United States Patent

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Continuation-in-part of application Ser. No. 646,496, June 16, 1967, now abandoned. This application July 7, 1969, Ser. No. 839,590

[54] **COMPRESSED TABLETS CONTAINING COMPACTED STARCH AS BINDER-DISINTEGRANT INGREDIENT**
8 Claims, 4 Drawing Figs.

[52] **U.S. Cl.** **424/361,** 106/210, 424/229, 424/230, 424/280, 424/300, 424/324, 252/1;99, 71/77, 99/140, 8/79, 264/118, 127/32

[51] **Int. Cl.** **A61j 3/10**

[50] **Field of Search** 424/361; 252/1

[56] **References Cited**

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ABSTRACT: A directly compressed tablet containing as a binder-disintegrant ingredient, a partially cold-water soluble, cold-water swelling starch material derived from compacted granular starch, e.g. compacted native corn starch. The compacted granular starch is a superficially dry, free-flowing powder in which the starch is in the form of a mixture of birefringent granules and nonbirefringent fragments of granules, in which some aggregates of granules and fragments are present. The use of the starch binder-disintegrant ingredient allows active ingredients, e.g. pharmaceuticals, to be tabletted by direct compression.

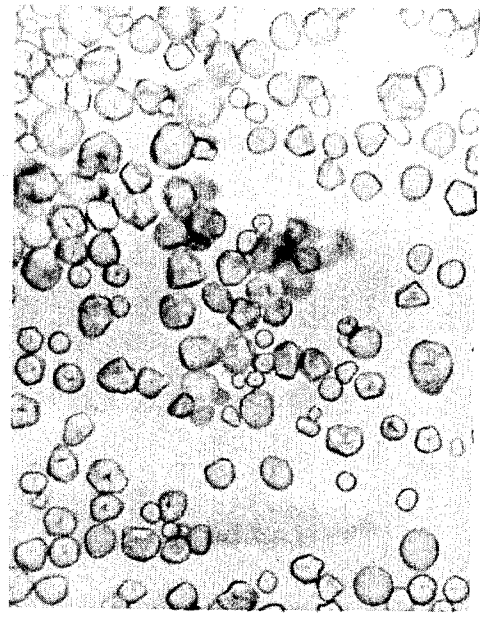

FIG. 1

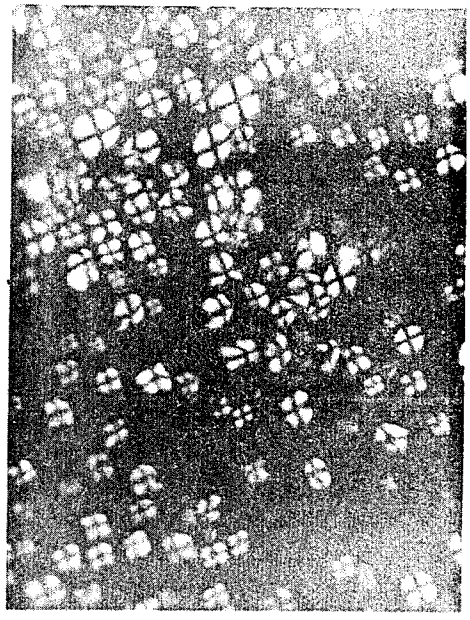

FIG. 2

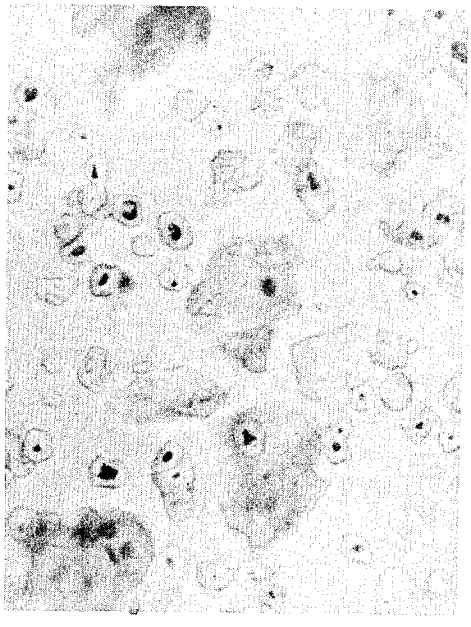

FIG. 3

FIG. 4

COMPRESSED TABLETS CONTAINING COMPACTED STARCH AS BINDER-DISINTEGRANT INGREDIENT

CROSS-REFERENCE

This application is a continuation-in-part of application Ser. No. 646,496, filed June 16, 1967 now abandoned.

DISCLOSURE OF THE INVENTION

This invention relates to the manufacture of compressed tablets and more particularly to compressed tablets which contain a starch binder-disintegrant ingredient in the form of a directly compressible compacted starch powder which permits the tablets to be made by the direct compression technique.

Of the multitude of forms in which pharmaceutical products may be dispensed, the compressed tablet form is, by far, that most frequently employed today. Ease of packaging and handling, and, most important accuracy of dosage in administration are among the advantages stemming from the use of medicament-containing tablets. For essentially the same reasons, the compressed tablet also plays an important role in other fields as a dispensing unit. Examples of nonpharmaceutical materials marketed in compressed tablet form include such diverse materials as laundry detergents, confections, artificial sweeteners, fish foods, plant growth regulators, pesticides, herbicides, and dyes. While the actual characteristics of various tablets differ depending on the particular nature and planned use of the several tablets, the generally more important characteristics fall into three areas of consideration.

Since most tablets are designed for use in accurately dispensing an active material into a fluid medium, an evaluation of the tablet includes a consideration of the tablet disintegration properties in the fluid medium. While some tablets such as those designed for use as a throat lozenge desirably are slowly disintegrative in the fluid medium in which they are placed for use, in most cases rapid disintegration of the tablet is desired. For example, a tablet embodying an ingestible analgesic, such as aspirin, should rapidly break down in the digestive fluid of the stomach to make the active ingredient promptly available to the organism. The present invention is particularly concerned with such tablets of relatively rapid disintegration capability.

The second and third important tablet characteristics, friability and hardness, are somewhat related in that as tablet hardness increases the friability of the tablet generally decreases. Excessive friability is undesirable since dusting and crumbling of the tablet results in at least some diminution in active ingredient dosage, detracts from the tablet appearance and consumer appeal, and reduces the effectiveness of any tablet markings. Insufficiently hard tablets, in addition to exhibiting the effects of excessive friability, are prone to breakage and chipping, particularly in transport where they may be subjected to repeated mechanical shock.

