ABSTRACT

Direct compression vehicle useful for preparation of tablets by the direct compression technique is obtained by dispersing a diluent such as sugar, in a fully hydrated hydratable polymer, such as starch, drying the resulting dispersion, and reducing the dried product to particles of the desired size. The vehicle can be admixed with the active material and, if desired, a lubricant, and the resulting mixture compressed without prior granulation or slugging to form a tablet.

10 Claims, No Drawings
DIRECT COMPRESSION VEHICLES

This invention relates to direct compression vehicles. More particularly, this invention relates to a particulate composition which can be admixed with an active and optionally, a lubricant, and the resulting mixture directly compressed into a tablet without the necessity of granulation or slugging of the mixture.

There are two general methods for forming tablets, i.e., compression of a dry particulate material and trituration, or molding of a wet material, of which the trituration technique is by far the most frequently employed. The compression technique may be further subdivided into three major categories, viz. direct compression, wet granulation and dry granulation. The direct compression technique is the most desirable, in that it employs the fewest steps and, in the case of the production of tablets containing sensitive or unstable actives, such as certain pharmaceuticals, minimizes the exposure to water or other conditions tending to adversely affect stability of the active. Unfortunately, however, it has been found that the direct compression technique is of limited applicability.

First, most active materials possess poor compression properties, and thus are unsuitable for this technique. In addition, many actives are required in such small amounts per unit dosage form that direct compression of the active alone is impractical, if not impossible. As a result, the active must be admixed with a direct compression vehicle, i.e., an inert composition which is compatible with the active and has good compressibility. In addition, the direct compression vehicle should have good flowability, good stability under normal ambient conditions, no adverse effect on tablet disintegration time, the ability to produce good tablet surfaces, and low cost.

To date, however, no material has been found which satisfies all of these criteria. For example, of the most popular such compression vehicles, spray-dried lactose possesses poor stability and discolors on storing, dicalcium phosphate provides tablets having poor strength, and microcrystalline cellulose is expensive.

It is an object of the present invention to provide a new direct compression vehicle.

It is a further object of this invention to provide a multicomponent compression vehicle which may be combined with an active and, if desired, a lubricant, and the resulting dry mixture subjected to direct compression.

The direct compression vehicles of the present invention comprise minute particles of a dispersion of certain water-soluble or dispersible inert diluents in a matrix of a hydratable high polymer. The diluent can be any normally solid material, i.e., any material which is solid under conditions of normal atmospheric pressures and temperatures, provided it is inert, edible and permisssible in the tablet formed from the direct compression vehicle. Thus, it can be water-soluble or insoluble in water. If insoluble, however, it must be capable of reduction to a size which is useful in the direct compression vehicle of this invention, i.e., a size below about 200 mesh, and preferably below about 10 microns.

Preferred diluents include normally saccharine materials, i.e., a mono or disaccharide such as glucose, mannose, galactose, fructose, arabinose, xylose, sucrose, maltose and lactose; as well as certain polyols of the formula HO(CH₂OH)nCH₂OH wherein n is 1-4, such as glycerol, erythritol, arabinol, xylitol, adonitol, mannitol, dulcitol and sorbitol. In addition, certain salts may be employed, including sodium chloride, sodium citrate, calcium carbonate, calcium sulfate and tricalcium phosphate. The diluent may be one or a mixture of two or more of the aforesaid substances. In the event the diluent is a sugar, it may be of synthetic or natural origin, and may be supplied to the mixing step in the form of a solution or syrup, such as molasses, affination syrup, invert syrup and the like.

The hydrated polymer includes hydrophilic polysaccharides, hydrocolloids or proteinaceous materials which when in a water-immiscible solvent, are hydrated upon ad-mixture with water, and when substantially fully hydrated form a clear aqueous sol of swollen polymer and water. Illus-
3,639,168

3,639,168

dehydrated film is removed by a doctor blade from its associated drum and transferred to the reel across a current of cooling air, having a 60°–80° F. temperature, which effects an initial cooling of the dehydrated material to near room temperature. This cooling effect is enhanced by the thinning or drawing down of the film as a consequence of having the reel operate at the greater peripheral speed. Since the reel is also cooled by 60°–80° F. air, the thin film is further cooled to a room temperature of about 70°F. to about 95°F. and the cooling air at the line of removal of the film from the reel aids both its removal therefrom and a final cooling to a brittle or fragile state. The fragile film then drops away from the reel as a brittle sheet or fragments onto a conveyor for transport to a storage bin or to a comminuting device for reduction to the desired particle size for direct tabletting.

