1 471 564

PATENT SPECIFICATION

(11) 1 471 564

(21) Application No. 41587/74 (22) Filed 24 Sept. 1974
(31) Convention Application No. 401 322
(32) Filed 27 Sept. 1973 in
(33) United States of America (US)
(44) Complete Specification published 27 April 1977
(51) INT CL² A61K 9/20
(52) Index at acceptance A5B 750 75Y

(19)



(54) DIRECT COMPRESSION TABLETTING COMPOSITION AND TABLETS PRODUCED THEREFROM

(71) We, CPC INTERNATIONAL INC., a corporation organized and existing under the laws of the State of Delaware, United States of America, of International Plaza, City of Englewood Cliffs, State of New Jersey, United States of America, 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:—

BACKGROUND OF THE INVENTION

(1) *Field of the Invention:*

This invention relates to direct compression tabletting compositions and the pharmaceutical tablets produced therefrom. More particularly, this invention relates to an improved direct compression tabletting composition prepared from a uniquely granulated mixture of a crystalline sugar such as dextrose monohydrate, and a maltodextrin having a measurable dextrose equivalent value not substantially above about 20. The improved direct compression tabletting compositions are capable of being directly compressed into commercially acceptable and hard tablets with large amounts of a variety of active materials. The new direct compression tabletting composition can be used as the sole binder and disintegrant in the tablets, the use of other adjuvants ordinarily used for this purpose being unnecessary.

(2) *Description of the Prior Art:*

The compressed tablet is the most popular unit dosage form for medicinal substances. The tablet as a dosage form can be traced to well over 1,000 years ago when a procedure for molding solid forms containing medicinal ingredients was recorded. As a result of the introduction of new carriers and compression vehicles, tablets are replacing all forms of pills, powders and capsules. Accordingly, tablets presently represent the largest production volume of all pharmaceuticals.

The reason for the widespread use of tablets is apparent, since tablets enable: (1) administration of medication in an accurate dose, (2) fast and accurate dispensing with less chance of error and contamination, (3) ease of administration, (4) administration in a form in which the time and area of contact between the active ingredient and the taste buds is reduced, thus obviating the physiological problems associated with the oral administration of drugs that possess a bitter taste and, in the case of coated tablets, with drugs that possess a disagreeable odor, (5) release of drugs at specific locations in the gastro-intestinal tract to: (a) prevent degradation of drugs sensitive to the low pH environment in the stomach, (b) prevent release of drugs that irritate the gastric mucosa in the stomach, (c) facilitate local action or preferential absorption at specific sites in the tract, (6) enhance stability by effecting a marked reduction in the surface of the drug exposed to the environment, (7) rapid production, and (8) economy and ease in storage, packaging and shipping.

It is well-known that in order to form a tablet of a given material, the material must possess fluidity and compressibility. It is essential that the material must flow uniformly from the hopper to the dies of the tablet press. Any defective flow of the material will affect the weight of the tablets, content uniformity, disintegration time, hardness, friability, and also the bioavailability of the active ingredient.

There are currently three basic methods for tabletting. They are the wet granulation method, the dry granulation method, and the direct compression method. The direct compression method is by far the most desired method from the standpoint of processing procedures, equipment and materials. However, only a very limited number of pharmaceutically acceptable substances possess enough cohesive strength and flowability to allow direct compression without previous granulation. Certain crystalline materials, such as potassium bromide and potassium chloride

can be compressed without preliminary treatment. Also, aspirin, phenolphthalein chlorohydrate can be directly compressed.

It has been stated that the ideal material to compress would be composed of crystals which, at the moment of compression, behaved like clay rather than rubber. The crystals should be such that on release of pressure they should not rebound into their original shape. Generally, most materials possess both plastic and elastic deformation properties. Therefore, most materials are not suitable for direct compression without previous granulation.

It has been estimated that about 20% of the materials used for tabletting in the pharmaceutical field may be compressed directly. In order to use this method to a considerable extent, many more materials should be modified by treatment or by use of additives. Modification may be undertaken, either by treating the material in some special way during earlier stages of preparation, or by adding a binder or excipient material which will surround the active ingredient and form an easily compressible carrier.

An ideal direct compression vehicle should possess the following properties: (1) low elastic modules, (2) high dislocation density, (3) inert, non-potent and non-toxic, (4) high degree of plastic deformation, (5) colorless, odorless, tasteless or without disagreeable taste, (6) free-flowing, (7) compatible with active ingredients and common additives like lubricants, colors, etc., (8) non-hygroscopic, or relatively low order of hygroscopicity, (9) fast disintegration properties, or should not delay the bioavailability of the drug, (10) limited range of particle size distribution, (11) stable against effects of ageing, and (12) reworkable and should possess high carrying capacity for active medicinal agents.

There are currently several available direct compression vehicles. They include spray-dried lactose; anhydrous lactose; microcrystalline cellulose; dicalcium phosphate dehydrate, unmilled; Cellutab; spray-congealed mannitol; Emcompress; Magnapol; Frodex; Di Pac; and Royal-T.

Microcrystalline cellulose is a natural cellulose in a specially processed form which makes it digestible. It normally produces good tablets with fast disintegration and drug release properties. It has been found to give better results if stored in a dry condition before use — exposure to a slightly humid atmosphere makes it compress less easily. It is quite fluffy by nature.

Spray-dried lactose has a heavy appearance when poured and is spherical in shape. It cannot be reworked, as the spherical shape is lost when ground. It has been disclosed that spray-dried lactose with 5—10% maize starch as a disintegrant and 0.5% magnesium stearate as a lubricant forms a useful direct compression base. However, it has the tendency to get brown in the presence of moisture, amines, phosphates, lactates and acetates. Borates and the stearate lubricants tend to retard the browning.

Dicalcium phosphate dehydrate has good flow and compressibility properties. The tablets from dicalcium phosphate are also easily embossed. The increased flow is believed to be due to its high density. It cannot be reworked. Due to its alkaline pH, stability of ingredients like Vitamin C or aspirin may be affected.

The vehicle mannitol, absorbs heat from the surroundings when going into solution, and results in good "mouth feel". Thus, it is commonly used in chewable tablets. It has been reported that a change in the compression characteristics of mannitol occurs when spray-congealing the product.

The vehicle known in the art as Cellutab is a spray-dried dextrose product. It has excellent flow characteristics. It is relatively coarse compared to other vehicles and contains approximately 8% moisture.

The product known in the art as Emcompress is essentially a blend of dicalcium phosphate dehydrate, unmilled; starch; Avacil; and magnesium stearate. It is free-flowing, self-lubricating and possesses good compression characteristics.

The vehicle known in the art as Royal-T is essentially an agglomerated mixture of a crystalline sugar such as dextrose and a maltodextrin such as Mor-Rex Code 1918. The preparation of this bold and new pioneering discovery in the direct compression vehicle art is described in British Patent No. 1,286,275, published August 23, 1972.

The vehicle known in the art as Di Pac is also a mixture of a crystalline sugar and a maltodextrin. The preparation of this product is generally described in the aforesaid British patent and, more specifically disclosed in U.S. Patent No. 3,642,535, granted February 15, 1972.

Although the direct compression method for preparing tablets is by far the method of choice by virtue of its simplicity, this method has several limitations which have hampered its use in the tabletting industry. These limitations include: (1) differences in the particle size, and bulk density between the diluent and the active ingredient may lead to stratification and variation in drug content of tablets, (2) unless the drug itself is easily compressible, the amount present is limited to a maximum of 25% of the tablet weight (Of course, the amount of vehicle and the weight of the tablet may be increased to reduce the percentage of active ingredient. Then there arises a question of economics and size of the tablet, a question that may be resolved only by wet granulation.), (3) the drug may interact with the vehicle, such as

amine compounds do with spray-dried lactose, and (4) static charges may develop on the drug during combination and mixing may prevent uniform distribution.

In light of the limitations mentioned hereinabove, the great majority of tabletting operations, therefore, have been forced to resort to other formulation techniques such as the wet and dry granulation methods. Thus, there is a continued search for an improved direct compression tabletting composition capable of being employed as a binder in the preparation of tablets by direct compression which are rapidly disintegrative, resistant to breakage and crumbling and compatible with the active material incorporated therein which forms the basis of the composition's utility.

According to one aspect of the present invention there is provided a process for producing a direct compression vehicle for tabletting comprising:—

(a) admixing a crystalline sugar with a maltodextrin having a measurable dextrose equivalent value not substantially above 20 to form a uniform admixture,

(b) contacting the said admixture with an aqueous solution containing dissolved therein a maltodextrin having a measurable dextrose equivalent not substantially above 20, the aqueous solution of dissolved maltodextrin being present in an amount sufficient to provide a damp mass of the uniform admixture and to cause granulation of the uniform admixture, and

(c) drying the granulated uniform admixture to a moisture content of less than 10% by weight, there being from 10% to 50% by weight of the maltodextrin in the so produced vehicle.