Accordingly, for most purposes, and particularly for pharmaceutical application, a hard, nonfriable tablet possessing acceptable disintegration characteristics is the goal of the tablet manufacturer. Other properties are, of course, important such as color stability and nonhygroscopicity but the desideratum remains the production of a tablet of the type described.

Certain materials such as sodium chloride, paradichlorobenzene, hexamethylenetetramine, and certain medicaments are readily directly compressed alone in dry form into a firm, coherent mass in a tablet machine. However, the majority of active ingredients in order to be tabletted require a binding agent to be added. The tabletted formulations generally also contain additional ingredients, such as lubricants, disintegrants, fillers, colorants, and the like. The terms "binding agent," "binder," and "filler" are self-explanatory. A disintegrant is an agent which is effective, when the tablet is placed in the proper fluid environment, to promote destruction of the tablet's physical integrity. A typical disintegrant employed in tabletting is granular starch.

A given material may perform more than one of the single functions of binding, filling, and promoting disintegration. The principal component, other than the active ingredient, that is employed to provide the improved compressed tablets of the present invention is such a dual-functioning material and is referred to herein as a "binder-disintegrant."

In general, three methods are known for the preparation of mixtures suitable to be employed in a tablet-making machine. In two of the methods commonly used for the preparation of tabletting machine feed material, the goal in each is the preparation of the feed material in the form of free-flowing granules. One technique involves a dry, and the other a wet, method of granulation. Dry granulation is also referred to as "slugging" or "double compression." In accordance with the slugging technique, the initially prepared pulverulent admixture of active ingredient, filler, binder and the like is formed into large tablets or slugs by dry compression molding. These slugs are then milled to granules of predetermined size adapted to be used as the feed to the tablet-making machine. This method is expensive, requiring considerable equipment, labor, and power. The technique, moreover, does not always provide suitable tablets.

The wet granulation technique involves adding a moistening agent such as water or ethylene glycol to the tabletting ingredient mixture to prepare a moistened mass, oven drying the wetted mass, and milling the dried mass into granules adapted to be used in the tabletting machine. The wet granulation method likewise is undesirably time consuming and expensive. This method, moreover, has the limitation of not being useful when the tablet ingredients are incompatible to wetting or are heat sensitive.

The third and simplest procedure employed in preparing tabletting formulations involves intimately and uniformly dry blending the ingredients employed, e.g. active ingredient, binder, filler, disintegrant, and lubricants, to provide a pulverulent mixture displaying the requisite flowability for adequate feeding to the tablet machine. Since in this method the granulation step is eliminated, the formulations are said to be "directly compressible" into tablets, and the tablet-forming operation is referred to as "direct-compression" tabletting. This procedure, by virtue of its simplicity, obviously is preferred for use. Using ingredients heretofore available, however, the ingredient mixtures obtained by mere dry mixing generally do not exhibit adequate flowability and are not adapted to be fed directly to the tabletting machine to prepare tablets of uniform and acceptable properties. The limited acceptance of preparing compressed tablets by direct compression has stemmed principally from the unavailability of suitable and inexpensive direct compression binding agents. Of those materials which do qualify by reason of their binding properties, moreover, few are characterized by satisfactory overall properties. For example, the most widely used material at present for binding tablets by the direct compression method, spray-dried lactose, is unacceptable in many uses because of its marked tendency to turn brown on aging. The great percentage of tabletting operations, therefore, have been forced to resort to other formulation techniques such as the wet and dry granulation methods, and the art has continued to search for an improved material 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 otherwise satisfactory.

Accordingly, it is an object of the present invention to provide an improved binder for the manufacture of compressed tablets. It is another object of the invention to provide such an improved binder having characteristics that permit it to function also as a disintegrant. It is an additional object of the invention to provide active ingredient, binder ingredient formulations directly compressible into tablets. It is yet a further object of the invention to provide a compressed tablet containing a binder-disintegrant ingredient, the tablet being hard, nonfriable, and readily disintegrative in an aqueous medium. Yet another object of the invention is to provide a method for

preparing compressed tablets. A particular object of the present invention is to provide a means whereby tablets of excellent properties can be prepared by direct compression. The means of attaining these and related objects will be evident from the following description and examples.

For a more complete understanding of the nature and scope of the invention reference may now be had to the following detailed description thereof with illustrative working examples, and to the accompanying drawings, wherein:

FIG. 1 is a photomicrograph, taken under bright field illumination of ordinary corn starch at a magnification of 425;

FIG. 2 is a photomicrograph corresponding to FIG. 1 but with the light polarized;

FIG. 3 is a photomicrograph, taken under bright field illumination of compacted corn starch, useful in accordance with the present invention, at a magnification of 425; and

FIG. 4 is a photomicrograph corresponding to FIG. 3 but with the light polarized.

Compacted starches constitute a known class of materials. They are prepared by subjecting a granular starch raw material to pressure in the presence of water to effect distortion and fracture of at least some of the granules and produce adhesion between particles of the resultant mass. The resultant compacted material may have differing cold-water swelling properties and contain varying amounts of cold-water soluble material depending primarily upon the particular pressure, temperature, and moisture conditions utilized. Specific techniques commonly employed include passing the starting starch through the nip of rotating rolls operating at the same or different speeds, as described in U.S. Pat. Nos. 2,098,293; 2,168,524; 2,464,081; and 3,196,044, and working the starch in the course of an extrusion operation as shown in U.S. Pat. Nos. 3,137,592 and 3,159,505. Compacted starches heretofore have found utility primarily as "dustless" carbohydrate nutrients in the brewing industry and as binders in the preparation of rough-molded products containing relatively coarse aggregate materials such as foundry cores and charcoal briquettes.

It now surprisingly has been discovered that certain compacted starch powers, described more fully hereinafter, advantageously are characterized by properties which enable them to be dry mixed with active ingredients and conventional tabletting aids, such as fillers, lubricants, and the like, to prepare active ingredient-containing formulations which are directly compressible into tablets in conventional tabletting equipment. The present invention therefore provides a highly valuable means whereby tabletting operations may be greatly simplified, and the troublesome and time-consuming preliminary granulation and slugging steps which characterized most tabletting operations heretofore available may be eliminated. The compacted starch powders employed in the present invention, moreover, advantageously are characterized by properties which satisfy both the requirements of a binder for the active ingredient and a disintegrant for the tablet in aqueous media. Consequently, suitable direct compression tablets of satisfactory hardness, friability, and disintegration properties advantageously may be prepared by means of the present invention using the compacted starch powders as a sole, dual-functioning binder-disintegrant, and the heretofore commonly required practice of adding separate ingredients as the binder and disintegrant with the attendant problems of properly mixing multiple ingredients and balancing dosage levels no longer need be followed. The starch binder-disintegrant ingredient employed in preparing direct compression tabets in accordance with the present invention, furthermore, easily and cheaply may be obtained from readily available and inexpensive starting raw materials, namely granular starches. Of such binder-disintegrant compacted starches many embodiments are characterized by low color, color stability, and acceptability for human consumption. The present invention, therefore, includes what may be said to be a "universal" ingredient for direct compression tabletting, whereby a wide range of active ingredients, including many pharmaceuticals tabletted heretofore only with great difficulty, if at all, now easily and inexpensively may be satisfactorily tabletted by direct compression.