If only one takeoff reel is used, it will, of course, be necessary to provide a scraper or other means on the opposite drum to prevent passage of the hot dehydrated film therearound and force it over onto the other drum.

Although in the foregoing description of the method mention has been made of a two-drum dryer with either a single or two takeoff reels, it will be appreciated that a single drum dryer with a single takeoff reel can be used with equal effectiveness.

The dried product is broken up into particles having the desired dimensions and, if necessary, screened to achieve the proper size range and distribution. The resulting particulate product comprises minute particles of the water-soluble additive dispersed throughout the high-polymer matrix, and is substantially different in appearance and properties from mixtures of the same dry materials which are obtained by dry blending, or even wet granulation techniques. The reason for the difference is that none of the heretofore known techniques for preparing tabletting materials or blends employs sufficient water to both hydrate the polymer and dissolve the additive.

On the other hand, U.S. Pat. No. 2,963,737 to Monti et al. discloses an icing percussion comprising agar or carrageen starch and/or sugar which is prepared according to the foregoing technique, and it has been found that the resulting product is an excellent direct compression vehicle in accordance with this invention. Previously known products which may be employed as directly compressible vehicles are the modified polysaccharide gums of Monti et al. disclosed in U.S. Pat. No. 3,042,668.

The granular direct compression vehicle of this invention is admixed with the active which it is desired to incorporate into tablet form and, if necessary, a lubricant, and the mixture tabletted by known direct compression procedures. The proportions of vehicle, active and lubricant are not critical, and obviously depend upon the active and the unit dose desired in the tablet. In general, however, the direct compression vehicle will comprise at least 10 percent of the tabletted mixture, and thus the resulting tablet, although amounts within the range of from about 70 percent to about 95 percent are most common.

By the term “active material” is meant any material intended for ingestion having a beneficial or desirable effect on the user. Suitable active materials include therapeutic materials, such as anesthetics, antibiotics, antiulceratives, vitamins, aspirin, antacids, and the like; foodstuffs such as cocoa, dried oats, fruit flakes and the like; edible dyes and other food additives; and so on. The vehicle is a free-flowing granular material and imparts improved flow characteristics to the active material and other components of the blend, thereby ensuring ease of tablettimg.

The blend of direct compression vehicle, active material and other additives is mixed and directly compressed to form a tablet employing conventional techniques and apparatus.

The following examples are illustrative. Unless otherwise specified, all parts and percentages are by weight.

**EXAMPLE 1**

A mixture of 182 pounds of sucrose, 35 pounds of tapioca flour, 300 pounds of starch and 400 gallons of water was heated to 180°F, and 714 pounds of a 70 percent invert syrup was added. The resulting mixture was drum dried to a moisture content of about 21.3 percent, and then broken up into flakes of about one half an inch. The resulting particulate flake material was admixed with calcium stearate in a ratio of 99 parts to 1 part and after pulverization to yield a product having a particle size of below about 200 mesh (95 percent through 200 mesh), compressed to form 13/32-inch, 0.5-grain tablets at 1,000 and 3,000. The resulting tablets had Stokes hardnesses of 3.25 and 4.1 kilograms, respectively, and evidenced no capping.

**EXAMPLE 2**

Employing procedures similar to those described in example 1, a flake product containing about 46 parts invert sugar, 25 parts starch, 28 parts sucrose and 1 percent water was produced and admixed with Cab-O-Sil brand silica gel to provide a mixture containing 98 parts flake and 2 parts silica gel. The resulting mixture, after pulverizing, was tabletted at 3,000 and 9,000 p.s.i. The tablets produced at 3,000 p.s.i. were ejected at a pressure of 100 p.s.i., evidenced only slight capping and had a hardness of 19.5. At 9,000 p.s.i. and ejection pressure of 350 p.s.i. no capping was observed and tablet hardness was in excess of 45 kg.