According to another aspect of the present invention there is provided a directly compressible material capable of being formed by direct compression at a pressure as low as 2000 pounds into hard substantially non-friable tablets having a Strong Cobb Hardness Unit (S.C.M.U.) valve of at least 6 comprising a vehicle as defined above in admixture with up to 80% by weight of the directly compressible material of at least one pharmaceutically active ingredient.

According to another aspect of the present invention there is provided a process for producing a directly compressible material for tabletting comprising:—

(a) admixing a crystalline sugar with a maltodextrin having a measurable dextrose equivalent value not substantially above 20 to form a uniform admixture,

(b) contacting the admixture with an aqueous solution containing dissolved therein a maltodextrin having a measurable dextrose equivalent value not substantially above 20, the aqueous solution of dissolved maltodextrin being present in an amount sufficient to provide a damp mass of the uniform admixture and to cause granulation of the uniform admixture,

(c) drying the granulated uniform admixture to a moisture content of less than 10% by weight to produce a material containing from 10% to 50% of the maltodextrin and

(d) admixing the dried granulated uniform admixture from (c) with up to 80% by weight of the compressible material of at least one pharmaceutical active ingredient.

According to another aspect of the present invention there is provided a directly compressed pharmaceutical composition in the form of hard and substantially non-friable tablets having a Strong Cobb Hardness Unit valve (S.C.H.U.) value of at least 6 when formed by direct compression at a pressure as low as 2000 lbs prepared from the directly compressible material obtained in the above process.

According to another aspect of the present invention there is provided a method for making a directly compressed pharmaceutical composition in tablet form comprising compressing the above-described directly compressible material, and a directly compressed pharmaceutical composition in tablet form when made by this method.

Preferably the vehicle contains from 15% to 35% by weight of said maltodextrin, more preferably from 20—30% by weight of said maltodextrin. The preferred crystalline sugar utilized is dextrose monohydrate.

It has been found that when a crystalline sugar such as dextrose monohydrate is granulated with at least 15% by weight of a maltodextrin having a measurable dextrose equivalent value not substantially above 20, the vehicle has an exceptionally high carrying capacity for a large variety of pharmaceutically active compounds. This result is quite unexpected, inasmuch as the compositions described in British Patent No. 1,286,275 have a relatively low carrying capacity for most pharmaceutically active compounds. Thus, the process of this invention provides a direct compression vehicle which can be directly compressed into commercially acceptable and hard tablets with large amounts of a variety of active materials and can be used as the sole binder disintegrant without the aid of other adjuvants ordinarily used for this purpose.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The crystalline sugars employed in the practice of the present invention include any type of crystalline sugar product, examples of which include dextrose, sucrose, lactose and blends thereof. Many of these crystalline sugars are well-known in the art and are conventional articles of commerce sold under various trade names. Such sugars are generally produced and crystallized by conventional

techniques. The preferred crystalline sugar employed in the practice of the present invention is dextrose, either in its monohydrate, anhydrous, or dehydrated form. Dextrose monohydrate is particularly preferred as the crystalline sugar to be utilized in the practice of the invention.

The maltodextrins having a measurable dextrose equivalent value not substantially above about 20 utilized in the practice of the present invention represent a known class of materials. The maltodextrins are also known as hydrolyzed cereal solids and such materials are commercially available under the tradenames Mor-Rex, manufactured and sold by CPC International Inc., Maltrin, manufactured and sold by Grain Processing Corporation, Frodex, manufactured by American-Maize Products Company, and Star-Dry 15, manufactured by A. E. Staley Manufacturing Company.

The terms "maltodextrins" and "hydrolyzed cereal solids" herein refer to those starch conversion products having a relatively small amount of dextrose and maltose. Generally, the dextrose content of the maltodextrins is less than about 2.4% by weight and the amount of maltose is less than about 9% by weight. As it is well-known in the industry, the dextrose equivalent value in a starch conversion product having a value above about 20 is generally referred to as a corn syrup solid; whereas starch conversion products having only a trace amount of dextrose are referred to as dextrins. The starch conversion products having a measurable dextrose equivalent value not substantially above about 20 and also having a trace amount of dextrose as hereinabove referred to, are known as hydrolyzed cereal solids or maltodextrins. It is the maltodextrins described hereinabove which are employed in the practice of this invention for the preparation of the direct compression tabletting compositions. The corn syrup solids having a dextrose equivalent value greater than about 20 are not suitable in the practice of the present invention, since these products do not possess the proper properties to effectively cause granulation and thereby produce a tabletting composition having a high carrying capacity for the active material. The corn syrup solids are also extremely hygroscopic, a property undesirable from the standpoint of flowability and mixing during the direct compression procedure for preparing the tablets.

The preferred maltodextrins or hydrolyzed cereal solids employed in the practice of the present invention are characterized as having a descriptive ratio of at least about 2. The descriptive ratio is the quotient of the sum of the saccharides having a saccharide content of 1 to 6 divided by the dextrose equivalent value. An especially preferred class of maltodextrins employed in the practice of the present invention are derived from waxy starch hydrolysates and have a dextrose equivalent value in the range of from 9 to 13 and a descriptive ratio of at least 2. These starch hydrolysates or maltodextrins are prepared by the method disclosed in British Patent No. 1,203,048, particularly Examples III and IV. These waxy starch hydrolysates or maltodextrins are commercially available under the tradename of Mor-Rex Code 1918, manufactured and sold by CPC International Inc.

The term "measurable dextrose equivalent value" (D.E.) referred to herein, is defined as the reducing value of the hydrolysate material compared to the reducing value of an equal weight of dextrose, expressed as percent, dry basis, i.e.,

$$D.E. = \frac{\text{Reducing Value of Hydrolysate Material}}{\text{Reducing Value of Dextrose}} \times 100$$

In the above equation, an equal weight of each of dextrose and the hydrolysate material is involved. The term dextrose equivalent value of a starch hydrolysate is a common expression in the art for describing the total reducing sugars content of a material calculated as dextrose and expressed as percent, dry basis.

An aspect of the invention comprises admixing (e.g., by spraying or by any other convenient means) an aqueous solution containing from 5 to 60 weight/volume percent of the above-described maltodextrin with a uniform mixture of a crystalline sugar and 10% to 50% by weight of the above-described maltodextrin. The admixing of the aqueous solution of the maltodextrin should be conducted while the uniform mixture of the crystalline sugar and the maltodextrin is being agitated to achieve uniform and homogeneous contact of the crystalline sugar particles and the maltodextrin with the aqueous solution containing the maltodextrin. Preferably, the aqueous solution will contain from 10% to 40% weight/volume of the maltodextrin.

The solution containing the maltodextrin is preferably admixed with the uniform mixture of the crystalline sugar and maltodextrin at ambient temperatures and pressures. Slight deviations may be imposed, provided that such conditions do not adversely affect the compositions.

The amount of the solution containing the maltodextrin utilized may vary, depending on the characteristics of the crystalline sugar, the amount of moisture in the homogeneous mixture of the crystalline sugar and/or the maltodextrin, etc. Generally, the amount of the

aqueous solution containing the maltodextrin utilized will be an amount such that its admixture with all of the materials provides a thoroughly admixed damp mass. Such amounts will generally be in the range of from about 20 ml. to about 100 ml. of the aqueous solution per one kilogram (kg.) of the uniform mixture of the crystalline sugar and the maltodextrin. A suitable "damp mass" can be obtained under ordinary conditions utilizing from about 40 ml. to about 60 ml. of the aqueous solution per one kilogram (kg.) of the uniform mixture.

After the aqueous solution containing the maltodextrin is added to the uniform mixture of the crystalline sugar and the maltodextrin, the entire admixture is thoroughly mixed to cause granulation. The granulated product is thereafter dried to a moisture content of less than 10% by weight, preferably less than 5% by weight moisture. The dried granulated product may be screened to provide a more homogeneous screen size. The final dried and screened product can be used "as is" as a direct compression tabletting composition whereupon it can simply be admixed with the desired active material and directly compressed into tablets.

The crystalline sugar hereinabove described may be admixed in either dry or wet form with the maltodextrin. Preferably, the crystalline sugar, e.g., dextrose monohydrate, is employed in its centrifuge cake form following crystallization, which cake has been washed and centrifuged so that the water content in the cake (excluding water of hydration) will be sufficient to provide the necessary amount of water to initially granulate the crystalline sugar with the maltodextrin. (When water of crystallisation is present the total water content comprises up to 16% of the cake weight). In this respect, the amount of water necessary to initially granulate the above-described composition of this invention, excluding water of hydration, is preferably from 1—8% by weight of the total composition. The initially granulated admixture may be dried, providing the amount of maltodextrin exceeds about 10% by weight of the total mixture. However, it has been found that in order to provide a direct compression vehicle having a high carrying capacity, it is necessary to spray the admixture of the crystalline sugar and maltodextrin with an aqueous solution containing dissolved therein at least about 5% weight/volume of the maltodextrin.