The compacted starch powders employed in the practice of the present invention are derived from appropriately compacted granular starch raw materials and are superficially dry, free flowing, partially cold-water soluble materials which swell in cold water and have a relatively high loose bulk density. The powders themselves are directly compressible in conventional tabletting equipment into relatively rapidly disintegrative placebo tablets of high hardness and low friability. Microscopic examination of the compacted starch powders reveals the starch content of the materials to be in the form of a mixture of birefringent granules and nonbirefringent fragments of granules, in which some aggregates of granules and fragments are present. These characteristics of the compacted starch powders on microscopic examination are apparent from the photomicrographs reproduced in FIGS. 1–4. In FIG. 1 granules of ordinary corn starch are shown as viewed with unpolarized light at 425 magnification. FIG. 2 shows the same granules viewed with the light polarized at the same magnification. It will be noted that in FIG. 2 the granules all exhibit birefringence (i.e. the crosses) which is characteristic of starch granules.

In FIG. 3 a sample of compacted starch powder, which is directly compressible into tablets in accordance with this invention, is shown as viewed with unpolarized light at 425 magnification. A number of starch granules appear in FIG. 3 along with aggregates and granular fragments. When the same sample of compacted starch powder is viewed under polarized light at the same magnification, it is clearly seen that the sample is a mixture of birefringent granules and nonbirefringent fragments of granules, in which there are aggregates of granules and fragments.

Compacted starch powders of the invention have the following characteristics:

Property	Broad	Preferred
Cold-water Solubility, %	4–40	6–20
Swelling Power	2.5–12	3.5–10
Loose Bulk Density, g./ml.	0.50 minimum	0.55–0.70
Placebo Tablet (Direct Compression) Properties		
Hardness, kg.	5 minimum	8 minimum
Friability, % wt. loss	1.0 maximum	0.5 maximum
Disintegration Time, min. (in water)	30 maximum	15 maximum

As used herein, the term "superficially dry" is intended to indicate a powder is dry in the visual and tactile sense. A "placebo" tablet is a tablet prepared by directly compressing one material alone such as a compacted starch powder. The terms "cold-water solubility," "swelling power," "hardness," "friability," "disintegration time," and "granular starch raw material" are defined as follows:

Cold-water solubility—The percent by weight of the starch dry substance which dissolves in water at 25° C. when determined by the following procedure: One gram of the starch product being tested is added to 100 ml. of water at 25° C. in a high-shear blender and mixing is carried out at 1,500 r.p.m. for 2 minutes. The resultant sample is then transferred to a 250 ml. round-bottom centrifuge tube and centrifuged for 15 minutes at 2,000 r.p.m. A 25 ml. aliquot of the clear centrifugate is transferred to a tared aluminum pan and evaporated to dryness on a steam bath. The dish is then dried to a constant weight at 110° C. The weight of the dried material in the pan multiplied by 400 and divided by the dry substance weight of the original sample is the cold-water solubility of the starch material. By this test commonly available granular starches are essentially cold-water insoluble, generally containing less than about 2 percent by weight cold-water solubles and in the case of unmodified starches less than about 1 percent.

Swelling power—a measure of the ability of a starch to swell in cold water as determined by method 56–20 of "Cereal Laboratory Methods" published by the American Association of Cereal Chemists. For reference purposes, uncompacted granular starches generally have a swelling power on the order of about 2.

Hardness—a measure of the strength of tablets (average of 10 or more tablets) and their ability to retain their physical integrity, expressed in terms of kilograms, as determined by the conventional procedure using a model B tablet hardness tester of the Strong-Cobb-Arner Company, Cleveland, Ohio, to obtain an indicated pressure gauge reading at fracture of the tablet (tablet mounted on edge in tester) and multiplying the indicated hardness value by a factor of 0.78 to convert the gauge reading to actual pressure. For example, a satisfactory active ingredient-containing tablet generally should have a hardness in this test of at least about 4 kg.

Friability—a measure of the tendency of tablets (average of 10 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). For reference purposes, an active ingredient-containing tablet displaying a weight loss of less than about 1.0 percent generally is considered to have acceptable friability.

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

Granular starch raw material—the starting starch which has been compacted in the preparation of the compacted starch powders of the invention. The starting starch suitably may be any granular starch derived from the root, stem, or fruit of a plant. Specific examples of starch-yielding sources include corn, rice, wheat, potato, tapioca, and arrowroot. The starting starch raw material suitably may be unmodified, modified, derivatized, or cross-linked. Examples of unmodified starches are the granular starches conventionally prepared from natural starch sources by removal of fiber, gluten, and other proteinaceous impurities, with or without subsequent washing, drying, screening, bleaching, and/or sterilization. Modified granular starches include thin-boiling starches made by heating a water slurry of an unmodified starch below the gelatinization temperature with a mineral acid (e.g. hydrochloric acid) or an oxidizing agent (e.g. alkaline hypochlorite). Derivatized granular starches include starch esters, e.g. starch acetate and starch propionate, and starch ethers, e.g. hydroxyethyl, carboxymethyl, and cyanoethyl starch, prepared from unmodified or modified granular starches with retention of the granular structure. Granular cross-linked starches include ungelatinized starch products made by reacting an unmodified, modified, or derivatized granular starch with a polyfunctional reactant, e.g. phosphorous oxychloride or epichlorohydrin.

The free-flowing property of the compacted starch powders employed in the invention is exemplified by the ability of the powders to meet the following arbitrary test: a sample of powder being tested is poured into a 24/40 standard taper glass powder funnel, the tip of which is suspended normal to, and one inch above, a horizontal, dry, smooth paper surface. Powder is poured through the funnel until the cone of powder formed on the paper surface below reaches the tip of the funnel, and the funnel plugs. The average radius of the cone base is determined by taking four radius measurements from the funnel tip along diameters intersecting at right angles and averaging the values. From the cone height (1 inch) and the average radius of its base, the angle formed by the inclined surface of the powder cone and the horizontal, herein referred to as the "angle of repose," can be determined using well-known trigonometric principles, i.e. by calculating the tangent of the angle of repose. A powder which is not free-flowing in the sense of the term as employed herein displays an angle of repose in this test of more than about 40° The more preferred free-flowing characteristics are displayed by compacted starch powders forming an angle of repose in the range of from about 20° to about 35°.

