DIRECT COMPRESSION VEHICLES

ABSTRACT: Tablets are formed directly without granulation or slugging from a mixture of an active material, such as a therapeutic material, and as a direct compression vehicle, a dry, free-flowing, granular sugar composition comprising generally spherical, porous, firm agglomerates of 100 parts of solid sugar in from about 0.1 to about 30 parts of a cementum or matrix. The sugar agglomerates are obtained by:

1. Spraying a particulate solid sugar with an aqueous solution of binder;
2. Providing the resulting mixture with sufficient high intensity agitation to uniformly intermingle the sugar and binder and to build up agglomerates of a desired size;
3. "Snowballing" the agglomerates to impart a general spherical shape thereto and to firm or densify the agglomerate;
4. Drying; and if necessary,
5. Separating over- and undersized agglomerates. The mixture may also contain additives such as colors, flavorants and the like.
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DIRECT COMPRESSION VEHICLES

This invention relates to tablets comprising an active material and a direct compression vehicle. More particularly, this invention is concerned with tablets comprising an active material and a direct compression vehicle, which are formed from a mixture thereof without prior granulation or slugging.

There are two general methods for forming tablets, i.e., compression of a dry particulate material and trituration, or molding of a moist material, of which the first technique is by far the most frequently employed. The compression technique may be further subdivided into three major categories, i.e., 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.

Direct compression vehicle. 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 capable of being compressed to good compressibility and binding action. 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, one of the most popular of 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.

One of the principal objects of this invention is to provide a direct compression vehicle.

Another object of the invention is to provide an improved tablet as the final product as a result of the more effective quality control made possible by eliminating variables in the manufacturing process.

Another object of the invention is to permit the use of a wide variety of materials in the manufacture of tablets.

Another object of the invention is to provide a novel method of manufacturing tablets in which the complicated steps inherent in a granulation process are avoided.

Other objects and advantages in this invention will be apparent to those skilled in the art of tablet manufacture when reviewing the specification and claims of this invention.

It has been discovered in accordance with this invention that certain sugar agglomerates are well suited for use as a direct compression vehicle for the production of tablets. This material comprises generally spherical, firm, porous agglomerates of sugar particles in a cementum or matrix. The agglomerates are dry (from about 0.1 to about 3 percent moisture), free-flowing particles having particle size within the range of from about 325 to about 12 mesh. Tablets formed using such sugar agglomerates as the direct compression vehicle are uniform, possess good physical properties, do not discolor on aging, and are stable in aqueous media.

These sugar agglomerates are obtained by:
1. Spraying a particulate solid sugar with an aqueous solution of binder;
2. Providing the resulting mixture with sufficient high intensity agitation to uniformly intermix the sugar and binder and to build up agglomerates of a desired size;
3. "Snowballing" the agglomerate so that it imparts a general spherical shape thereto and to firm or densify the agglomerate;
4. Drying; and if necessary,
5. Separating over- and undersized agglomerates.

The particulate sugar can be a mono-, di- or tri-saccharide, such as arabinose, xylose, ribose, fructose, mannose, galactose, glucose, sucrose, maltose, lactose and the like, including mixtures of two or more of such sugars, with sucrose being preferred. The particulate sugar can be obtained synthetically, or it can be a refined natural product, such as corn syrup solids, molasses solids, honey solids, maple syrup solids and the like. The particle size of the sugar is not narrowly critical so long as it is small enough to permit formation of agglomerates of the desired size. For most purposes, ordinary 6X powered sugar, of which most (95 to 97 percent) passes through a 200-mesh screen, is suitable. Fine agglomerates is to be employed in the production of a chewable tablet, however, it is desirable that more finely divided sugar be used to avoid "grittiness." For this use, the sugar should have substantially no particles, i.e., not more than 1 percent, having sizes greater than about 40 microns, and at least 50 percent of the particles should have sizes below about 25 microns. Preferred are sugars having an average particle size of about 15 microns.