As stated hereinabove, the amount of maltodextrin employed in the direct compression compositions of this invention is critical. The final composition will generally contain more than about 10% by weight of the maltodextrin which is introduced into the matrix of the crystalline sugar composition, either by the initial blending of the maltodextrin with the crystalline sugar and/or by the admixture treatment with the aqueous solution containing the maltodextrin which follows the blending of the crystalline sugar and the maltodextrin. Preferably, the tabletting composition will contain from about 15% to about 35% by weight of the maltodextrin based on the total amount of the direct compression vehicle. Particularly good results are obtained when the level of maltodextrin in the tabletting composition is in the range of from about 20% to about 30% by weight.

In one typical example of the above-described process of preparing the direct compression vehicle for tabletting, a premix is formed by admixing 80 parts by weight of dextrose monohydrate crystals and 20 parts by weight of a maltodextrin having a dextrose equivalent value in the range of from about 9 to about 13, the water content of the mixture being in the range of from about 2% to about 15% by weight. The mixture is thereafter thoroughly agitated and sprayed with an aqueous solution containing the above-described maltodextrin in an amount such that a damp mass is formed. The amount of maltodextrin dissolved in the aqueous solution is preferably 10% to 40% by weight based on the volume of the solution (g./100 ml.). In a typical example, 50 ml. of a 20% weight/volume aqueous solution containing the aforedescribed maltodextrin is sprayed onto 1 kg. of the dextrose-maltodextrin admixture (800 grams of dextrose and 200 grams of maltodextrin). The sprayed mixture is thereafter dried to a moisture content of less than about 10%, preferably less than about 5% by weight. Alternatively, the granulated mixture may be wet screened through a number 6 sieve prior to drying to the final desired moisture content. However, satisfactory results are obtained by drying the granulated mixture prior to screening.

The particle size of the direct compression vehicle for tabletting is rather important. Most pharmaceutical compounds have a particle size of less than 100 mesh. Accordingly, the carrier must be coarser or have a particle size larger than the pharmaceutical compound. If the particle size of the direct compression vehicle is broadly dispersed, stratification will occur and uniform amounts of ingredients in the respective tablets will not be successfully accomplished. Therefore, it is important that the particle size of the direct compression vehicles have a relatively narrow particle size distribution. The particle size distribution found to be most desirable should be such that the particles of the composition fall within the range of −20 to about +200. However, better results are obtained wherein the vehicle has a particle size in the range from about −30 to about +150 and, more preferably, in the range of from about −40 to about +100.

In the preferred preparation of pharma-

ceutical tablets by the present invention, at least one pharmaceutically active ingredient is thoroughly mixed by any suitable dry blending technique with the above-described direct compression vehicle in relative amounts required to provide a resultant superficially dry, free-flowing material directly compressible into tablets, and the material is then tabletted by direct compression.

Active ingredients contemplated to be employed in the preparation of tablets by the present invention constitute all active ingredients compatible with the above-described direct compression vehicles. The present invention is particularly suitable for the use in preparing tablets containing the well-known pharmaceutically active materials. Specific examples of pharmaceutically active ingredients which advantageously may be tabletted by the present invention include ascorbic acid, sodium salicylate, acetaminophen, sodium bicarbonate, aluminum hydroxide, magnesium trisilicate, Vitamin E acetate, calcium lactate, ferrous sulfate and mixtures thereof.

Particularly preferred pharmaceutically active materials include ascorbic acid (Vitamin C), acetaminophen (APAP), aluminum hydroxide in combination with sodium bicarbonate (an antacid); citric acid in combination with sodium bicarbonate (an antacid), and magnesium trisilicate in admixture with aluminum hydroxide (in a ratio of 2:1, respectively, as another antacid).

The pharmaceutically active materials may be present at relatively high levels in the tablets produced from the vehicles of the present invention. These tablets, even when they contain a high level of the active material, possess acceptable hardness and friability values, not possessed by other sugar-based tablets such as those described in British Patent No. 1,286,275. The tablets of the present invention may be prepared by direct compression utilizing relatively small amounts of pressure in high speed tabletting machines. Due to the unusual structural integrity of the direct compression tabletting vehicles of the present invention, the vehicles may be simply dry mixed with the desired active materials, and, alternatively with conventional tabletting aids such as fillers, lubricants and the like, to obtain active ingredient-containing formulations which are directly compressible into tablets in conventional tabletting equipment. These directly compressed tablets exhibit the desired hardness and friability even though they are sugar-based compositions. The fact that the tablets are sugar-based and also contain the new relatively tasteless maltodextrins renders the tablets quite suitable for chewable type formulations. In other words, the sugar in the tablets masks the undesirable flavor of many active materials. Thus, the present invention provides pleasant tasting chewable tablets which may contain a high level of active material therein and still have the appropriate hardness and friability necessary for commercial manufacture and shipping of these tablets.

The novel tabletting vehicles of the present invention are also characterized as having porperties which satisfy the requirements of a binder for the active material and a disintegrant for the tablet in an aqueous medium. Thus, the materials of the present invention are capable of being directly compressible into tablets having commercially acceptable hardness, friability and disintegration properties merely by blending the vehicles of the present invention with an active material and compressing the mixture with conventional tabletting equipment.

The actual reason why the novel tabletting vehicles of the present invention are capable of carrying relatively high levels of active materials and still maintain commercially acceptable hardness, friability and disintegration properties when directly compressed at low pressures is not fully understood. These unusual properties are not as evident in the "agglomerated" dextrose-maltodextrin tabletting compositions described in British Patent No. 1,286,275. Not wishing to be bound by any theory, it is believed, however, that the addition of the aqueous solution containing the maltodextrin dissolved therein to the uniform mixture of the crystalline sugar and maltodextrin achieves a form of granulation which provides a unique structural integrity in the vehicle. This structural integrity, it is believed, provides a matrix whereby the active material can be locked therein and the resulting composition thereby possesses a low elastic modulus, a high dislocation density and a high degree of plastic deformation. Since the vehicles of the invention are free-flowing, non-hygroscopic and compatible with active ingredients and common additives, as well as having fast disintegration properties, they are excellent direct compression vehicles.

It is the structural integrity of the direct compression vehicles of the invention which makes it possible for the granulated mixture of a crystalline sugar such as dextrose and from 10% to 50% by weight of a water soluble maltodextrin having a measurable dextrose equivalent value not substantially above 20, wherein said granulated mixture contains less than 10% by weight moisture, to be formed into hard, substantially non-friable tablets by direct compression when in admixture with up to 80% by weight of at least one pharmaceutically active ingredient, said tablets having a Strong Cobb Hardness Unit Value (S.C.H.U.) of 6 or more.

In many instances, the tablets of the invention which contain the aforesaid active ingredients will have a hardness value greater than

7 S.C.H.U. and quite often greater than 9 S.C.H.U. The hardness values referred to herein are generally obtainable by compressing the dry blended vehicle of the present invention with the active material at pressures as low as 2,000 pounds and, more consistently, such hardness values are obtained when the dry mix is compressed at pressures of 3,000—5,000 pounds (as is generally the case in some commercially available tabletting machines). The hardness and friability properties are further improved when the level of maltodextrin is increased to a value of from 15—35%, the most preferred levels being in the range of from 20—30% by weight.

A preferred embodiment of the invention comprises a directly compressed pharmaceutical composition in tablet form, comprising a dry-blended mixture of up to 80% by weight of a pharmaceutically active ingredient such as ascorbic acid or acetaminophen and at least 20% by weight of a granulated mixture of dextrose and 15% to 35% by weight of a water soluble maltodextrin having a measurable dextrose equivalent value not substantially above 20, said granulated mixture containing less than 10% by weight moisture, said directly compressed pharmaceutical composition having a Strong Cobb Hardness Unit (S.C.H.U.) value of at least about 6. Typically, the preferred tablets of the invention will contain from 15% to 35% by weight of the pharmaceutically active ingredient. Of course, the level of active ingredient in the tablet having the desired hardness value will vary from one active ingredient to another. For example, higher levels of ascorbic acid can be tolerated as compared to Vitamin E acetate to attain the desired hardness values with the vehicles of the present invention at comparable pressures of preparation. In any event, it is quite unexpected that a crystalline sugar such as dextrose based vehicle is capable of providing substantially non-friable, hard tablets when directly compressed with high levels of active ingredients.

As mentioned hereinabove, various known additives such as lubricants, fillers, colors, disintegrants, binders and mixtures thereof may be added to the novel vehicles of the present invention for their known purposes. Such additives include magnesium stearate, talc, Cab-O-Sil (Registered Trade Mark), Cellutab, Sta-Rx 1500 and Magnapol. These additives may be present in amounts ranging from about 0.25% by weight to about 10% by weight or more. The amount of additive, such as the suitable lubricant, will generally depend on the active material employed, and the speed and pressure of the tabletting machine utilized.