Due to the availability and low cost of the starting raw material required, compacted starch powders derived from corn starch, and more preferably an unmodified corn starch, constitute the binder-disintegrant ingredients preferred for utilization in the present invention. Such starch raw materials, moreover, provide resultant binder-disintegrant ingredients which display excellent color stability during storage and in the ultimate tablet. By reason of the excellent overall properties of tablets which can be obtained by the use thereof, the particularly preferred binder-disintegrant ingredients are superficially dry, free-flowing powders of the above-described type characterized by a cold-water solubility of from about 6 to about 15 percent and a swelling power of from about 5 to about 8 and being derivatives of a bleached native corn starch, e.g. hypochlorite-bleached native corn starch.

The starch binder-disintegrant ingredients employed in the present invention are prepared from the starting granular starch raw materials by the same basic steps heretofore utilized in preparing powders of compacted starches and in general involving compacting the starting starch raw materials in the presence of water, comminuting the resultant compacted material, and classifying the comminuted intermediate into the desired particle size fraction.

The compaction step suitably may be carried out in any convenient device conventionally employed for this purpose. As described above, the more commonly used devices include differential roll mills, concurrent roll mills, extruders, and the like. The moisture content of the granular feed starch and the temperature which the starch attains during the compaction are important variables in achieving a suitably modified compact. In preparing compacted starches suitable for use in the present method, temperatures should be limited to those below the gelatinization temperature of the particular starch used. Higher temperatures provide compacts which, when comminuted, yield powders which are overgelatinized and have poor disintegrant properties. Optimum compaction conditions generally include temperatures in the range of from about 20° to about 50° C.

The water content of the granular starch feed must be in the range whereby the properties of the granular starch feed are altered to the desired degree in the compaction treatment. For a given starch and a given compaction device, limits for the moisture content will exist at which the starch feed is either too dry or too wet for the compaction to sufficiently change the properties of the starting starch. For a given starch and compacting device, however, the operable and optimum water content ranges easily may be determined in the manner known and described hereafter, i.e., varying the feed starch moisture content and noting the degree of starch modification achieved in terms of the effect on the cold-water solubility and swelling power of the starch. As a general rule, in most conventional starch compaction equipment, water content in the feed granular starch in the range of from about 20 to about 50 percent of the starch total weight is used to achieve the desired amount of compaction. The lower moisture levels in this range, e.g. from about 20 to about 30 percent, are generally more adapted for use in roll-type compaction equipment such as differential roll mills, and the higher water contents in this range, e.g. from about 30 to about 50 percent, are better adapted for use in devices effecting the desired working in a confined space such as in a screw-containing barrel-type extruder. Since commonly available granular starches generally have a moisture content on the order of 10–12 percent, water usually must be added to the granular feed starch prior to compaction.

While, as stated above, the particular compaction technique employed in preparing the starches employed as binder-disintegrants in the present invention is not critical, a compaction method which is particularly useful is exemplified by that disclosed in U.S. Pat. No. 2,464,081 entailing the use of a dif-

ferential mill. In a typical application of this technique, a granular starch feed having an adjusted moisture content in the range of from about 24 to about 32 percent by weight is fed through the mill operated with a gap between the rolls in the range of 3 to 12 mils. Typical roll speeds vary between 35 to about 70 feet (linear) per minute using a speed differential of from about 10 to about 20 feet per minute. Roll temperatures maintained by circulating water through the rolls generally vary between about 10° to about 40° C. More than one pass through the rolls generally is required to sufficiently modify the starting starch properties with up to four passes being common.

Another particularly useful compaction technique utilizes a rotating pellet mill which is adapted to subject the starch feed to the sufficient amount of working during the formation of pellets therefrom. An example of a typical pelletting operation which achieves suitable compaction generally employs a pellet mill having dies 3/16 inch in diameter and 1½ inches in length in which the starting granular starch at a moisture content of from about 20 to about 30 percent by weight is pelletized at a feed rate of 900 to 1,000 lbs. per hour with the mill rotating at 125–150 r.p.m. Advantages of utilizing a pellet mill are that one pass through the mill usually is sufficient to provide the desired starch modification and that a significantly reduced amount of fines is produced as compared to most other compaction techniques.

The material produced by the required amount of compaction then is ground and screened to a suitable particle size, the moisture content being adjusted during the recovery of the desired powder from the compact. For optimum results, the compact is dried prior to being ground. Drying lessens the proportion of fines produced in the grinding step and guards against possible further undesirable starch alteration during grinding. In the drying, the moisture content of the compacted material is commonly reduced to from about 4 to about 14 percent by weight.

The grinding suitably may be carried out in any grinder, mill or combination of comminuting devices adapted to reduce the compact to a free-flowing, directly compressible powder. It has been found that the more suitable tablet binder-disintegrant powders are those which are relatively fine. In the grinding step, therefore, the compacted starch generally is reduced to a powder of which at least about 30 percent of the total weight thereof is material of −270 mesh. The term "-mesh," as used herein, refers to the U.S. Standard Sieve Series, A.S.T.M. specifications. The presence of too great a proportion of fines is not conducive to optimum tabletting so it generally is preferred to control grinding to provide a powder containing less than about 90 percent by weight material of −270 mesh. The more preferred powders obtained in the grinding step, by virtue of the properties of the tablets obtained therefrom and their adaptability to tabletting machine operation, are those ground to from about 45 to about 75 percent by weight material of −270 mesh. A specific grinding technique suitable for use involves initially grinding the compact to −10 mesh and then completing grinding in a mill adapted to recycle all +100 mesh material.

The water content of the compacted starch powder has an effect on the binder-disintegrant properties of the material. Too low or too high a water content detracts from the properties of the ultimate tablets formed. Generally moisture contents in the range of from 9 to about 16 percent of the powder total weight are suitable with the more preferred results usually being obtained at moisture contents in the range of from about 11 to about 13 percent by weight. Accordingly, following grinding, the moisture content of resultant powder preferably is adjusted, if necessary, by drying or the addition of water.

