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PROCESS OF PRODUCING SOLID FAT-SOLUBLE VITAMIN PELLETS

Johan Myhre, Oslo, Norway, assignor, by mesne assignments, to Collett-Week Corporation, a corporation of New York

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This application is a continuation in part of my application Serial No. 143,350 filed February 9, 1950.

This invention relates to a pellet or tablet and the process of making the same. The pellet or tablet is primarily adapted for use as a pharmaceutical product although it may also be used for other purposes.

According to this invention, a pellet is made by heating a sugar syrup to evaporate most of the water therefrom, dispersing a lipid in the thick sugar syrup and cooling the dispersion so that it sets to a solid material.

Any lipid substance may be formed into a solid pellet in accordance with the invention. By lipid substance is meant any organic substance which is insoluble in water but soluble in ether or other fat solvents, including fatty acids, soaps, neutral fats, waxes, phospholipids, cerebrosides and fatty alcohols such as the sterols. These substances are sometimes referred to as "oily substances" herein, although it will be understood that they are not all oils in the usual sense of the word. These materials may be of a pharmaceutical nature, or may be suitable for other purposes such as flavoring. As examples of pharmaceutical preparations it has been found that the oil soluble vitamins, A, D, E and K may be used as well as other substances of an oily nature, such as penicillin in oil, sex hormones and the like. The hormones are particularly well adapted for pelleting in accordance with the invention, since such pellets are adapted for buccal administration, i. e. the pellets may be held in the cheek and the active ingredients will be directly absorbed through the mucous membranes of the mouth as the pellet slowly dissolves. The pellets are also useful in the food processing industry as essential oils, such as oil of garlic, oil of clove, oil of dill and various other spice oils may be formed into pellets. These oils are ordinarily difficult to store and dispense, but when they are pelleted the problem is simplified. For instance, in the preparation and canning of pickles, oil of dill can be formed into pellets, the pellets being made so that one or more pellets contains the exact amount of oil desired in each jar. Then, as the jars are filled, the proper number of pellets can be dropped in each jar. The pellets can be handled by automatic machinery much more easily than could the oil itself and can be dispensed more accurately.

Since the invention is particularly well adapted to the compounding of the oil soluble vitamins, a large portion of the following description is de-

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voted to preparations containing these vitamins. However, it should be understood that this is done only for the purpose of illustration and that the invention relates broadly to the compounding of oily or fatty substances.

Pellets made in accordance with this invention are hard, clear solids and could be described as substantially moisture-free, supercooled sugar solutions of glass-like consistency.

Much work has been done in recent years showing that the oil soluble vitamins have superior biological utilization when they are taken in the form of an aqueous dispersion. Further, when the oil soluble vitamins are taken in an undispersed form an unpleasant after-taste frequently develops as the result of eructation. By an "undispersed form" is meant vitamin capsules which contain the oil as such and tablets made by taking up the oil in an inert carrier such as sugar or starch and forming the sugar or starch into a tablet in a tablet press. Despite the inferior biological results and the unpleasant after-taste, oil soluble vitamin tablets or capsules have remained popular with the public since these products are easier to carry and take and since a more accurate dosage is obtained by this method. The present invention enables one to prepare pellets of a fat soluble vitamin which have a biological utilization at least equal to, and in the preferred embodiment superior to, the aqueous dispersions, combined with convenience of carrying, administration and accurate dosage of a tablet or capsule.

In carrying out the process, any sugar may be used. Good results have been obtained with sucrose, glucose and corn syrup. A mixture of sugars such as glucose and sucrose may advantageously be used since such mixtures frequently have better "working" properties. Impure sugar syrups such as molasses and corn syrup have been found to be satisfactory. The selection of the proper sugar mixture to produce a suitable pellet is well known to those familiar with the art of candy making as the finished pellets resemble hard candy. If too much glucose is used the product will tend to be hygroscopic, while if too much sucrose is used the pellets will crystallize. The tendency towards crystallization when using sucrose may be overcome by using an agent to invert a small amount of the sugar such as cream of tartar or citric acid. It is believed that corn syrup, which contains dextrines, is advantageous inasmuch as the dextrines cause the pellets to disintegrate more readily upon ingestion. The quantity of water which is used should be sufficient to make a fairly thick syrup but which is

sufficiently thin so that the vitamin may be readily dispersed therein.