Because of the plethora of terms that are in common use in the art, a few definitions are made to simplify the present application and permit it to be more concise.

The terms "tablet hardness", "tablet friability", "weight variation", "tablet disintegration", and "accelerated stability study" are defined as follows:

Tablet Hardness — a measure of the strength of tablets (average of ten or more tablets) and their ability to retain their physical integrity, expressed in terms of Strong Cobb Hardness Units (S.C.H.U.), as determined by conventional procedure using a Strong Cobb Hardness tester of the Strong-Cobb-Arner Company, Cleveland, Ohio, and the average of these readings is reported herein as "mean hardness". The hardness tester was actuated by hand at 60±5 strokes per minute.

Tablet Friability — a measure of the tendency of tablets (average of ten or more tablets) to crumble and dust, expressed in terms of percent weight loss, as determined by the "Roche" test described in the *Journal of the American Pharmaceutical Association*, Scientific Edition, Vol. 45, pages 114—116 (1956). This is conducted by sampling ten or more tablets from each batch by first de-dusting the tablets and weighing the same. The tablets are then subjected to the friability test in a Roche Friabilator at 20 revolutions per minute. The tablets are allowed to roll and fall for four minutes and thereafter de-dusted and weighed again. The loss of weight is reported as percentage loss from the original weight. It is well-known that an active ingredient-containing tablet displaying a weight loss of less than about 1% generally is considered to have acceptable friability. Such a tablet characteristic is herein defined as "substantially non-friable".

Weight Variation — this test is conducted by accurately weighing ten or more tablets from a batch on a Mettler Balance and the high and low limits of the tablet weights are noted and the mean of these two limits is taken.

Tablet Disintegration — the time observed for tablets (range of six tablets) to disintegrate in water, as determined by a modification, in which the use of this is eliminated, of the procedure for uncoated tablets described in *Pharmacopeia of the United States of America*, 16th. Edition, pages 934—936 (1960).

Accelerated Stability Study — this test is conducted by taking tablets from each batch and packing the same in a wide-mouthed bottle which is tightly stoppered and storing the same in a tray-type dryer at 50°C for seven days. The tablets are then removed and subjected to tests for hardness, disintegration, and friability. Any change in physical appearance is thereafter noted.

The following examples further illustrate the present invention and will enable others skilled in the art to understand it more completely. It should be understood, however,

that the invention is not limited solely to the particular examples given below. The parts are parts by weight, unless otherwise indicated.

EXAMPLE 1.

Evaluation of Pressure-Hardness Profile on Dextrose Monohydrate, Dehydrated Dextrose, Anhydrous Dextrose, And Royal-T Obtained on Carver Press

The pressure-hardness profiles were obtained from several dextrose products and Royal-T ("agglomerated" mixture of dextrose monohydrate wet filter cake and about 5% by weight Mor-Rex Code 1918) on a Carver Press. This test was strictly comparative.

Prior to the experiment, the die walls and punch faces of the Carver Press, which was utilized to measure the pressure-hardness profiles, were swabbed with 5% solution of stearic acid in chloroform and allowed to dry. One-half gram of the test material was placed in the die and compressed on the Carver Press at various pressures, maintaining a constant dwell time of ten seconds in all cases. The compressed tablet was ejected from the die by pushing out with the upper punch and its hardness (breaking strength) was determined on the Strong Cobb Hardness tester. Five tablets were compressed at each pressure level, and their average hardness value determined. Table 1 indicates the pressure-hardness values of dextrose monohydrate, dehydrated dextrose, anhydrous dextrose and Royal-T.

TABLE 1

Pressure-Hardness Comparison Expressed in S.C.H.U.

	HARDNESS VALUE IN S.C.H.U. AT:					
SUBSTANCE TESTED	1000 lbs.	2000 lbs.	4000 lbs.	6000 lbs.	8000 lbs.	10,000 lbs.
Regular Dextrose (dextrose monohydrate)	N.T.(a)	0.75	6.5	9.5	3.0	2.0
Dehydrated Dextrose	N.T.	4.2	6.0	0.0	N.T.	N.T.
Anhydrous Dextrose	N.T.	Did not form tablets.				
Royal-T	N.T.	9.4	21.6	B.S.	B.S.	B.S.

(a) N.T. = Not Tested

(b) B.S. = Beyond Scale

The above data are indicative that all of the dextrose exhibit poor compressibility and, therefore, they are not suitable as direct compression vehicles. The Royal-T product without any active ingredient exhibited a satisfactory compressibility profile.

EXAMPLE 2.

Evaluation of Mixtures of Various Ratios of Dextrose Monohydrate and Maltodextrin Prepared by Different Methods, on Carver Press

(a) *Dry Blends of Dextrose Monohydrate and Maltodextrin:*

Four (4) one kilogram batches of a dry blend of dextrose monohydrate and a maltodextrin (Mor-Rex Code 1918) were prepared in ratios of 95/5, 80/20, 65/35 and 50/50, respectively, in a Hobart Bowl Mixer. Each of the blends was mixed for 7 minutes, and subjected to a pressure-hardness profile evaluation on a Carver Press. The results are set forth in Table 2.

TABLE 2

BLEND		HARDNESS VALUE IN S.C.H.U. AT:				
Dextrose Monohydrate % by Wt.	Maltodextrin % by Wt.	2000 lbs.	4000 lbs.	6000 lbs.	8000 lbs.	10,000 lbs.
95	5	4.5	14.4	22.8	25.8	17.4
80	20	6.4	22.4	B.S.(a)	B.S.	B.S.
65	35	5.2	25.4	B.S.	B.S.	B.S.
50	50	5.6	27.4	B.S.	B.S.	B.S.

(a) B.S. =Beyond Scale

Based upon the data in Table 2, it is quite evident that dry blends of a crystalline sugar such as dextrose and a maltodextrin would not be suitable as a vehicle for carrying high levels of a pharmaceutically active ingredient, since hardness values of the mixture above 2,000 pounds are generally less than 6.

(b) *Dextrose Monohydrate Granulated with Aqueous Solutions Containing a Maltodextrin:*

Five (5) one kilogram batches of dextrose monohydrate were each granulated with 30 ml. of a solution containing 5%, 10%, 20%, 30% and 40% W/V of a maltodextrin (Mor-Rex Code 1918, a waxy starch hydrolysate having a D.E. of about 9—13 which readily dissolves in water in concentrations of up to 40% W/V). The granulation was accomplished by slowly adding the maltodextrin solution to the dextrose to obtain a damp mass. The damp mass was thoroughly mixed in a Hobart Bowl Mixer. The damp mass was screen through a No. 6 sieve and dried in an oven to a final moisture content of 8.2% to 8.8%. The moisture content was determined on an Ohaus Moisture Determination Balance. The heating element was set at a point corresponding to 100°C, and the timer was set for 60 minutes. The loss in weight was noted every 15 minutes until there was no further loss. The percentage moisture lost was read off the scale directly. All the granulations were dry screened to obtain a particle size such that 100% passed through a No. 16 screen and 49% passed through a No. 80 screen. (The "screening" described herein and throughout this specification was conducted on a Syntron Test Sieve Shaker, Model: TSS25B, manufactured by the Syntron Company, Homer City, Pennsylvania, and U.S. Standard Sieves (A.S.T.M. specifications), manufactured by Fisher Scientific Company, New York, New York.) All the granulations were subjected to the pressure-hardness profile evaluation on the Carver Press. The details of the amounts of the solvents used in each batch and the results of the pressure-hardness profile are set forth in Table 3.

TABLE 3

Quantity of Dextrose (grams)	Solvent System Used to Granulate (W/V Aq. Sol. #1918)	Quantity of Solvent Used	HARDNESS VALUE IN S.C.H.U. AT: 2000 lbs	4000 lbs	6000 lbs	8000 lbs	10,000 lbs
1000	5%	30ml.	5.0	9.2	11.2	14.4	4.0
1000	10%	30ml.	5.0	12.2	16.6	17.6	17.2
1000	20%	30ml.	5.0	14.6	18.4	22.8	25.0
1000	30%	30ml.	5.6	14.8	23.6	28.0	23.2
1000	40%	30ml.	6.0	14.4	22.8	26.4	9.6

The data in Table 3 clearly indicate that simple granulation of a crystalline sugar such as dextrose with an aqueous solution containing a maltodextrin does not provide a tabletting composition having commercially acceptable hardness values at the commercially utilized pressures of 2,000 pounds.

EXAMPLE 3.

Granulation of Dextrose Monohydrate-Maltodextrin Mixture with Aqueous Solutions Containing Maltodextrin

This experiment illustrates the granulation of various levels of a mixture of dextrose monohydrate and maltodextrin with various solutions containing maltodextrin dissolved therein.