As stated, the binder-disintegrant starch powders preferred for use contain a low proportion of coarse particles. Generally, it is desired that the powder contains less than about 10 percent by weight material of +80 mesh. The more preferred powders are essentially free of +40 mesh material and contain less than about 5 percent of material of 40–80 mesh. The preferred materials, therefore, are screened to −40 mesh and preferably −80 mesh before actual use. Screening is particularly desirable if the powder from the grinding step subsequently is moistened to adjust its moisture content since the moistening step increases the amount of +80 mesh material in the powder. Oversize material can be ground to the desired smaller particle size material.

Typical compacted starch powders suitable for use in the present invention here are characterized by the following particle size distribution:

Particle Size	Proportion of Powder, % total weight
40–80 mesh	0–5
80–200 mesh	5–30
200–270 mesh	10–40
through 270 mesh	45–75

At least 10 percent should be between 80 and 270 mesh to help in imparting free-flowing characteristics.

In the preferred preparation of tablets by the present invention, an active material ingredient is thoroughly mixed by any suitable dry blending technique with one or more of the above-described compacted starch powders in relative amounts required to provide a resultant superficially dry, free-flowing formulation directly compressible into tablets, and the formulation then is 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 compacted starch powders in formulations directly compressible into tablets. The present invention is particularly adapted for use in preparing tablets containing pulverulent pharmaceutically active materials. Specific examples of pharmaceutically active ingredients which advantageously may be tabletted by the present invention include ascorbic acid, sodium p-aminosalicylate, phenacetin, and N-acetyl-p-aminophenol, all materials which heretofore generally have been tabletted only with great difficulty. The particular nature of the active material is not critical, however, and nonpharmaceutical active materials, e.g. pulverulent detergents, dyes, pesticides, and foods, forming directly compressible mixtures with the compacted starch powders can also be employed.

The amount of active material ingredient employed in preparing tablets according to the present technique depends, inter alia, upon the nature and relative compatibility of the active material, and the end use for which the tablet is desired, the latter dictating thereby the tolerable properties in terms of hardness, friability, and/or disintegratability of the final tablet. Given the minimum and preferred characteristics desired in the final tablet, the tolerable limits on the weight ratio of active ingredient to binder-disintegrant for a particular active ingredient easily may be determined by the known technique of sequentially increasing the active ingredient content of the tablet. In general, acceptable active material-containing tablets are those which display a hardness of at least about 4 kg., preferably above about 5 kg., and a friability corresponding to a weight loss of less than about 1.0 percent, preferably less than about 0.5 percent. For a tablet having suitable friability, a lower hardness generally can be tolerated.

Depending upon the type and contemplated use of the final tablet, the disintegration requirements may vary over a wide range. A particular feature of the present invention is that a wide range of active ingredients may be tabletted to provide tablets displaying disintegration times in aqueous media of generally less than 30 minutes and more usually less than 15 minutes and in the range of from about 0.5 to about 10 minutes. The rapid disintegration rates of tablets prepared by the present method, as stated, stem from the advantageous characteristics of the compacted starch powders to function

not only as excellent binding agents but as agents which accelerate tablet disintegration as well. In general, specific embodiments of tablets prepared in the invention contain from about 5 to about 90 percent by weight active ingredient, dry substance basis. An additional feature of the present invention is that, by the use of the binder-disintegrant compacted starch powders, even many pulverulent active ingredients which themselves are noncompressible or only poorly compressible, exemplified by the pharmaceuticals named, may be formed into suitable tablets containing from about 20 to about 50 percent and above of the active ingredient based on the tablet dry substance weight.

Adjuvants, such as tabletting lubricants, fillers, antisticking agents, coloring agents, and the like, conventionally employed in preparing particular tablets by direct compression, suitably may be incorporated in appropriately effective amounts into the compressible formations formed in the present invention. A lubricant such as talc, magnesium stearate, or stearic acid, when employed, generally is added in an amount ranging up to about 10 percent by weight of the total tabletting formulation. Colloidal silica constitutes a typical antisticking agent or so-called "glidant." A glidant such as colloidal silica, when incorporated in a formulation, usually is added in an amount ranging up to about 2 percent of the formulation total weight. Fillers, which may also function as supplemental binders or disintegrants, where employed, must not be added in amounts which impair undesirably the direct compressibility of the tabletting formulations.

While the compacted starch powders employed in the present invention are capable of satisfying the dual requirements of a binder-disintegrant, the present invention, as stated, also contemplates embodiments wherein effective amounts of another direct compression binder such as lactose and the like and/or a separate disintegrating agent such as native cornstarch also is incorporated into the formulation. In most cases, however, the addition of such additional binders is unimportant in view of the excellent characteristics of the binder-disintegrant compacted starch powder of this invention. In view of this, it will be understood the present invention is directed primarily to embodiments wherein the superficially dry, free-flowing binder-disintegrant starch of this invention is the major binder ingredient employed, i.e. present in an amount corresponding to at least 50 percent of the total weight amount of tablet binding agent employed, and more preferably is the sole binding agent added to the formulation for this purpose. In some instances, a supplemental disintegrant may provide some improvement. An example of this is in the preparation of tablets of sodium p-amino-salicylate dihydrate wherein the disintegration rate of the tablet advantageously may be further accelerated by the addition of a conventional granular starch disintegration aid.

The more desirable tablets are prepared from superficially dry formulations containing from about 5 to about 15 percent moisture based on the formulation total weight. Accordingly, appropriate adjustment of the moisture content may be made, where necessary or desirable, during the formulation operation to improve the tabletting characteristics of the mixture. It may also be desirable, after mixing the ingredients, to screen the formulation to remove any oversize particles introduced in the active ingredient or tabletting aids and thereby to improve tabletting efficiency. In this respect, removal of +40 mesh particles by screening generally is desirable.

In accordance with the present invention any conventional single or rotary tablet making apparatus suitably may be employed in the tabletting operation. As is standard in conventional tabletting practice, optimum results are obtained for particular formulations by the use of the highest pressure settings consistent with good tablet press operation.

Tablets prepared from a given batch of tabletting formulation by means of the present invention are essentially uniform in thickness, weight, and active ingredient dosage level and have excellent surface smoothness as indicated by the lack of pits and cracks. A further characteristic of the tablets made according to the invention is that a substantial duplication of tablet properties is obtained by grinding the tablets to a free-flowing powder and retabletting.

