositions in the form of dry powders which are capable of being compressed into tablets without prior granulation and with tablets produced therefrom.

Tablets which contain vitamin-A as the active ingredient and processes for their manufacture are well known. However, it is equally well known that conventional stabilized pharmaceutical powders which contain vitamin-A esters (for example, vitamin-A acetate and vitamin-A palmitate), even when they are admixed with the usual tabletting excipients and adjavants, cannot be compressed into tablets using ordinary tabletting equipment without prior granulation. Thus, in the production of vitamin-A tablets, it is the normal practice to prepare a granulation containing conventional tablet excipients and adjuvants, to add the vitamin-A ester thereto and to mix the ester therewith and, subsequently, to compress such mixture into tablets.

It has now been surprisingly found in accordance with the present invention that when a vitamin-A ester in the form of a conventional stabilized pharmaceutical powder is admixed with *either* a microcrystalline cellulose *or* a mixture of a microcrystalline cellulose and dicalcium phosphate *or* a mixture of microcrystalline cellulose and tricalcium phosphate there is obtained a powdery product which is capable of being compressed without prior granulation into tablets having outstanding physical properties and characteristics.

Accordingly, the novel vitamin-containing compositions provided by the invention comprise (i) from 30% to 60% by weight of a vitamin-A ester in the form of a stabilized pharmaceutical powder and (ii) from 40% to 70% by weight of either microcrystalline cellulose *or* a mixture of microcrystalline cellulose and dicalcium phosphate *or* a mixture of microcrystalline cellulose and tricalcium phosphate; said mixture of microcrystalline cellulose and dicalcium phosphate or tricalcium phosphate containing at least 35% by weight of microcrystalline cellulose.

In producing the compositions of this invention, the vitamin-A component is provided in the form of a stabilized pharmaceutical powder. The vitamin-A ester which is present as the active ingredient in these stabilized powders can be, for example, vitamin-A acetate or vitamin-A palmitate. These stabilized powders containing the vitamin-A ester are well known in the art and are characterized in that the vitamin ingredient is embodied in some appropriate protective matrix. While suitable powders are commercially available under a variety of trade names, it is preferred to use the stabilized beadlet-powder containing 500,000 International Units of vitamin-A palmitate which is marketed under the Trade Name "Palm-Abeads". However, in place of a powder containing vitamin-A palmitate, a powder which contains vitamin-A acetate as the active ingredient can also be used. Preferably, a vitamin-A acetate powder having a potency of 500,000 U.S.P. units per gram is used.

In general, any commercially available microcrystalline cellulose can be employed in this invention. However, the microcrystal-

[Price 4s. 6d.]

line cellulose which is manufactured and sold by American Viscose Company, Markus Hook, Pennsylvania under the Registered Trade Mark AVICEL is used in producing the preferred compositions of the invention. It will be appreciated, however, that while the invention will be described hereinafter with particular reference to the use of AVICEL, other types of microcrystalline cellulose can also be used.

As indicated earlier, the compositions of the invention can contain a mixture of microcrystalline cellulose with either dicalcium phosphate or tricalcium phosphate. The powdery compositions which are produced by mixing a vitamin-A ester with such a mixture, like those produced by mixing the vitamin-A ester with AVICEL alone can be compressed directly (that is to say, without prior granulation) into tablets having outstanding chemical and physical properties and characteristics.

The quantities of the various ingredients used in formulating the compositions of this invention can be varied within rather wide limits. In the ordinary practice of this invention a mixture is formulated containing from 30% to 60% by weight of a stabilized vitamin-A ester powder having a potency of 500,000 International Units per gram. The quantity of microcrystalline cellulose which is used in preparing the present compositions is similarly variable. In general, the invention contemplates the formulation of a composition which, prior to its compression into tablets, contains from 40% to 70% by weight of microcrystalline cellulose. Preferably, however, the compositions contain from 50% to 70% by weight of the microcrystalline cellulose and from 30% to 50% by weight of the vitamin-A ester since such compositions, on direct compression, give especially useful tablets.

Alternatively, the microcrystalline cellulose is present in admixture either with dicalcium phosphate or with tricalcium phosphate; the combined weight of the microcrystalline cellulose and dicalcium phosphate or tricalcium phosphate comprising from 40% to 70% by weight (preferably, from 50% to 70% by weight) of the composition. The quantity of dicalcium phosphate or tricalcium phosphate present in the (microcrystalline cellulose)/phosphate mixture is variable. However, the weight of the dicalcium phosphate or tricalcium phosphate should not exceed 65% of the total weight of the mixture and the weight of the microcrystalline cellulose should comprise at least 35% of the total weight of the mixture. Preferably, the mixture contains from 40% to 60% by weight of microcrystalline cellulose.

The compositions of this invention are readily produced by mixing the powder containing the vitamin-A ester *either* with the microcrystalline cellulose *or* with the mixture of microcrystalline cellulose and dicalcium phosphate *or* with the mixture of microcrystalline cellulose and tricalcium phosphate. The compositions thus obtained are powders which can be directly converted without recourse to the many and various steps involved in conventional granulation procedures into tablets having outstanding physical and chemical characteristics. The tabletting operation is carried out using conventional tabletting procedures and techniques employing ordinary tabletting equipment.