A calculated quantity of dextrose monohydrate was screened through a No. 20 sieve (to remove any lumps) and mixed with varying amounts of maltodextrin (Mor-Rex Code 1918) in a Hobart Bowl Mixer for 5—7 minutes. The weight of the mixture in each batch was one kilogram. To each mixture there was added 50 ml. of a solution containing dissolved therein the maltodextrin (Mor-Rex Code 1918) to obtain a damp mass. The damp mass was mixed an additional 7 minutes following the addition of the maltodextrin solution to cause granulation, whereupon the granulated damp mass was wet screened through a No. 6 sieve and dried in an oven to a final moisture content of 8.2% to 8.6%. The dried, granulated products were evaluated on a Carver Press to ascertain their ability to form commercially acceptable tablets. The details of the preparation and the results of the hardness profile evaluation are set forth in Table 4.

TABLE 4

Quantity of Dextrose (grams)	Quantity of Malto-dextrin (grams)	Solvent System Used to Granulate (W/V Aq. Sol. of Maltodextrin)	HARDNESS VALUES IN S.C.H.U. AT: 2000 lbs.	4000 lbs.	6000 lbs.
900	100	20%	9.8	25.0	B.S.(a)
850	150	20%	14.3	28.0	B.S.
800	200	10%	11.4	24.0	B.S.
800	200	20%	10.8	22.2	B.S.
800	200	30%	10.0	22.2	B.S.

(a) B.S. = Beyond Scale

The above data are indicative that the granulation of a mixture of a crystalline sugar such as dextrose and at least about 10% by weight of a maltodextrin with an aqueous solution containing dissolved therein a maltodextrin provides a tabletting composition having excellent hardness profiles at commercially utilized pressures. Based upon the above hardness profile values of the foregoing granulations, these compositions can be used as direct compression tabletting compositions, whereas the compositions described in Examples 1 and 2 (with the exception of Royal-T, which has limited capacity to carry high levels of pharmaceutical materials) are not acceptable as direct compression vehicles.

EXAMPLE 4.

Evaluation of Compressibility and Carrying Capacity of Dextrose-Maltodextrin Granulated Direct Compression Vehicles

In this experiment, the compressibility and carrying capacity of the dextrose-maltodextrin granulated direct compression vehicle was evaluated. The granulated vehicle used herein was prepared in the same manner described in Example 3 by admixing 80% by weight of dextrose monohydrate with 20% by weight of the maltodextrin (Mor-Rex Grade 1918, a waxy starch hydrolysate having a D.E. of 9—13) and thereafter granulating the admixture with a 20% W/V aqueous solution of the maltodextrin (50 ml. of solution per 1,000

grams of dextrose monohydrate and maltodextrin admixture). The particle size of the direct compression vehicles utilized in this experiment was such that they passed through a No. 20 sieve.

The vehicles with and without the active ingredient were formed into tablets in a Stokes Model B—2, 16 station rotary tablet machine which had been set up with four $\frac{3}{8}$" s.c. tooling and a standard feed frame to enable gravity feed. All samples of the granulation were first inspected for physical appearance. In each instance, 0.5% concentration of magnesium stearate was used as a tablet lubricant. The tablets were prepared at the maximum load obtainable, which was determined by gradually increasing the press pressure until a distinct knocking sound caused by a pressure overload was heard, and then easing off on the pressure until the knocking sound ceased. The hardness values for tablets produced at maximum pressure were obtained and recorded. The operating press pressure was then reduced to produce tablets with hardness values approximately one-third of the maximum and two-thirds of the maximum readings. In this manner, tablets were obtained with three different hardness values, ranging from one-third to maximum hardness for each material evaluated. The tablets were evaluated for weight variation, hardness, friability, disintegration and stability. The die fill in all cases was adjusted so as to produce tablets weighing 0.5 gram. The flow of the base from the hopper to the dies under operating conditions was observed and noted.

Each of the active ingredients (ascorbic acid (granular), as supplied by Hoffman-LaRoche Inc. and acetaminophen (APAP), special powder, supplied by S. B. Penick & Co.) were mixed with the granulated direct compression vehicle in a proportion of 50%—50% in a Hobart Bowl Mixer for 5—7 minutes. Then, 0.5% to 0.75% by weight of magnesium stearate was mixed with the vehicle and active ingredient as a lubricant. The mixture was then fed into the tablet press, described above in this Example. In the event that tablets were not formed with a given mixture of active ingredients and granulated direct compression vehicle, the ratio was altered to increase the amount of vehicle while lowering the level of the active ingredient. This procedure was followed until the ratio which produced acceptable tablets under identical operating conditions was produced.

"Acceptable" tablets are defined as those which possess minimum friability, effective hardness and rapid disintegration time. Samples of tablets produced at different pressures were taken and subjected to tests for hardness, weight variation, friability, disintegration and stability. The details of these experiments and their results are tabulated in Table 5.

TABLE 5

Formulation % Active Ascorbic Acid (1)	(2) APAP	% Lubricant Magnesium Stearate	EVALUATION (3) Tablet Hardness In S,C.H.U.	Tablet Disintegration Time In Min.	Friability %
--	--	0.5	a. 24.1	a. 7.5	a. 0.12
--	--	--	b. 17.3	b. 7.5	b. 0.22
--	--	--	c. 8.8	c. 7.0	c. 0.21
30	--	0.5	7.5	10.5	0.46
--	25	0.75	10.0	10.5	0.90

(1) Ascorbic Acid (granular).
(2) APAP (special powder, S.B. Penick & Co.).
(3) Ten tablets of each batch were subjected to this test using a Strong Cobb Hardness Tester and the averages of these readings were reported as "Mean Hardness" in Strong Cobb Hardness Units. The hardness tester was actuated by hand at 60±5 strokes per minute.

In each instance, the granulated direct compression composition was indicated as having excellent compressibility characteristics and carrying capacity. The granulated direct compression composition exhibited excellent flow from the hopper to the dies of the tablet press. However, the flow properties of the APAP compositions were not quite as good as the ascorbic acid containing compositions. The weight variation of the tablets was also excellent.

The tablets prepared hereinabove were also subjected to an Accelerated Stability Study, wherein the tablets from each batch were packed in a wide-mouth bottle, which was tightly stoppered and stored in a tray-type drier at 50°C±2°C, for seven (7) days. The tablets were then removed and subjected to tests for hardness, disintegration and friability. Any change in physical appearance was also noted. The comparative results of the Accelerated Stability Study are set forth in Table 6.

TABLE 6

FORMULATION			ACCELERATED STABILITY STUDY (1)							
% Active		% Lubricant	Hardness S.C.H.U.		Disintegration Time In Min.		% Friability		Physical Appearance (4)	
Ascorbic Acid (2)	APAP (3)	Magnesium Stearate	Before	After	Before	After	Before	After	Before	After
--	--	0.5	24.1	B.S.	7-1/2	8-1/4	0.12	0.10	White	A
			17.3	B.S.	7-1/2	7-3/4	0.22	0.06	White	A
			8.8	B.S.	7.0	7-1/2	0.21	0	White	A
30	--	0.5	7.5	B.S.	10-1/2	11.0	0.46	0.08	White	A
--	25	0.75	10.0	20.4	16.0	16.0	0.9	0.06	White	A

(1) Stored at 50°C for 7 days.

(2) Ascorbic acid granular.

(3) APAP (special powder, S.B. Penick & Co.).

A = Acceptable

The results tabulated in Table 6 clearly reveal that the granulated direct compression vehicles of the invention provide excellent tablets. The Accelerated Stability Studies indicate that there is a substantial increase in tablet hardness with a noticeable decrease in friability and no change in the disintegration time of the tablets. All of the tablets had an excellent white appearance.

EXAMPLE 5.

In this experiment, the flowability, compressibility, and carrying capacity of granulations of different particle sizes are compared.

In each of the tests, the vehicle was prepared by the granulation process of Example 3, wherein 80% by weight of dextrose monohydrate was admixed with 20% by weight of the maltodextrin (Mor-Rex Code 1918, a waxy starch hydrolysate having a D.E. of 9—13) and thereafter the admixture was granulated with a 20% W/V aqueous solution of the maltodextrin (50 ml. of the solution per 1,000 grams of dextrose monohydrate and maltodextrin admixture). Each of the granulations tested was passed through a Fitz Mill using a suitable screen (#2A or #1) with knives forward at medium speed. The comminuted granulations were then hand sieved so as to obtain three particle size ranges, *viz.*: −20+60, −40+100, and −100+200. The granulations (except the controls which did not contain active ingredient) were dry blended with sodium bicarbonate, aluminum hydroxide gel, dried; magnesium trisilicate, dried; (all three supplied by Rugar Chemical Co., New York), acetaminophen (APAP) regular powder, (as supplied by S. B. Penick & Co.) as indicated in Table 7. Each of the samples tested contained a lubricant. The mixtures of the vehicle and the active ingredient were placed in a Colton Model #204, 4 Station Rotary tablet machine which had been set up with $\frac{3}{8}$" S.C. tooling and a standard feed frame to enable gravity feed. The die fill in all cases was adjusted so as to produce tablets weighing 0.5 gram. The flow of the base from the hopper to the dies under operating conditions was observed and noted. Also, each of the mixtures and resulting tablets was inspected for physical appearance. The tablets were prepared at three different pressure levels as described hereinabove. The results of the tests are summarized in Table 7 hereinbelow.