While the above discussion has been limited to the preparation of tablets by direct compression, it further will be understood that the described free-flowing, directly compressible active ingredient and compacted starch powder-containing formulations, of course, also can be employed in the preparation of compressed tablets either by the double compression technique wherein slugs initially are prepared from a formulation and the slugs subsequently dry granulated to prepare tablet machine feed material or by the wet granulation method wherein a wetting agent, such as water, is added to a formulation, the moistened mass is dried without gelatinizing the compacted starch powder ingredient, and the resultant dried material is ground into granular feed for the tabletting machine. Compressed tablets which can be prepared by either method have essentially the same characteristics as those produced by direct compression. In view of the adaptability of the formulations prepared hereby to direct compression tabletting, however, the dry and wet granulation methods are impractical and can be anticipated to be rarely, if ever, employed.

The invention having been described in detail, the following examples are presented to show specific embodiments thereof. It will be understood the examples are given for illustration purposes only and not by way of limitation.

EXAMPLE I

This example illustrates the preparation of suitable tablet binder-disintegrant starches from an unmodified cornstarch and the use of the binder-disintegrant starches in the preparation of tablets by direct compression.

Three samples of ground hypochlorite-bleached native cornstarch (starch A) having the properties set forth in table 1 were converted to compacted starch powders by three different techniques. The techniques employed were as follows:

Technique 1 (Pelletizing)

One sample of the hypochlorite-bleached native cornstarch was moistened to a water content of 24–25 percent by weight and the moistened starch was pelletized at a rate of about 960 pounds/hour on a California Process Series CM-FB Master pellet mill having dies 3/16 inch in diameter and 1½ inches in length and operated at about 130 r.p.m. The resultant pellets (¼ inches length) were then dried in a rotary drier to 7.4 percent by weight moisture. The dried pellets were then ground to −10 mesh in a Model DS–6 Series 1606 stainless steel Fitzmill grinder, and the −10 mesh material was further ground to −100 mesh in a Model PC 20 Strong-Scott Pulvocron grinder operated at 3,500 r.p.m. with the classifier at 1,000 r.p.m. and the tailings return at 100 percent. The resultant powder was remoistened to 11.5–12.5 percent by weight water in a horizontal ribbon blender, and the moistened material was screened to −40 mesh. The properties of the resultant compacted starch powder (starch A_p) are set forth in table 1.

Technique 2 (Differential Roll-Milling)

The second sample of the ground hypochlorite-bleached native cornstarch was compacted, after being moistened to a water content of about 25.2 percent by weight, in an EEMCO Laboratory differential roll mill having 12-in. length rolls of 6 in. diameter. The mill was operated with a mill gap of 12 mils, and roll speeds of 50 and 70 linear feet/min. on the respective rolls. Roll temperature was maintained at about 23° C. by cooling water circulating through the rolls. The compacted starch sheet stripped from the rolls was then subjected to three additional passes through the mill. The resultant compact was then dried to a moisture content of 6–9 percent by weight. The dried compact was ground first to less than about 1.0 mm. in a Wiley mill and then to less than about 0.5 mm. in a Raymond hammer mill. The ground material was then remoistened with water to a moisture content of 11.8 percent by weight, and screened to −80 mesh. The resultant compacted starch powder (starch A_{DRM}) had the properties set forth in table 1.

Technique 3 (Compaction in Allis-Chalmers Compacter)

The third sample of the ground hypochlorite-bleached native cornstarch was adjusted to a moisture content of 21.6 percent by weight and then treated using force feeding in a compacter manufactured by Allis-Chalmers Corp. having rolls 24 inches in diameter and 8 inches in length. The compacter was operated with the rolls at ambient temperatures, a roll gap of 0.05 inch, a roll speed of 2.5 r.p.m., a force feeder speed of 15 r.p.m., and a starting bearing pressure of 1,000 p.s.i.g. The ribbonlike compact obtained was dried to 7 percent by weight water and then ground as in technique 2 above. The ground material was then adjusted to a moisture content of about 12.0 percent by weight, and then finally screened to −80 mesh. The properties of the resultant compacted starch powder (starch A_{AC}) are set forth in table 1.

TABLE 1

Starch	Description	H_2O content, percent	Cold-water solubility, percent	Swelling power	Loose bulk density, gm./ml.	Flowability, angle of repose
A	Hypochlorite bleached native corn starch	10.0	0.2–0.5	1.9–2.1	0.52–0.56	44–45
A_P	Pelletized Starch A	12.4	9.2	6.6	0.57	33
A_{DRM}	Differential roll-milled starch A	11.8	13.1	6.8	0.60	31
$A_{A.C.}$	Roll mill compacted starch A	12.0	11.6	7.2	0.59	31

The data in table 1 indicates that the three different compaction methods can each produce compacted starch powders essentially equivalent in these properties.

Superficially dry tabletting formulations were prepared by thoroughly blending the resultant compacted starch powders, each in turn, with separate powdered preparations of ascorbic acid, phenacetin, sodium p-amino-salicylate dihydrate (NaPAS) a N-acetyl-p-aminophenol (APAP) in the proportions set forth below in table 2, incorporating talc and/or colloidal silica (Cab-o-Sil) as tabletting aids into the formulations, and screening the resultant mixtures to −40 mesh. The free-flowing powders obtained were then directly tabletted on a Colton No. 204 four-punch press manufactured by the Colton Division of Cherry-Burrell Corporation, Detroit, Mich. A set of ⅜ inch diameter standard cap punches and dies was employed, and the press was operated at 35 r.p.m. to produce 140 tablets/min. The pressure setting of the press was increased in each run to a value consistent with good press operation as indicated by a "thump" in the tabletting. A sample of each of the compacted starch powders also was tabletted using the same tabletting procedure. The properties of the tablets obtained also are set forth in table 2.

The above data indicates that the compacted starch powders are directly compressible into tablets themselves and that suitably hard, nonfriable, rapidly disintegrative tablets containing relatively high levels of heretofore difficult-to-tablet drugs, i.e. ascorbic acid, phenacetin, and APAP, advantageously can be prepared using the compacted starch powders as sole dual-functioning binder-disintegrant ingredients. Although the NaPAS-containing tablets disintegrated relatively slowly, these tablets had suitable hardness and friability properties; the compacted starches are satisfactory binders even of this previously difficult-to-tablet drug.

EXAMPLE II

In order to compare the binder-disintegrant properties of the compacted starch powders employed in the present invention with those of other compacted starches, the starting bleached native cornstarch (starch A) of example I was converted to a compacted starch powder using technique 3 of example I with the exception that the moisture content of the starting starch was initially adjusted to about 18 percent by weight so that the starch was worked and modified to a lesser degree. The resultant compacted starch powder was characterized by a 2.9 percent cold-water solubles content, a swelling power of 3.0, a loose bulk density of 0.49 gm./ml., and flowability corresponding to an angle of repose of more than 40°.