The second component which is employed to form the agglomerate is a noncrystallizing aqueous solution of a polyhydroxy compound as a binder. Illustrative polyhydroxy compounds include propylene glycol, glycerol, erythritol, arabitol, xylitol, adonitol, mannitol, dulcitol, sorbitol, sugars, such as arabinose, xylose, ribose, glucose, mannose, fructose, sucrose, maltose and the like, with polyols of the formula HOCH₂(CH₂OH)ₙCH₂OH, wherein n is 1 to 4, and sugars being preferred. Propylene glycol, glycerol, mannitol, sorbitol, glucose, fructose and invert sugar are of particular interest, with invert sugar being most preferred. The aqueous binder composition can be a solution of a pure compound, or can comprise two or more polyhydroxy binders. The aqueous medium can be obtained synthetically, or it can be a refined natural product, such as corn syrup, molasses, honey, maple syrup and the like. Invert syrup is preferred.

The concentration of binder in the aqueous medium is not narrowly critical provided that it is not so high as to cause crystallization or provide solutions so viscous as to prevent spraying and intimate intermingling and uniform distribution of binder and solids. Thus, the concentration will depend upon the solubility of the binder. For example, glucose ordinarily cannot be employed in amounts greater than about 48 percent, whereas propylene glycol, glycerol, mannitol and sorbitol can be present in amounts up to about 80 percent. When invert sugar is the binder, concentrations of from about 50 to about 80 percent are employed, with concentrations from from about 70 to about 75 percent being preferred. Other than this, the amount of water in the aqueous medium is unimportant and is related with the desired ratio of binder to sugar that agglomeration occurs. Thus the amount of water should be insufficient to form a paste and yet sufficient to minimize the presence of powder, or unagglomerated sugar. In general, it has been found that the mixture of particulate sugar and aqueous binder medium should contain from about 2 to about 6 percent water, with amounts of about 4 percent water being preferred.

The initial contact of the solids and liquids is effected by spraying the aqueous medium onto the dry solids at a rate such that there is employed from about 0.1 to about 30 parts of binding agent per 100 parts of solid.

The mixing is ordinarily conducted at about room temperature (65°-75°F). Higher and lower temperatures can be employed, if desired, provided the properties of the aqueous medium and the agglomerate product are not adversely affected. In particular, the temperature of the aqueous medium may be varied to achieve a desired viscosity for spraying. However, if the temperature is too low, e.g., below about 50°F, the aqueous medium is ordinarily too viscous to be easily sprayed; and if the temperature is too high, e.g., above 200°F, water may evaporate too rapidly to permit adequate control of the characteristics of the binding solution. In addition, the use of elevated temperatures during processing tends to result in a discolored product, and also may cause dissolu
tion of the dry ingredient and thus adversely affect particle size and quality.

Simultaneously with the spraying, the mixture is agitated to thoroughly intermingle the solid sugar and the aqueous binder medium and to effect agglomeration. This requires high intensity mixing, such as is obtained with a Patterson-Kelley blender or a Lodige mixer.

Agitation is continued until agglomerates of the desired size are formed, and ordinarily for a time sufficient to form agglomerates about 325 mesh, but insufficient to form signiﬁcant amounts of agglomerates larger than about 12 mesh. The size of the agglomerate is also affected by the ratio of aqueous binder to particulate sugar, with larger agglomerates being formed when a greater proportion of liquid medium is present.

The agglomerates typically have a narrow size distribution. That is, high yields, normally 80 percent or more, of the agglomerates fall within a few screen sizes. For example, when operating to produce a 20- to 80-mesh agglomerate, at least 80 percent, and in some instances 90 percent or more, of the agglomerated product will fall within this range.

Simultaneously with and/or subsequent to agglomeration, the agglomerates are “snowballed,” i.e., subjected to a tumbling or rolling operation, to impart a general spherical shape thereto. In addition, the agglomerates are ﬁred or densiﬁed whereby the bulk density is increased by about 50-100 percent over that of the dry particulate sugar, and normally is in the range of from about 30 to about 50 pounds per cubic foot.

The apparatus employed can be any suitable equipment which will achieve the desired results. A particularly preferred apparatus is the Patterson-Kelley blender, which performs all three operations of mixing, agglomerating and snowballing.