TABLE 7

DETAILS OF EXPERIMENTS ON CAPACITIES OF DIFFERENT PARTICLE SIZE RANGES OF GRANULATED VEHICLE

Granulation (particle size range)	FORMULATION						EVALUATION		
	% ACTIVE				% LUBRICANT				
	Sodium Bicarbonate	APAP	Magnesium Trisilicate	Aluminum Hydroxide Gel, Dried	Magnesium Stearate	Talc	Hardness In S.C.H.U.	Disintegration in Min.	% Friability
−20+60	--	--	--	--	0.75	--	28.5	12.0	0.03
							17.2	12.5	0.03
							8.5	10.0	0.13
	30	--	--	--	1.0	--	7.5	20	0.6
	--	15	--	--	1.75	--	6.5	30	4.0
	--	--	25	--	2.0	1.0	8.5	70	0.17
	--	--	--	25	1.0	1.0	10.0	82	0.1
−40+100	--	--	--	--	0.75	--	27.6	13.5	0.04
							18.0	12.5	0.01
							11.0	10.0	0.08
	35	--	--	--	0.75	--	8.0	15.0	0.9
	--	15	--	--	2.0	1.0	7.0	24	1.1
	--	--	25	--	2.0	1.0	7.0	85	0.13
	--	--	--	25	1.0	1.0	7.5	92	0.11
−100+200	--	--	--	--	0.75	--	19.0	12.0	0.05
							9.5	12.0	0.14
	30	--	--	--	1.0	--	5.0	20	0.29
	--	15	--	--	2.0	--	5.0	14	Caps
	--	--	20	--	2.0	1.0	6.0	62	0.2
	--	--	--	20	1.0	1.0	8.5	79	0.19

The evidence set forth in Table 7 demonstrate that all three particle size ranges of −20+60, −40+100 and −100+200 have excellent compressibility characteristics. In general, the −40+100 particle size range carried the maximum amount of actives. At the pressures utilized in the experiments, sodium bicarbonate was carried by all three particle size ranges at the maximum level, while APAP was carried the least. The flowability of the granulations alone or in admixture with the active was good to excellent for all formulations. The weight variation (U.S.P.) test was also good to excellent. However, the −20+60 and −40+100 particle size ranges illustrated the best uniformity.

EXAMPLE 6.

This experiment compares the vehicles of the present invention alone or in combination with various actives at various moisture content levels.

The vehicle used in this experiment was prepared in the same manner as previously described in Examples 3—5. The vehicle was a granulated admixture of 80% by weight of dextrose monohydrate and 20% by weight of the maltodextrin granulated with a 20% W/V solution of a maltodextrin. The final granulated admixture was screened to a particle size range of −40+100. The granulation was dried in an oven at different temperatures and for different lengths of time so as to obtain at least three different moisture content levels, 8.0%, 4.0% and 2.0%, by weight. The tablets were prepared on a Colton Model #204, 4 station rotary tablet machine in the same manner described in the previous examples. The tablets were evaluated for weight variation, hardness, friability and disintegration. All four active medicinal ingredients (described in Table 8) which had been dry blended with the vehicle of the invention were selected to evaluate the capacities of the granulations in the same manner previously described. The details of the experiment are set forth in Table 8.

As it can be seen from the data in Table 8, there was no significant difference in the compressibility and carrying capacity of the granulation at higher and lower moisture content levels. The tablets made from the granulations with lower moisture content were checked for capping and capping of the tablets was not observed. Although no significant role was attributed in the tablets having less than 10% by weight moisture, it is desirable to keep the moisture content as low as possible from the standpoint of stability of the active medicinal ingredient (e.g., some actives are moisture sensitive).

TABLE 8

DETAILS OF EXPERIMENTS ON CAPACITY OF GRANULATED VEHICLE AT DIFFERENT MOISTURE CONTENT LEVELS

FORMULATION

Granulated Vehicle % Moisture Content	% ACTIVE				% LUBRICANT		EVALUATION			
	Sodium Bicarbonate	APAP	Magnesium Trisilicate	Aluminum Hydroxide Gel, Dried	Magnesium Stearate	Talc	Capping If Any	Hardness In S.C.H.U.	Disintegration In Min.	% Friability
8.2 (±0.2%)	--	--	--	--	0.75	--	--	11.0	10.0	0.08
	35	--	--	--	0.75	--	--	8.0	15.0	0.9
	--	15	--	--	1.25	--	--	7.0	24	1.1
	--	--	25	--	2.0	1.0	--	7.0	85	0.13
	--	--	--	25	1.0	1.0	--	7.5	92	0.11
4.2 (±0.2%)	--	--	--	--	0.75	--	--	10.2	9.0	0.06
	35	--	--	--	0.75	--	--	8.7	13.0	0.93
	--	15	--	--	1.25	--	Slight	8.2	18.0	0.63
	--	--	25	--	2.0	1.0	--	6.5	79	0.11
	--	--	--	25	1.0	1.0	---	8.2	89	0.2
2.2 (± 0.2%)	35				0.75			10.8	8.5	0.07
					0.75			8.0	14.5	0.57
		15			1.25			8.7	13.0	0.71
			25		2.0	1.0		7.0	82	0.15
				25	1.0	1.0		8.0	93	0.13

EXAMPLE 7.

This experiment was performed to evaluate the carrying capacities of the granulations of the present invention with additional active medicinal agents.

Each of the active ingredients (ascorbic acid (type S); calcium salicylate; ferrous sulfate (exsiccated); and Vitamin E acetate; 50% S.D.) were mixed with the granulated vehicle of Example 3 and tested in exactly the same way as described in Example 4. Each of the blended mixtures of granulated vehicle and active medicinal ingredient had excellent flow characteristics from the hopper to the tablet die. The tablets also had a very narrow weight variation. All of the active ingredients were carried very well and the resulting tablets were of extremely high quality, having a friability of less than 2%. Sodium salicylate was carried the least and it required a larger amount (2%) of lubricant. Vitamin E acetate (1:1) was carried up to 55%. The addition of 0.25% Cab-O-Sil as a glidant was extremely helpful in aiding the flow characteristics of the blend from the hopper to the tablet die. Calcium lactate and ferrous sulfate, exicated, were carried up to 35% and had excellent hardness and friability characteristics. Ascorbic acid (type S) at the 20% level produced excellent tablets having less than 1% friability and a hardness value of about 6. The details of the experiments and results are tabulated in Table 9.

TABLE 9

DETAILS OF EXPERIMENTS ON CARRYING CAPACITIES OF GRANULATED VEHICLE WITH ACTIVE MEDICINAL INGREDIENTS

FORMULATION					EVALUATION		
	%	% LUBRICANT					
Active Medicinal Agent	Active Carried By Granulated Vehicle	Magnesium Stearate	Talc	Cab-O-Sil	Hardness In S.C.H.U.	Disintegration In Min.	% Friability
Ascorbic Acid[1]	20	0.5	--	--	5.8	8.5	0.21
Vitamin E Acetate[2] (50% S.D.)	55	0.5	--	0.25	4.0	16.0	0.04
Calcium Lactate	35	1.0	--	--	12.5	12.0	0.14
Ferrous Sulfate, Exsiccated	30	0.5	--	--	7.6	25	0.31
Sodium Salicylate	10	2.0	--	--	5.0	23	1.4

(1) Ascorbic Acid (type S), Hoffman-La Roche, New Jersey.

(2) Vitamin E Acetate (50% S.D.) Hoffman-La Roche, New Jersey.

EXAMPLE 8.

This experiment was performed to determine the effect of Sta-Rx 1500 (available from A. E. Staley Mfg. Co., Decatur, Illinois) on the disintegration time of the tablets of the granulations *per se*, as well as in combination with various active medicinal agents.

The same granulated vehicle used in the previous Example 3 was employed, which was an admixture of 80% by weight dextrose monohydrate and 20% of the water soluble maltodextrin granulated with a 20% W/V solution of the maltodextrin. The dried granulated vehicle was screened to obtain a mesh size in the range of −40+100. The screened granulated vehicle (except the control) was blended with Sta-Rx 1500 to obtain 10% by weight of Sta-Rx of the total mixture. The Sta-Rx 1500 was also added to the formulations containing the active medicinal ingredients, displacing the granulated direct compression vehicle. The tablets were prepared in the same manner as described in Example 4, keeping the hardness the same as the tablets without Sta-Rx 1500.