The resultant compacted starch powder was tabletted alone using the procedure of example I. The tablets obtained had an average hardness of 3 kg., a friability corresponding to an average weight loss of 1.93 percent, and a disintegration time in water of 0.5–1.5 minutes. As evidenced by the poor flowability of the powder and the low hardness and high friability of the tablets prepared therefrom, the low cold-water solubles content powder is not suitable for use as a sole dual-functioning binder-disintegrant ingredient in preparing acceptable tablets by direct compression.

TABLE 2

	Formulation composition					Tablet properties			
				Adjuvants, percent by weight total formulation			Average—		
	Starch binder	Drug	Drug/binder weight ratio [1]	Talc	Colloidal silica	H_2O content, percent	Hardness, kg.	Friability percent weight loss	Disintegration time, minutes
Tablet Number:									
1	A_P		0:100			12.4	13.7	0.08	4.5–5.0
2	A_P	Ascorbic acid	40:60	7.5	0.0128	7.3	5.9	0.19	1.5
3	A_P	Phenacetin	35:65		0.0092	8.4	5.9	0.44	2.5
4	A_P	APAP	40:60	6.0	0.0087	7.4	5.7	0.23	1.5
5	A_P	NaPAS	50:50	7.0	0.0096	13.3	6.4	0.39	70–80
6	A_{DRM}		0:100			11.8	14.0	0.12	6.5–7.0
7	A_{DRM}	Ascorbic acid	35:65	5.0	0.0082	7.7	4.5	0.37	2.0–2.5
8	A_{DRM}	Phenacetin	25:75		0.0091	9.1	5.4	0.35	4.0
9	A_{DRM}	APAP	25:75	3.0	0.0082	8.4	6.6	0.20	2.5–3.0
10	A_{DRM}	NaPAS	40:60	5.0	0.0082	13.3	5.8	0.51	60–90
11	A_{AC}		0:100			12.0	14.7	0.1	9.0–9.5
12	A_{AC}	Ascorbic acid	30:70	5.0	0.0092	8.2	6.3	0.16	3.0
13	A_{AC}	Phenacetin	30:70		0.0091	8.6	6.7	0.42	3.0–3.5
14	A_{AC}	APAP	30:70	3.00	0.0093	8.4	7.2	0.43	2.0
15	A_{AC}	NaPAS	35:65	3.5	0.0076	12.7	6.4	0.31	90–105

[1] Based on binder dry substance weight.

EXAMPLE III

This example illustrates the preparation of suitable tablet binder-disintegrant starches from oxidized cornstarch and the use of the resultant binder-disintegrant starches in the preparation of tablets by direct compression.

Two samples of ground alkaline hypochlorite-oxidized cornstarch (starch B) were converted to compacted starch powder using techniques 2 and 3 of example I. However, in using technique 2 the feed starch had a moisture content of 31.0 percent by weight and the roll temperature was maintained at 31° C. and in using technique 3 the feed starch had moisture content of 27.1 percent by weight, the roll gap was 0.02 in., and the force feeder speed was 5 r.p.m. The properties of the resultant compacted starch powders (starch B_{DRM} and starch B_{AC}, respectively) are set forth in table 3 below. Using the procedure of example I, tablets were formed from each of the compacted starch powders alone and formulations prepared by thoroughly mixing each powder separately with certain drugs and tabletting aids. The compositions of the tablets and their properties are shown in table 4 below.

EXAMPLE IV

This example illustrates the preparation of a suitable tablet binder-disintegrant starch from native cornstarch and the use of the resultant binder-disintegrant starch in making tablets.

Native cornstarch (starch C) was converted to a compacted starch powder using technique 2 (differential roll-milling) of example I except that a starch feed moisture content of 28.6 percent by weight and a roll temperature of 10° C. were employed. The properties of the starting starch and resultant compacted powder starch (starch C_{DRM}) are set forth in table 3. As in the procedure of the previous examples the compacted starch powder was tabletted alone and thoroughly mixed with various drugs and tabletting aids to provide formulations which were tabletted. The compositions and properties of the tablets obtained are shown in table 4.

EXAMPLE V

This example illustrates the preparation of a tablet binder-disintegrant starch from a native high amylose starch and the use of the resultant binder-disintegrant starch in preparing tablets.

The procedure of technique 2 (differential roll-milling) of example I was employed to convert a native high amylose starch (commonly known as "Amylomaize" and designated starch D) to a compacted starch powder except that a starch feed moisture content of 27.6 percent by weight and roll temperature of 10° C. were used. The properties of the starting starch and resultant compacted starch powder (starch D_{DRM}) are set forth in table 3. The properties of placebo and drug-containing tablets prepared using the compacted starch powder in the general tabletting procedure of example I are shown in table 4.

TABLE 3.—STARCH PROPERTIES

Example No.	Starch	Description	H_2O content, percent	Cold water solubility, percent	Swelling power	Loose bulk density, gm./ml.	Flowability, angle of repose
III	B	Oxidized corn starch	11.3	1.3	2.1		
	B_{DRM}	Differential roll-milled starch B	11.7	10.2	3.6	0.56	34
	B_{AC}	do	12.3	33.6	7.1	0.63	27
IV	C	Native corn starch	11.1	0.3	1.9		36
	C_{DRM}	Differential roll-minded starch C	11.9	6.9	4.8	0.59	28
V	D	Native high amylose starch	10.9	0.4	2.6		29
	D_{DRM}	Differential roll-milled starch D	11.9	4.0	3.9	0.53	31
VI	E	Acid-modified corn starch	10.9	1.1	2.3		38
	E_{DRM}	Differential roll-milled starch E	12.0	17.7	4.0	0.63	31
VII	F	Derivatized corn starch	10.9	0.8	2.1		45
	F_{DRM}	Differential roll-milled starch F	12.1	31.5	6.5	0.63	34
VIII	G	Cross-linked starch	10.7	1.9	2.3		28
	G_{DRM}	Differential roll-milled starch G	11.9	21.1	7.0	0.60	29
IX	H	Native potato starch	13.9	0.6	2.2		31
	H_{DRM}	Differential roll-milled starch H	12.1	21.0	2.5	0.59	32