Finally, and when necessary, the agglomerates are dried to a moisture content of less than about 3 percent, and preferably less than about 1.5 percent. Although complete drying is theoretically possible, the moisture content of the product need not be less than about 0.1 to 0.2 percent. The temperature at which drying occurs is not narrowly critical in all cases, but ordinarily the temperature of the agglomerate should not exceed about 140°F. To achieve such drying, the product is preferably contacted with hot air at a temperature not exceeding 190°F. A preferred drying technique is the use of a fluid bed dryer in a manner very ﬁne particles, i.e., dust, are separated from the product.

If desired, the dried product may be screened to remove oversized and undersized particles. Oversized particles are discarded or can be reduced to smaller size. Undersized particles can be recycled.

The resulting agglomerate is admixed with the active material and the resulting mixture compressed without granulation or slugging to form a tablet. The amount of the agglomerate obviously will depend upon the properties of the active and any other additives which are to be incorporated into the ﬁnished tablet, for it is well known that the compatibility of tablet compounds and mixtures are subject to wide variation. In general, however, the agglomerate will comprise at least 10 percent of the tabletting mixture and, therefore, at least 10 percent of the tablet. In most cases, however, the agglomerate will comprise from about 70 to about 95 percent of the tabletting mixture and the tablet.

By the term “active material” is meant any material intended for ingestion and having a beneﬁcial or desirable effect on the user. Suitable active materials include therapeutic materials, such as anesthetics, antibiotics, antispasmodics, vitamins, aspirin, antacids, and the like; food stuffs such as cocoa, dried oats, fruit ﬂakes, and the like; edible dyes and other food additives; and so on.

In addition to the sugar direct compression vehicle and the active material, there may be employed other commonly em- ployed tablet and wafer additives such as coloring agents, ﬂavorants, lubricants, gums and the like. Although ordinarily not required because of the ready solubility of the product tablet in aqueous media, disintegrants may also be employed.

The vehicle is a free-ﬂowing granular material and imparts improved ﬂow characteristics to the active material and other components of the blend, thereby assuring ease of tabletting. 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. As used throughout this application, all parts and percentages are by weight unless otherwise stated.

EXAMPLE 1

To 90 parts of finely pulverized sucrose is rapidly added over a period of 5 minutes by spraying at room temperature and while agitating the pulverized sugar 14 parts of an aqueous invert sugar solution (72 percent total solids) in a Patterson-Kelley liquids-solids blender. After continuing agitation for an additional 10 minutes, the agglomerated material is screened through a vibrating 16-mesh screen and the screened material is dried to a moisture content of 1.5 percent or less. To 97 parts of dry agglomerated product is added, under agitation, 1 part of dry citric acid, 0.25 part of dry ﬂavoring material and 1.75 part of magnesium stearate. The properly blended material is fed to a tabletting press and wafers are formed from it.

EXAMPLE 2

Employing procedures similar to those described in example 1, 98 parts of finely pulverized sucrose is mixed with about 6.7 parts of an aqueous invert sugar solution (30 percent total solids). The agglomerated material is screened through a vibrating mesh screen and the screened material is dried to a moisture content of 1.5 percent or less.

Equal parts of the agglomerate and vitamin C are blended. This blend can be further mixed with other dry ingredients such as minerals or other nutritionally active ingredients before being compressed into tablets.

EXAMPLE 3

Employing procedures similar to those described in example 1, a blend of 100 parts of finely pulverized dextrose monohydrate is sprayed with 14 parts of dextrose syrup (48 percent total solids). The agglomerated material is screened and dried to a moisture content of 1.5 percent or less.

The agglomerated material can be directly compacted after adding and blending the proper release agent (magnesium stearate). Rapidly disintegrating ingredients can also be included in the formulation prior to tabletting.

EXAMPLE 4

Employing procedures similar to those described in example 1, a blend of 90 parts of finely pulverized sucrose and 10 parts of finely comminuted dextrose are sprayed with about 14 parts of invert syrup (72 percent total solids). The agglomerated materials are screened, and dried to a moisture content of 1.5 percent or less.