In a second run equal parts of the flake and sucrose were mixed and pulverized, and then magnesium stearate was blended in to provide 49 parts each of flake and sucrose and 2 parts magnesium stearate. Tablets compressed at 3,000 p.s.i. and ejected at 60 p.s.i. had a hardness of 20.75 and evidenced no capping, and those compressed at 9,000 p.s.i. and ejected at 95 p.s.i. had a hardness of 37.5 kg and evidenced no capping.

**EXAMPLE 3**

Employing procedures similar to those described in example 1, a mixture of 350 pounds of starch and 284 pounds sucrose in 450 gallons of water and 571 pounds of 70 percent invert sugar was drum dried to about 2 percent moisture and crushed to form flakes having a size of about one-half an inch. The resulting product, after further pulverizing to below about 200 mesh, was compressed at 3,000 and 9,000 p.s.i. and 35 p.s.i. ejection pressure to form 13/32-inch tablets weighing 0.5 grams. Tablet hardness was 35.5 and greater than 45, respectively, and no capping was observed.

The flake product was admixed with sucrose and calcium stearate to provide a mixture containing 60 parts flake, 39 parts sucrose and 1 part stearate, and the resulting mixture tabletted. At 3,000 p.s.i. the ejection pressure was 50 p.s.i. and tablet hardness was 13.5. At 9,000 p.s.i. the ejection pressure was 45 p.s.i. and tablet hardness was 22. No capping was observed at either pressure.

**EXAMPLE 4**

Employing procedures similar to those described in example 1, a flake product containing 22.5 percent invert sugar, 42.4 percent sucrose, 32.1 percent starch and 3 percent moisture was blended to form a mixture of 66.6 parts flake, 32.35 parts sucrose and 1.0 parts calcium stearate. Tablets pressed at 1,000, 3,000 and 9,000 p.s.i. had hardnesses of 6.5, 14.5 and 23.0, respectively.

**EXAMPLE 5**

Employing procedures similar to those described in example 1, a mixture of 1 part locust bean gum, 25 parts sugar and 100 parts water was heated to 180°F. and drum dried to less than 1 percent moisture and reduced to ⅛-inch flakes. The resulting product, after pulverization to a product of less than about 200 mesh, was compressed at 4,500 p.s.i. to form a tablet having a hardness of greater than 42 kg.
3,639,168

EXAMPLE 6

Employing procedures similar to those described in example 1, a mixture of 4 parts of agar, 70 parts sucrose and 200 parts water was boiled and then drum dried and flaked. After pulverizing, the product was compressed at 4,500 p.s.i. to form a tablet having a hardness of greater than 42 kg.

EXAMPLE 7

Employing procedures similar to those described in example 1, a mixture of 4 parts carrageen, 70 parts sucrose and 200 parts water was drum dried and flaked. The flake product, after pulverizing, was compressed at 4,500 p.s.i. to form a tablet having a hardness of greater than 42 kg.

Each of the direct compression vehicles of the foregoing examples can be blended in accordance with the following recipes and compressed to form tablets or wafers.

**CONFECTIONERY TABLETS OR WAFERS**

1. Lemon-flavored confectionery tablet:
   - 100.0 pt. direct compression vehicle
   - 1.0 pt. citric acid, dry
   - 0.25 pt. encapsulated lemon flavor
   - 0.10 pt. yellow color No. 5
   - 1.0 pt. magnesium stearate

2. Grape-flavored confectionery tablet:
   - 50.0 pt. direct compression vehicle
   - 5.0 pt. 6x powdered sugar
   - 2.0 pt. tartaric acid
   - 0.25 pt. grape flavor
   - 0.05 pt. grape color
   - 0.5 pt. calcium stearate

3. Cherry-flavored confectionery tablet:
   - 100.0 pt. direct compression vehicle
   - 2.0 pt. fumaric acid
   - 0.2 pt. cherry flavor
   - 0.1 pt. red color
   - 1.0 pt. magnesium stearate

**B. PHARMACEUTICAL FORMULATIONS**

1. 50.0 pt. direct compression vehicle
   - 37.5 pt. aluminum hydroxide
   - 1.0 pt. magnesium stearate

2. 100.0 pt. direct compression vehicle
   - 25.0 pt. calcium carbonate
   - 5.0 pt. magnesium carbonate
   - 1.0 pt. peppermint oil
   - 2.0 pt. magnesium stearate

3. 100.0 pt. direct compression vehicle
   - 25.0 pt. acetyl salicylic acid
   - 15.0 pt. corn starch
   - 2.0 pt. magnesium stearate

4. 90.0 pt. direct compression vehicle
   - 10.0 pt. vitamin C in dry form
   - 2.0 pt. magnesium stearate

Other active ingredients of use in blends with the direct compression vehicle are: sodium bicarbonate, aceti nacid, phensacitin, and magnesium trisilicate.