An essential part of the present invention is the use of emulsifying agents in the compositions. An emulsifying agent is not necessary from a "mechanical" standpoint, as the oily substances can be emulsified in the sugar syrup by mechanical means. However, it has been found that in the case of vitamin A, the emulsifying agents increase the biological utilization of the vitamin, and it is hypothesized that this improved utilization will carry through to other oil soluble medicinal agents.

The preferred surface active agents are the vegetable gums such as gum acacia or tragacanth and the partial esters of polyoxyethylene derivatives of sorbitol with fatty acids. Other surface active agents which have been found suitable include the bile acids and bile salts, chondrus, agar, albumin, soap bark, triethanolamine and its esters, cholesterol, cetyl alcohol, sodium lauryl sulfate, sodium alginate, methyl cellulose, lecithin, sulfated hydrogenated castor oil and quaternary ammonium compounds. These emulsifying agents can be employed in quantities of from 0.5 to 15% by weight of the concentrated sugar syrup.

A flavoring agent may be added to the hot emulsion in order to produce pellets having a more desirable flavor. Oil of orange, oil of lemon, vanillin, methyl salicylate, licorice, chocolate, coumarin and malt extract are suitable for this purpose.

In addition to the oil soluble substance which is dispersed in the sugar base, water soluble substances may also be dissolved in the base or water and oil insoluble particles may be dispersed in the base. For instance, water soluble vitamins may be dissolved in the sugar syrup and oil soluble vitamins may be dispersed in the base to produce a multivitamin pellet.

In carrying out the invention, one starts with a sugar syrup. The sugar syrup may be a commercial syrup such as corn syrup or may be prepared by adding water to sugar. The sugar syrup is then heated. The oily substance may be added before the heating is started or after the syrup reaches an elevated temperature, but it is preferred to delay adding the oily substance until the sugar syrup has partially cooled. Ordinarily the syrup is heated to about 150° C., although either a higher or lower temperature may be used. The heating may be done under an atmosphere of nitrogen or under vacuum if desired. After heating has continued until only the desired quantity of water is left, the concentrated sugar syrup is allowed to cool. The desired quantity of water which is left in the sugar syrup may be readily determined by experiment, and is that quantity which will yield a product of the desired solidity upon final cooling. The quantity of water may be varied from 0.5 to 7.5% by weight of the finished pellets. If the oily substance is not heat labile, or if it is not added until one starts to cool the syrup, the syrup can be brought to a boil and the boiling temperature will be indicative of the amount of water present. When using sucrose, a boiling temperature of 140° to 155° C. will indicate that the syrup is of the proper concentration to set to a solid upon cooling. As soon as the oily substance is added to the syrup, the syrup is stirred to emulsify the oily substance therein and stirring is ordinarily continued until the syrup becomes too thick to be readily stirred. When cooling has progressed to the point where the

mixture has attained a very viscous consistency, it may be rolled onto a slab and permitted to solidify as a solid sheet. This sheet may then be broken up into pieces of the desired size. A preferred method is to first cool the hot emulsion only to the extent that it becomes a plastic, readily workable mass which possesses sufficient rigidity to retain any shape to which it is formed. When the emulsion is in this semi-solid condition it can be rolled into sheets and the sheets fed into an ordinary candy drop machine to produce pellets of any desired size and shape. After passing through the drop machine the pellets are permitted to cool to room temperature, whereupon they become solid. The semi-solid emulsion can also be extruded through a die to form rods which can be broken up into convenient lengths.

After the pellets are formed and cooled they are suitable for use in an industrial process but do not have a finished appearance. If the pellets are of a pharmaceutical nature they are ordinarily put through a finishing process which may consist of tumbling the pellets to polish off their surfaces followed by coating. The coating may be any of the ordinary coatings such as sugar, chocolate, gelatin or pearl or it may be a special purpose coating such as an enteric coating. The coating may itself contain medicinal substances.