Equal parts of the agglomerate and aluminum hydroxide are blended together. This blend can be further mixed with small amounts of ﬂavoring or other dry ingredients before being compressed into a commercial antacid tablet.

EXAMPLE 5

Employing procedures similar to those described in example 1, 95 parts of finely pulverized dried molasses are sprayed with about 6.5 parts of afﬁnition syrup (76 percent total solids). The agglomerated material is screened and dried to a moisture content of 1.5 percent or less. Equal parts of the agglomerate and dried ground oats are blended. This product can be mixed with other dry ingredients such as minerals or other nutritives. After compacting, wafers for animal feeding are obtained.
EXAMPLE 6

To 90 parts of pulverized sucrose having an average particle size of 15 microns, less than 1 percent thereof exceeding 40 microns, and more than 50 percent thereof less than 25 microns in size, the said pulverized sugar being in a Patterson-Kelley liquids-solids blender, there is rapidly added by spraying at room temperature (65°F.), and while agitating the pulverized sucrose, about 14 parts of an aqueous invert sugar solution (72 Brix). A small amount of monocalcium phosphate is added to adjust the pH to 4.5–4.8 to prevent discoloration. After the addition of the invert syrup has been completed, the blender is run for about 2 minutes to complete the agglomeration. The total time of operation, i.e., spraying and agglomeration, is about 6 minutes.

The resultant agglomerated material, which contains about 3.8 percent water, is then screened through a vibrating 20-mesh screen. The agglomerates coarser than 20 mesh are still relatively soft and can be rubbed through an auxiliary screen and added to the first product. The screened material is then placed in a rotary drier and warm air at about 180°F. is circulated through the drier to dry the agglomerates to a water content of 1 percent. The drier is operated so that the temperature of the agglomerates does not rise about 140°F. The dried product is then further screened on an 80-mesh screen. The material remaining on the screen is the finished product. That passing through the screen may be returned to the blender for reprocessing, or may be employed as a fine particle size granular product.

This agglomerate can be blended in accordance with the following recipes and compressed.

A. CONFECTIONERY TABLETS OR WAFERS
1. Lemon Flavored Confectionery Tablet:
   100.0 pts. agglomerate
   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 Tablet:
   50.0 pts. agglomerate
   50.0 pts. 6X powdered sugar
   2.0 pts. tartaric acid
   0.25 pt. grape flavor
   0.05 pt. grape color
   0.5 pt. calcium stearate
3. Cherry Flavored Confectionery Tablet:
   100.0 pts. agglomerate
   2.0 pts. fumaric acid
   0.2 pts. cherry flavor
   0.1 pt. red color
   1.0 pt. magnesium stearate

B. PHARMACEUTICAL FORMULATIONS
1. 50.0 pts. agglomerate
2. 37.5 pts. aluminum hydroxide
   1.0 pt. magnesium stearate
3. 100.0 pts. agglomerate
   25.0 pts. calcium carbonate
   5.0 pts. magnesium carbonate
   1 drop peppermint
   2.0 pts. magnesium stearate
4. 100.0 pts. agglomerate
   25.0 pts. acetyl salicylic acid
   15.0 pts. corn starch
   2.0 pts. magnesium stearate
5. 90.0 pts. agglomerate
   10.0 pts. vitamin C in dry form
   2.0 pts. magnesium stearate

Other active ingredients of use in blends with the agglomerate are: sodium bicarbonate, acetanilid, phenacetin, and magnesium trisilicate.

C. SPECIALTY PRODUCTS
1. Invertase Sugar Tablet
   96.4 pts. agglomerate
   3.6 pts. liquid triple strength invertase (K=0.9)
   1.0 pt. magnesium stearate
2. Cocoa-Sugar Tablet
   90.0 pts. agglomerate
   10.0 pts. high fat cocoa
   0.2 pts. dendritic salt
   1.0 pt. magnesium stearate
3. Sugar-Synthetic Sweetener Tablet
   450.0 pts. agglomerate
   7.16 pts. calcium cyclamate
   0.8 pts. sodium saccharin
   5.0 pts. calcium stearate
4. Highly Concentrated Color Tablet
   90.0 pts. agglomerate
   10.0 pts. dried yellow FD&C No. 6
   10.0 pts. sodium benzoate
5. Yeast Food Tablet
   34.0 pts. calcium sulfate (2H2O)
   23.0 pts. flour
   9.0 pts. ammonium chloride
   0.25 pt. potassium bromate
   17.75 pts. sodium dihydrogen phosphate
   16.0 pts. salt
   900.0 pts. agglomerate
   10.0 pts. magnesium stearate