**C. SPECIALTY PRODUCTS**

1. Invertase sugar tablet
   - 96.4 pt. direct compression vehicle
   - 3.6 pt. liquid triple strength invertase (Kn0.9)

2. Cocoa-sugar tablet
   - 90.0 pt. direct compression vehicle
   - 10.0 pt. high fat cocoa
   - 0.2 pt. steamed salt
   - 1.0 pt. magnesium stearate
   - After blending, the mixture is tabletted to form a cocoa-sugar tablet.

3. Sugar-synthetic sweetener tablet
   - 450.0 pt. direct compression vehicle
   - 7.16 pt. calcium cyclamate
   - 0.8 pt. sodium saccharin
   - 3.0 pt. calcium stearate

4. Highly concentrated color tablet
   - 90.0 pt. direct compression vehicle
   - 10.0 pt. direct yellow FD&C No. 6
   - 10.0 pt. sodium benzoate

5. Yeast Food Tablet
   - 34.0 pt. calcium sulfate (2H2O)
   - 23.0 pt. flour
   - 9.0 pt. ammonium chloride
   - 0.25 pt. potassium bromate
   - 17.75 pt. sodium dibicyclonitrogen phosphate
   - 16.0 pt. salt
   - 90.0 pt. direct compression vehicle
   - 10.0 pt. magnesium stearate

What is claimed is:

1. In a method for producing a tablet by the direct compression of a mixture including an active material and a direct compression vehicle, the improvement of employing a dry granular direct compression vehicle comprising an inert, edible diluent dispersed throughout a matrix of a hydrophilic polymer prepared by mixing said diluent and said polymer with water in proportions sufficient to provide a substantially fluid mixture of an aqueous solution or dispersion of diluent dispersed throughout swollen, hydrated polymer, and thereafter drying said mixture, and forming particles therefrom.

2. A method according to claim 1 wherein said diluent is selected from the group consisting of sucrose or invert sugar.

3. A method according to claim 1 wherein said diluent is selected from the group consisting of a monosaccharide, a disaccharide, a polyol of the formula HOCH2(OH)2nCH2OH wherein n is 1 to 4, sodium chloride, sodium citrate, calcium carbonate, calcium sulfate or tricalcium phosphate.

4. A method according to claim 1 wherein said diluent is selected from the group consisting of a monosaccharide, a disaccharide, a polyol of the formula HOCH2(OH)2nCH2OH wherein n is 1 to 4, sodium chloride, sodium citrate, calcium carbonate, calcium sulfate or tricalcium phosphate.

5. A method according to claim 1 wherein said diluent is selected from the group consisting of a monosaccharide, a disaccharide, a polyol of the formula HOCH2(OH)2nCH2OH wherein n is 1 to 4, sodium chloride, sodium citrate, calcium carbonate, calcium sulfate or tricalcium phosphate.

6. A dry, granular direct compression vehicle comprising an inert, edible diluent dispersed throughout a matrix of starch prepared by mixing said diluent and starch with water in proportions sufficient to provide a substantially fluid mixture of an aqueous solution or dispersion of diluent dispersed throughout swollen, hydrated starch, and thereafter drying said mixture and forming particles therefrom.

7. A vehicle according to claim 6 wherein said diluent is selected from the group consisting of a monosaccharide, a disaccharide, a polyol of the formula HOCH2(OH)2nCH2OH wherein n is 1 to 4, sodium chloride, sodium citrate, calcium carbonate, calcium sulfate or tricalcium phosphate.

8. A vehicle according to claim 6 wherein said diluent is present in an amount of from about 0.25 to about 250 parts per part of starch.

9. A vehicle according to claim 8 wherein said diluent is selected from the group consisting of a monosaccharide or a disaccharide.

10. A vehicle according to claim 8 wherein said diluent is selected from the group consisting of sucrose or invert sugar.