The following are examples of some applications of the process:

Example 1

About 2.4 kilograms of glucose syrup (containing 80% solid matter) and 2.8 kilograms of sucrose are placed in a vessel and heated with stirring to form a melt. The temperature is slowly raised to 150° C. to evaporate most of the water. The mass is then cooled to about 105° C. and there is added 253 grams of a vitamin concentrate containing 467,000 units of vitamin A and 46,700 units of vitamin D per gram and 20 grams of orange essence and 12 grams of Tween 60 (polyoxyethylene sorbitol monostearate). The mass is stirred to produce an emulsion and the emulsion is cooled to a suitable consistency. The emulsion is then plastic and is placed in a candy drop machine to form pellets. The pellets may then be coated in the usual manner.

Example 2

About 4.8 kilograms of glucose syrup (containing 80% solid matter) is placed in a vessel with 235 grams of gum acacia and heated to the boiling temperature. When the boiling temperature has reached 149° C. the mass is cooled to about 105° C. and there is added 250 grams of vitamin A concentrate. The mass is stirred to form an emulsion and the emulsion is further cooled and formed into pellets as in Example 1.

Example 3

The process of Example 2 is repeated except that no vitamin A concentrate is added. This produces blank pellets which contain only sugar and gum and are valuable for use in comparing the pellets with other vitamin A preparations.

Example 4

The process of Example 2 may be repeated, using 275 grams of vitamin E (alpha tocopherol) instead of the vitamin A concentrate to produce pellets containing vitamin E.

Example 5

One may make polyvitamin pellets by dissolving 50 kilograms of sugar in sufficient water to

make a thick syrup and boiling the syrup until it contains about 1% of water. A small amount of cream of tartar may be added to the syrup. To the thick syrup is added the following:

100 grams thiamine hydrochloride
100 grams riboflavin
25 grams pyridoxine hydrochloride
50 grams calcium pantothenate
1 kilogram nicotinamide
5 kilograms ascorbic acid

After the above substances are dissolved, the syrup is cooled to about 105° C. and there is added 130 grams of Tween 80. Then the mixture is stirred rapidly and there is added 2.5 kilograms of a vitamin A and D concentrate containing 100,000 U. S. P. units of vitamin A per gram and 20,000 U. S. P. units of vitamin D per gram. The thick syrup is then further cooled and molded into pellets. This will make 50,000 pellets, each weighing slightly over one gram and each containing at least the accepted daily minimum requirements of the vitamins listed.

In order to compare the efficiency of the pellets with other vitamin A preparations, a number of tests were carried out using human subjects. The method used is described in detail in the article by Week and Sevigne in the Journal of Nutrition, vol. 40, No. 4, pages 563 to 576 (April, 1950). Briefly, the method consists of feeding the subjects a measured amount of a vitamin containing preparation, drawing blood samples at stated intervals and analyzing the blood for vitamin A. The quantity of vitamin A in the blood serum rises and the height and duration of the rise is taken as an indication of the efficiency of the intestinal absorption of vitamin A. The times at which blood samples were drawn were 0, 2, 4, 5, 6, 8 and 24 hours. The vitamin A was administered at 0.5 hour. The zero figure is useful only in determining the amount of vitamin A which the subject's blood contained at the start of the test, and the 24 hour figure was obtained only to show that the vitamin A in the blood had returned to substantially the normal level for the particular subject. Therefore, the values obtained at intervals of 2, 4, 5, 6 and 8 hours are considered to be the significant values. These values may be lumped by plotting on a graph the various values with the micrograms of vitamin A per 100 ml. of blood serum on one coordinate with time as the other coordinate. Before plotting, there is deducted from each value the subject's blood level at zero hours. The area under the curve for the time intervals of 2, 4, 5, 6 and 8 hours is measured and is hereinafter referred to as the "microgram-hours" and this figure is the measure of the intestinal absorption. In a few cases a blood sample was taken at three hours instead of five hours, but the results were calculated in the same manner.