As will be evident from the foregoing, the present invention provides a practical and efficient means for producing vitamin-containing compositions containing relatively high levels of vitamin-A esters which can be directly compressed into high-potency vitamin-A tablets. The tablets are characterized by their outstanding physical and chemical characteristics. For example, the tablets have a high vitamin-potency and yet they are relatively light in weight and small in size. Furthermore, tablets produced from the present compositions have an exceptionally long shelf life; that is to say, the vitamin-A ester therein is exceedingly stable. Furthermore, the tablets possess outstanding hardness characteristics and they exhibit completely acceptable disintegrating properties.

The following Examples illustrate the manner in which the compositions and tablets provided by the invention can be obtained:

EXAMPLE 1.

115 parts of a stabilized vitamin-A palmitate powder containing 500,000 International Units of vitamin-A palmitate per gram (the powder used was the product sold under the Trade Name "PalmAbeads-Type 500"), 115 parts of dicalcium phosphate dihydrate and 115 parts of microcrystalline cellulose (the microcrystalline cellulose used was the product marketed under the Registered Trade Mark AVICEL) were charged into a suitable mixing device and intimately admixed with one another. The mixture obtained was compressed into tablets each weighing 690 mg using a 13 mm standard concave bisected punch. Each tablet contained the equivalent of 115,000 International Units of vitamin-A palmitate per gram. The tablets exhibited outstanding properties and characteristics: the vitamin-A component thereof was found to be highly stable and hence the tablets had exceptional shelf life; the tablets also had excellent hardness and disintegration characteristics.

EXAMPLE 2.

160 parts of vitamin-A acetate powder containing 500,000 International Units of vitamin-A acetate per gram and 160 parts of AVICEL (see Example 1) were intimately

admixed. The mixture obtained was compressed into tablets each weighing 320 mg using an 11 mm standard concave bisected punch. Each tablet contained the equivalent of 80,000 International Units of vitamin-A acetate. The tablets possessed outstanding physical and chemical characteristics. Thus, for example, the vitamin-A acetate was found to be exceedingly stable in this formulation and the tablets therefore had an outstanding shelf life. Furthermore, the tablets possessed completely satisfactory hardness and disintegrating characteristics.

EXAMPLE 3.

Tablets each weighing 320 mg were prepared by the procedure described in Example 2, using the same ingredients and the same quantities thereof as were used in Example 2, with the sole exception that the 160 parts of vitamin-A acetate powder employed in Example 2 were replaced by 160 parts of the vitamin-A palmitate powder which is marketed under the Trade Name of "PalmA-beads". The tablets obtained possessed completely satisfactory physical and chemical properties. For example, as a result of the outstanding stability of the vitamin A palmitate component thereof, the tablets possessed outstanding shelf life. The tablets furthermore exhibited completely satisfactory hardness and disintegrating characteristics.

EXAMPLE 4.

240 parts of dry vitamin-A acetate powder containing 500,000 International Units of vitamin-A acetate per gram and 240 parts of AVICEL (see Example 1) were admixed. The mixture obtained was compressed into tablets each weighing 480 mg using an 11 mm standard concave bisected punch. The tablets obtained contained the equivalent of 120,000 international units of vitamin-A acetate per gram. They exhibited outstanding physical and chemical characteristics. For example, the tablets had a relatively long shelf life due to the exceptional stability of the vitamin-A acetate therein. They also possessed completely satisfactory hardness and disintegrating properties.

WHAT WE CLAIM IS:—

1) A vitamin-containing composition which is directly compressible into tablets comprising (i) from 30% to 60% by weight of a vitamin-A ester in the form of a stabilized pharmaceutical powder and (ii) from 40% to 70% by weight of *either* microcrystalline cellulose *or* a mixture of microcrystalline cellulose and dicalcium phosphate *or* a mixture of microcrystalline cellulose and tricalcium phosphate; said mixture of microcrystalline cellulose and dicalcium phosphate or tricalcium phosphate containing at least 35% by weight of microcrystalline cellulose.

2) A vitamin-containing composition as set forth in claim 1, wherein said mixture of microcrystalline cellulose and dicalcium phosphate or tricalcium phosphate contains from 40% to 60% by weight of microcrystalline cellulose.

3) A vitamin-containing composition as set forth in claim 1, wherein the vitamin-A ester is vitamin-A acetate or vitamin-A palmitate.

4) A tablet produced by the direct compression of a composition as set forth in any one of claims 1 to 3 inclusive.

5) A tablet as set forth in claim 4, wherein vitamin-A acetate or vitamin-A palmitate is present as the vitamin-A ester.

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EXAMPLE 4.

240 parts of dry vitamin-A acetate powder containing 500,000 International Units of vitamin-A acetate per gram and 240 parts of AVICEL (see Example 1) were admixed. The mixture obtained was compressed into tablets each weighing 480 mg using an 11 mm standard concave bisected punch. The tablets obtained contained the equivalent of 120,000 international units of vitamin-A acetate per gram. They exhibited outstanding physical and chemical characteristics. For example, the tablets had a relatively long shelf life due to the exceptional stability of the vitamin-A acetate therein. They also possessed completely satisfactory hardness and disintegrating properties.

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2) A vitamin-containing composition as set forth in claim 1, wherein said mixture of microcrystalline cellulose and dicalcium phosphate or tricalcium phosphate contains from 40% to 60% by weight of microcrystalline cellulose.

3) A vitamin-containing composition as set forth in claim 1, wherein the vitamin-A ester is vitamin-A acetate or vitamin-A palmitate.

4) A tablet produced by the direct compression of a composition as set forth in any one of claims 1 to 3 inclusive.

5) A tablet as set forth in claim 4, wherein vitamin-A acetate or vitamin-A palmitate is present as the vitamin-A ester.

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