The tablets were evaluated for their weight variation, hardness, friability and disintegration. The addition of the directly compressible starch, Sta-Rx 1500, did not effect the carrying capacity of the granulated vehicle of the invention. However, very slight capping was observed in the case of the calcium lactate formulation. This result was expected, since tablets containing starches have a tendency to cap. There was a decrease in disintegration time for the tablets containing Sta-Rx 1500, as compared to those tablets without it. The reduction of time was about one-third of the original time. The flow from the hopper to the tablet die for all samples was excellent. The friability in all of the experiments measured less than 1%. All of the tablets had good hardness values. The hardness value for Vitamin E acetate tablets ranged from 3.8 to 4.0, simply because of the reference pressure for the control tablets to produce a hardness value of 10.8. The hardness value of these tablets could be increased to about 6 or more by simply increasing the pressure used to form the tablets. The tablets nevertheless had an excellent physical appearance.

The details of the experiment and results thereof are set forth in Table 10.

TABLE 10

EFFECT OF STA-RX 1500 AS A DISINTEGRANT ON GRANULATED VEHICLE WITH AND WITHOUT ACTIVE MEDICINAL INGREDIENTS

FORMULATION						EVALUATION			
% ACTIVE		% LUBRICANT							
Vitamin E Acetate (50% S.D.)	Calcium Lactate	Magnesium Stearate	Talc	Cab-O-Sil	Sta-Rx 1500	Capping, If Any	Hardness In S.C.H.U.	Disintegration In Min.	% Friability
--	--	0.75	--	--	--	--	10.8	8.5	0.07
--	--	0.75	--	--	10%	Slight	11.9	5.0	0.24
55	--	0.5	--	0.25	--	--	4.0	16.0	0.04
55	--	0.5	--	0.25	10%	--	3.8	12.0	0.08
--	35	1.0	--	--	--	--	12.5	12.0	0.14
--	35	1.0	--	--	10%	Slight	12.4	8.0	0.21

EXAMPLE 9.

This experiment was conducted to evaluate the rate of moisture pick-up by the granulations of the present invention *per se*, and in combination with active medicinal agents at a given relative humidity to ascertain the stability of the active medicinal agents with the granulated vehicle and the performance of the formulations containing the granulated vehicle under industrial working conditions, where a whole batch runs for eight hours or more, when moisture pick-up is possible.

The experiment was performed using the same granulated vehicle used in the previous Examples which had been prepared by admixing 80% by weight of dextrose monohydrate with 20% by weight of the maltodextrin, and thereafter granulating the admixture with a 20% W/V aqueous solution of the maltodextrin (50 ml. of solution per 1,000 grams of dextrose monohydrate and maltodextrin admixture). Vitamin C and Vitamin E acetate were blended with several samples to provide 20% and 55% by weight of the active medicinal agent in the total blend, respectively. The rate of moisture

pick-up of the granulated vehicle, *per se*, and in combination with the active medicinal agents was studied at 50%, 70% and 90% relative humidity at room temperature.

The moisture pick-up of the samples tested was determined using the below-described procedure.

The Rosano Surface Tensiometer, Model: LG, manufactured by the Federal Pacific Electric Company, New Jersey, was employed in conjunction with Scheibler Desiccators, containing constant relative humidity solutions. One (1) gram of the test material which was placed in an aluminum pan (supported by a wire ring) was hooked onto the Surface Tensiometer with a thread passing through a 2-inch length of rubber tubing partly slipped over a 3-inch length of plastic tubing. The glass tubing was fitted into the tubulature of the desiccator top through a one-hole rubber stopper. The test material, the aluminum pan with the ring, the nylon thread were counterbalanced by necessary weights to produce a tensiometer reading of 0.00 mg. Readings were taken at the end of each hour and the increase in weight was noted.

All of the samples exhibited very little moisture pick-up. The samples subjected to 50% relative humidity exhibited a maximum moisture pick-up after 4—5 hours of less than 2.8%, by weight (increase in weight attributed to moisture pick-up). The samples subjected to 70% relative humidity exhibited a maximum moisture pick-up after about 5 hours of less than 6%, by weight. The samples subjected to 90% relative humidity exhibited a maximum moisture pick-up after 11 hours of less than 20%, by weight. Based upon the results of the above moisture pick-up tests, it is apparent that the granulated vehicles, *per se*, or in combination with the active medicinal agents are not troubled by moisture pick-up when exposed to relative humidities of less than about 75%. This desired result is quite unexpected in light of the propensity of dextrose containing compounds to be hygroscopic, i.e., they tend to pick-up moisture upon standing.

EXAMPLE 10.

This experiment demonstrates the excellent density and fluff characteristics possessed by the granulated vehicles of the present invention, which characteristics enable the vehicle to have the good flow properties from the hopper to the tablet die. As it is well-known, the tablet thickness actually depends on the volume occupied by the vehicle in the die cavity. Tablet thickness is related to the density of the granulation as volume and is inversely proportional to the density. Thus, the denser the granulation, the less volume will be occupied at a given weight, producing thinner tablets. The thickness of the tablets determines the choice of a given packaging unit and even the toolings to be used in their manufacturing. This Example determines the fluff and top densities of the granulations; first, the weight of the material at a given volume, and secondly, the volume is evaluated at a given weight of material. In each test, the granulated vehicle was prepared as previously described in Example 3, using 80% by weight of dextrose monohydrate and 20% by weight of the maltodextrin.

The details of the procedure employed to determine the fluff density and top density of the granulated vehicle of the invention are as follows:

Fluff Density — Each granulated vehicle sample was poured down a gentle slope into a tarred 10-ml. cylinder. The weight of the material contained in this volume was noted, and was reported as "Fluff Density" in grams/ml.

Top Density — Each granulated vehicle sample (50 grams) was accurately weighed and transferred to a 100-ml. cylinder. The cylinder was gently topped on a thick layer of cloth, until no further perceptible decrease in volume was observed. The weight of the granulations was divided by the volume obtained, and the result was reported as "Top Density" in grams/ml.

The results of the tests revealed that the granulated vehicle tested had a Fluff Density of 0.65 gram/ml. and a Top Density of 0.71 gram/ml. These values are indicative of excellent characteristics of the granulated vehicles of the present invention.

EXAMPLE 11.

Several granulated vehicles were prepared utilizing the unique procedure described in Example 3, except that in place of Mor-Rex Code 1918, an acid hydrolysate having a D.E. of about 15 (Frodex, available from American Maize-Products), an enzyme hydrolysate having a D.E. of about 5 (Mor-Rex P908), and two (2) dextrins (Globe Dextrin and Excello Dextrin, available from CPC International Inc.) were employed in amounts of 10%, 20% and 30% by weight in the initial blend with the dextrose monohydrate. The respective maltodextrin or dextrin was placed in water and the solution or dispersion (containing 20% W/V of the maltodextrin or dextrin) was used to granulate the blend. The blends were dried to a moisture content of 3—5% and screened of oversize granules above a No. 14 mesh. Each of the granulated vehicles was mixed with 1.0% magnesium stearate for lubrication and was formed into tablets on a Model F single stroke tabletting machine set at a ratio of 45 strokes per minute and at 1¼ tons of pressure.

In all instances, the granulated vehicles

were free-flowing and had acceptable compressibilities. Slight scoring of tablets was observed in the vehicles prepared from the acid hydrolysate (Frodex) and Mor-Rex P908, therefore, necessitating a higher amount of lubricant or inclusion of an anti-adherent. From a hardness and friability standpoint, all blends made acceptable tablets. All of the granulated vehicles demonstrated very little hygroscopicity at 50%, 70% and 90% relative humidity. The acid hydrolysate (Frodex) containing vehicles were slightly more hygroscopic than the other vehicles tested. The dextrin containing vehicles, while they provided suitable tablets, were not acceptable because the tablets possessed a yellow color and had a burnt flavor. Thus, it is necessary to employ the maltodextrins to product commercially acceptable granulated vehicles for use in the pharmaceutical industry.

As it can be seen from the foregoing evidence, the present invention has now provided a unique granulated vehicle having an unusual structural integrity and density. The structural integrity and density of the granulated vehicles provides a tabletting composition having excellent flowability and capability of forming strong, hard and substantially non-friable tablets, even when the tablet contains up to about 80% by weight of the tablet of a pharmaceutically active material. By referring to a substantially non-friable tablet, it is meant a tablet which loses less than about 1% by weight, as determined by the "Roche" test described in page 21 herein.

WHAT WE CLAIM IS:—

1. A process for producing a direct compression vehicle for tabletting comprising:—

(a) admixing a crystalline sugar with a maltodextrin having a measurable dextrose equivalent value not substantially above 20 to form a uniform admixture,

(b) contacting the said admixture with an aqueous solution containing dissolved therein a maltodextrin having a measurable dextrose equivalent not substantially above 20, the aqueous solution of dissolved maltodextrin being present in an amount sufficient to provide a damp mass of the uniform admixture and to cause granulation of the uniform admixture, and

(c) drying the granulated uniform admixture to a moisture content of less than 10% by weight,

there being from 10% to 50% by weight of the maltodextrin in the so produced vehicle.