In the foregoing examples, the direct compression vehicle has been a spherical agglomerate. In some instances, in which a high degree of composition uniformity is desired, the use of the agglomerate per se has been found disadvantageous. It is readily appreciated that the ratio of invert to particulate sugar increases with increasing agglomerate size. For example, in the case of a product having agglomerates in the 80–100 mesh range, the invert content of the 200-mesh size particles is substantially less than the invert content of the 80-mesh particles. It has been further found that the agglomerates tend to segregate according to size upon handling. For example, when a 80–200 mesh fraction of the agglomerates is stored in a bag, the 200-mesh particles tend to settle out in the bottom of the bag during handling. As a result of the different composition and size segregation, the composition of tablets made from the agglomerates will vary depending upon whether the agglomerate is taken from the top or the bottom of the bag.

To avoid such product variations, it has been found desirable to pulverize the agglomerate and then compact the pulverized agglomerate, as for example by the use of a Fitzpatrick Chilsonator, and reduce the resulting compacted sheet to particles of a desired size. If desired, the granules of compacted agglomerate may be screened to provide a product of more restricted size variation.

The resulting compacted agglomerate may be employed in a manner identical to the agglomerate itself. Thus, it may be substituted for the agglomerate in any of the foregoing examples to achieve a tablet of substantially identical characteristics.

What is claimed is:

1. A method for preparing tablets containing as a direct compression vehicle a sugar composition comprising the steps of (a) forming a uniform nongranulated mixture of an active material and a dry, free-flowing, generally spherical, porous agglomerate of 100 parts of a solid pulverized sugar in 0.1 to about 30 parts of a matrix of a polyhydroxy compound, and (b) compressing said mixture into tablets, said agglomerate comprising at least 10 percent of said mixture, and having a particle size of from about 12 to about 325 mesh, a moisture content of from about 0.1 to about 3 percent, and having been
prepared by a process including the steps of: (1) Spraying a particulate solid sugar with an aqueous solution of binder; (2) Providing the resulting mixture with sufficient high intensity agitation to uniformly intermingle the sugar and binder and to build up agglomerates of a desired size; and (3) "Snowballing" the agglomerates to impart a general spherical shape thereto and to firm or densify the agglomerate.

2. A tablet prepared in accordance with claim 1.

3. A method according to claim 1, wherein said matrix is a carbohydrate.

4. A tablet prepared in accordance with claim 3.

5. A method according to claim 3, wherein said sugar is sucrose and said carbohydrate is invert sugar.

6. A tablet prepared in accordance with claim 5.

7. A method for preparing a direct compression vehicle comprising compacting a dry, free-flowing, generally spherical, porous agglomerate of 100 parts of a solid pulverized sugar in 0.1 to 30 parts of a matrix of a polyhydroxy compound, said agglomerate having a particle size of from about 12 to about 325 mesh and a moisture content of from about 0.1 to about 3 percent, said agglomerate being prepared by a process including the steps of:

1. Spraying a particulate solid sugar with an aqueous solution of binder;

2. Providing the resulting mixture with sufficient high intensity agitation to uniformly intermingle the sugar and binder and to build up agglomerates of a desired size; and

3. "Snowballing" the agglomerates to impart a general spherical shape thereto and to firm or densify the agglomerate,

and thereafter comminuting said compacted agglomerate to a desired particle size.

8. The product of claim 7.

9. A method for preparing a tablet comprising forming a uniform admixture of the product of claim 8 and active material, said product comprising at least 10 percent of said mixture, and compressing the mixture into tablets.

10. A tablet produced according to claim 9.