Nine male human subjects were tested in accordance with the above procedure. Each subject was fed vitamin A acetate, the quantity in each case being the equivalent of 125,000 micrograms of vitamin A alcohol. The vitamin was fed in the following forms:

1. Pellets.—The pellets were made in accordance with Example 2 set forth above.
2. Soft gelatin capsules containing vitamin A.
3. An emulsion made by emulsifying the vitamin A in water with the aid of Tweens 20 and 60.
4. The vitamin A was enclosed in a hard gelatin capsule and a number of blank pellets made in accordance with Example 3 were fed simultane-

ously. The number of blank pellets used was equal to the number of active pellets used in 1.

- The nine subjects were fed the four above preparations and the "microgram-hours" value for the subjects were averaged for each preparation with the following results:

Preparation.....	1	2	3	4
10 Average "microgram-hours".....	4,495	2,118	3,872	2,819

From the above data, the following conclusions can be drawn: The pellets (1) were superior to the conventional soft gelatin capsules (2) and even surpassed the aqueous dispersion (3) in efficiency. The results from (4) show that the superior biological utilization was not due to the mere presence of the gum-sugar mixture in the stomach, but the vitamin A must be dispersed in the gum-sugar mixture to produce the superior results.

The pellets made according to this invention are characterized by the large amount of the oily substance which they contain. Those containing medicinal substances are active pharmaceutical preparations. The percentage of the oily substances is preferably at least 3% and may be as high as 12%. In the event it is desired to utilize highly purified pharmaceutical materials, such as crystalline vitamin A or high potency vitamin A concentrate, the percentage of lipid can be substantially lower than 3%. For instance, if one makes a pellet weighing 0.25 gram from crystalline vitamin A containing 5,000 units of vitamin A, the lipid content would be about 0.0015 gram or approximately 0.6% of the total pellet weight.

I claim:

1. The process of producing a solid vitamin containing material comprising heating a sugar syrup containing from about 0.5% to 7.5% by weight of water and a small quantity of an emulsifying agent, emulsifying a fat soluble vitamin in the heated syrup and cooling the syrup to produce a solid material.

2. The process of preparing a solid vitamin containing material comprising heating a sugar syrup to a temperature of about 150° C. to produce a syrup having from about 0.5% to 7.5% of water, and containing an emulsifying agent, cooling the syrup to about 105° C. and adding thereto a fat soluble vitamin material to produce an emulsion, and cooling said emulsion to produce a solid material.

3. The process of claim 1 wherein the emulsifying agent is gum acacia.

4. The process of claim 1 wherein the emulsifying agent is a polyoxyethylene derivative of a partial ester of sorbitol and a fatty acid.

5. The process of producing a solid pellet containing vitamin A comprising heating a sugar syrup to evaporate water therefrom to produce a syrup containing from about 0.5% to 7.5% of water, said heated syrup containing an emulsifying agent, cooling the syrup to about 105° C., emulsifying vitamin A therein, cooling the emulsion to the extent that it becomes a semi-solid, molding the emulsion in the form of small pellets, and further cooling the pellets to produce a solid material.

6. The process of producing solid vitamin pellets comprising adding about 4.8 kilograms of glucose syrup containing 80% solid material to about 235 grams of gum acacia, heating the mixture to a temperature of about 150° C. to evapo-

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rate water therefrom and to produce a mass containing from about 0.5% to 7.5% water, cooling the mass to about 105° C., emulsifying a vitamin A concentrate in said mass, and cooling said mass to produce a solid material.

7. The process of preparing a solid vitamin containing material comprising heating a sugar syrup to a temperature of about 150° C. to produce a melt of thick syrup of the proper concentration to set as a solid hard candy upon cooling to room temperature, and containing an emulsifying agent, partially cooling the syrup and adding to the thick syrup a fat soluble vitamin material and further cooling to room temperature to produce a solid material.

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