2. The process as claimed in claim 1, wherein said crystalline sugar is dextrose.

3. The process as claimed in either claim 1 or claim 2, wherein said crystalline sugar contains up to 16% by weight moisture.

4. The process as claimed in any one of claims 1 to 3, wherein said vehicle includes from 15% to 35% by weight, based on the vehicle, of said maltodextrin.

5. The process as claimed in any one of claims 1 to 4, wherein said vehicle includes from 20% to 30% by weight, based on the vehicle, of said maltodextrin.

6. The process as claimed in any one of claims 1 to 5, wherein said aqueous solution contains from 5% to 60% by weight, based on the volume of the solution, of said maltodextrin.

7. The process as claimed in any one of claims 1 to 6, wherein said aqueous solution contains from 10% to 40% by weight, based on the volume of the solution, of said maltodextrin.

8. The process of claim 1, wherein said maltodextrin is a waxy starch hydrolysate having a dextrose equivalent value in the range of from 9 to 13 and a descriptive ratio of at least 2, said descriptive ratio being the quotient of the sum of the saccharides having a saccharide content of 1 to 6 divided by the dextrose equivalent value.

9. A direct compression vehicle whenever produced by a process as claimed in any one of the preceding claims.

10. A directly compressible material capable of being formed by direct compression at a pressure as low as 2000 pounds into hard substantially non-friable tablets having a Strong Cobb Hardness Unit (S.C.H.U.) value of at least 6 comprising a vehicle as defined in Claim 9 in admixture with up to 80% by weight of the directly compressible material of at least one pharmaceutically active ingredient.

11. The directly compressible material as claimed in claim 10, wherein said crystalline sugar is dextrose.

12. The directly compressible material as claimed in either claim 10 or claim 11, wherein said water soluble maltodextrin is present in an amount ranging from 15% to 35% by weight based on the weight of the vehicle.

13. The directly compressible material as claimed in any one of claims 10 to 12, wherein the moisture content of said vehicle is less than 5% by weight.

14. The directly compressible material as claimed in any one of claims 10 to 13, wherein said pharmaceutically active ingredient is ascorbic acid, sodium salicylate, acetaminophen, sodium bicarbonate, aluminum hydroxide, magnesium trisilicate, Vitamin E acetate, calcium lactate, ferrous sulfate or a mixture thereof.

15. The directly compressible material as claimed in any one of claims 10 to 14 which additionally includes an effective amount of at least one lubricant, colour disintegrant, binder or a mixture thereof.

16. A directly compressible material as

were free-flowing and had acceptable compressibilities. Slight scoring of tablets was observed in the vehicles prepared from the acid hydrolysate (Frodex) and Mor-Rex P908, therefore, necessitating a higher amount of lubricant or inclusion of an anti-adherent. From a hardness and friability standpoint, all blends made acceptable tablets. All of the granulated vehicles demonstrated very little hygroscopicity at 50%, 70% and 90% relative humidity. The acid hydrolysate (Frodex) containing vehicles were slightly more hygroscopic than the other vehicles tested. The dextrin containing vehicles, while they provided suitable tablets, were not acceptable because the tablets possessed a yellow color and had a burnt flavor. Thus, it is necessary to employ the maltodextrins to product commercially acceptable granulated vehicles for use in the pharmaceutical industry.

As it can be seen from the foregoing evidence, the present invention has now provided a unique granulated vehicle having an unusual structural integrity and density. The structural integrity and density of the granulated vehicles provides a tabletting composition having excellent flowability and capability of forming strong, hard and substantially non-friable tablets, even when the tablet contains up to about 80% by weight of the tablet of a pharmaceutically active material. By referring to a substantially non-friable tablet, it is meant a tablet which loses less than about 1% by weight, as determined by the "Roche" test described in page 21 herein.

WHAT WE CLAIM IS:—

1. A process for producing a direct compression vehicle for tabletting comprising:—

(a) admixing a crystalline sugar with a maltodextrin having a measurable dextrose equivalent value not substantially above 20 to form a uniform admixture,

(b) contacting the said admixture with an aqueous solution containing dissolved therein a maltodextrin having a measurable dextrose equivalent not substantially above 20, the aqueous solution of dissolved maltodextrin being present in an amount sufficient to provide a damp mass of the uniform admixture and to cause granulation of the uniform admixture, and

(c) drying the granulated uniform admixture to a moisture content of less than 10% by weight,

there being from 10% to 50% by weight of the maltodextrin in the so produced vehicle.

2. The process as claimed in claim 1, wherein said crystalline sugar is dextrose.

3. The process as claimed in either claim 1 or claim 2, wherein said crystalline sugar contains up to 16% by weight moisture.

4. The process as claimed in any one of claims 1 to 3, wherein said vehicle includes from 15% to 35% by weight, based on the vehicle, of said maltodextrin.

5. The process as claimed in any one of claims 1 to 4, wherein said vehicle includes from 20% to 30% by weight, based on the vehicle, of said maltodextrin.

6. The process as claimed in any one of claims 1 to 5, wherein said aqueous solution contains from 5% to 60% by weight, based on the volume of the solution, of said maltodextrin.

7. The process as claimed in any one of claims 1 to 6, wherein said aqueous solution contains from 10% to 40% by weight, based on the volume of the solution, of said maltodextrin.

8. The process of claim 1, wherein said maltodextrin is a waxy starch hydrolysate having a dextrose equivalent value in the range of from 9 to 13 and a descriptive ratio of at least 2, said descriptive ratio being the quotient of the sum of the saccharides having a saccharide content of 1 to 6 divided by the dextrose equivalent value.

9. A direct compression vehicle whenever produced by a process as claimed in any one of the preceding claims.

10. A directly compressible material capable of being formed by direct compression at a pressure as low as 2000 pounds into hard substantially non-friable tablets having a Strong Cobb Hardness Unit (S.C.H.U.) value of at least 6 comprising a vehicle as defined in Claim 9 in admixture with up to 80% by weight of the directly compressible material of at least one pharmaceutically active ingredient.

11. The directly compressible material as claimed in claim 10, wherein said crystalline sugar is dextrose.

12. The directly compressible material as claimed in either claim 10 or claim 11, wherein said water soluble maltodextrin is present in an amount ranging from 15% to 35% by weight based on the weight of the vehicle.

13. The directly compressible material as claimed in any one of claims 10 to 12, wherein the moisture content of said vehicle is less than 5% by weight.

14. The directly compressible material as claimed in any one of claims 10 to 13, wherein said pharmaceutically active ingredient is ascorbic acid, sodium salicylate, acetaminophen, sodium bicarbonate, aluminum hydroxide, magnesium trisilicate, Vitamin E acetate, calcium lactate, ferrous sulfate or a mixture thereof.

15. The directly compressible material as claimed in any one of claims 10 to 14 which additionally includes an effective amount of at least one lubricant, colour disintegrant, binder or a mixture thereof.

16. A directly compressible material as

claimed in any one of claims 10 to 15, wherein the vehicle is a direct compression vehicle as claimed in claim 9.

17. A process for producing a directly compressible material for tabletting comprising:

(a) admixing a crystalline sugar with a maltodextrin having a measurable dextrose equivalent value not substantially above 20 to form a uniform admixture,

(b) contacting the admixture with an aqueous solution containing dissolved therein a maltodextrin having a measurable dextrose equivalent value not substantially above 20, the aqueous solution of dissolved maltodextrin being present in an amount sufficient to provide a damp mass of the uniform admixture and to cause granulation of the uniform admixture,

(c) drying the granulated uniform admixture to a moisture content of less than 10% by weight to produce a material containing from 10% to 50% of the maltodextrin and

(d) admixing the dried granulated uniform admixture from (c) with up to 80% by weight of the compressible material of at least one pharmaceutically active ingredient.

18. A directly compressible material whenever prepared by the process as claimed in claim 17.

19. A directly compressed pharmaceutically composition in the form of hard and substantially non-friable tablets having a Strong Cobb Hardness Unit value (SCHU) value of at least 6 when formed by direct compression at a pressure as low as 2000lbs prepared from the directly compressible material obtained from the process as defined in claim 17.

20. Tablets as claimed in claim 19 when made by direct compression of the material claimed in any one of claims 10 to 16.

21. A method for making a directly compressed pharmaceutical composition in tablet form comprising compressing the directly compressible material as claimed in any one of claims 10 to 16.

22. A directly compressed pharmaceutical composition in tablet form when made by the method as claimed in claim 21.

STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
5, Quality Court, Chancery Lane,
London, W.C.2.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