TABLE 4

Example	Tablet No.	Starch binder	Drug	Formulation composition: Drug binder weight ratio [1]	Percent by weight total adjuvants, formula: Talc	Colloidal silica	Tablet properties (Average—): H_2O content, percent	Hardness, kg.	Friability, percent weight loss	Disintegration time, minute
III	18	B_{DRM}		0:100			11.7	14.0	0.12	6.5–7.0
	19	B_{DRM}	Phenacetin	40:60		0.0103	7.4	5.4	0.43	3.5
	20	B_{DRM}	Ascorbic acid	40:60	5.0	0.0055	7.0	5.0	0.16	3.0
	21	B_{DRM}	NaPAS	40:60	5.0	0.0078	12.8	8.4	0.34	45–60
	22	B_{DRM}	APAP	35:60	3.0	0.0108	7.7	7.8	0.18	3.5–4.0
	23	B_{AC}		0:100			12.3	10.8	0.09	15.0
	24	B_{AC}	Phenacetin	25:75		0.0118	8.3	4.6	0.41	5.0–6.0
IV	25	C_{DRM}		0:100			11.9	14.3	0.10	5.0–6.5
	26	C_{DRM}	Phenacetin	40:60		0.0046	7.7	7.7	0.38	3.0–4.0
	27	C_{DRM}	Ascorbic acid	40:60	5.0	0.0093	7.1	6.0	0.31	5.5–6.0
	28	C_{DRM}	NaPAS	50:50	5.0	0.0094	13.3	6.7	0.28	70–80
	29	C_{DRM}	APAP	35:65	3.0	0.0094	7.7	8.4	0.14	3.5–4.0
V	30	D_{DRM}		0:100			11.9	13.3	0.05	3.5–4.0
	31	D_{DRM}	Phenacetin	35:65		0.0138	7.9	7.1	0.34	2.5
	32	D_{DRM}	Ascorbic acid	45:55	6.0	0.0092	6.4	5.4	0.31	3.0–3.5
	33	D_{DRM}	NaPAS	50:50	5.0	0.0094	13.3	7.5	0.28	75–85
	34	D_{DRM}	APAP	35:65	3.0	0.0094	7.7	7.7	0.26	2.0–2.5
VI	35	E_{DRM}		0:100			12.0	9.5	0.11	4.0
VII	36	F_{DRM}		0:100			12.1	9.8	0.05	9.5–10.5
VIII	37	G_{DRM}		0:100			11.9	9.5	0.11	4.0
IX	38	H_{DRM}		0:100			12.1	10.1	0.12	29.0

[1] Based on binder dry substance weight.

EXAMPLE VI

This example illustrates the preparation and use of a tablet binder-disintegrant starch derived from an acid-modified starch raw material.

An acid-modified starch (starch E) having an alkali fluidity of about 62 cc. (10 g. starch, as is basis, 77° F. and 0.375 N sodium hydroxide) was converted to a compacted starch powder employing technique 2 (differential roll-milling) of example I except that the starch feed moisture content utilized was 28.0–30.5 by weight, the roll gap was 6 mils, and the roll temperature was maintained at 23°–26° C. A comparison of the properties of the starting granular starch and the resultant compacted starch powder (starch E_{DRM}) obtained are set forth in table 3. Following the tabletting procedure of example I, placebo tablets (without drugs) were prepared using the compacted starch powder alone. The properties of the tablets obtained are reflected in table 4.

The results of these tests indicate the resultant compacted starch powder is a suitable binder-disintegrant ingredient for use in preparing acceptable drug-containing tablets by direct compression as in the previous examples.

EXAMPLE VII

This example illustrates the preparation an use of a tablet binder-disintegrant starch obtained from a derivatized granular starch raw material.

A granular derivatized cornstarch containing about 2.5 percent acetyl groups (starch F) was converted to a compacted starch powder using technique 2 (differential roll-milling) of example I except that the feed starch moisture content was 28.3–31 percent by weight, a roll gap of 12 mils was employed, and roll temperatures were maintained at 23–24° C. The properties of the starting starch and the resultant compacted starch powder (starch F_{DRM}) are set forth in table 3. Using the tabletting procedure of example I, placebo (drug-free) tablets were prepared from the compacted starch powders. The properties of the tablets are shown in table 4.

When substituted as the binder-disintegrant ingredient in the preparation of the drug-containing tablets described in the preceding examples, the compacted starch powder provides tablets of properties comparable to those mentioned.

EXAMPLE VIII

This example illustrates the preparation and use of a tablet binder-disintegrant starch obtained from a cross-linked granular starch raw material.

The procedure of example VI was repeated with the exception of substituting a granular cross-linked cornstarch obtained by reacting oxidized cornstarch with phosphorus oxychloride (starch G) for the acid-modified starch. The properties of the starting starch and resultant compacted starch powder (starch G_{DRM}) are set forth in table 3. The characteristics of the tablets obtained are shown in table 4. Drug-containing tablets prepared by direct compression, using the resultant compacted starch powder as a binder-disintegrant ingredient as in the preceding examples, have characteristics similar to such tablets described above.

EXAMPLE IX

This example illustrates the preparation and utilization of a tablet binder-disintegrant starch derived from potato starch.

The procedure of example VII was repeated except that native potato starch (starch H) was substituted for the derivatized cornstarch. A comparison of the properties of the starting starch and the resultant compacted starch powder (starch H_{DRM}) is shown in table 3, and the characteristics of the placebo tablets prepared therefrom are listed in table 4. When employed as a binder-disintegrant ingredient in preparing drug-containing compressed tablets, such as those prepared above by direct compression, the resultant compacted starch powder provides acceptable tablets.

EXAMPLE X

This example illustrates an embodiment of the present invention wherein a binder-disintegrant starch is employed in combination with an uncompacted starch in the preparation of active ingredient tablets by direct compression, the uncompacted starch being employed as a filler and disintegrant ingredient in the tablets.

A sample of starch D_{DRM} (differential roll-milled native cornstarch) described above in example IV was thoroughly mixed with sodium p-aminosalicylate dihydrate (NaPAS) and ground bleached native cornstarch containing about 10 percent by weight moisture in a weight ratio of drug:compacted starch:uncompacted starch of 30:60:10, starch dry substance basis. Talc and colloidal silica (Cab-o-Sil) also were added during the mixing in amounts of 6.0 percent and 0.0109 percent by weight of the total formulation, respectively. The resultant powder which had a moisture content of 12.1 percent by weight was tabletted directly using the procedure of example I. The resultant tablets were characterized by an average hardness of 8.7 kg., a friability corresponding to an average weight loss of 0.24 percent, and a disintegration time of 20–26 minutes.

EXAMPLE XI

This example illustrates embodiments of the present invention wherein a binder-disintegrant starch is employed in the preparation of tablets by direct compression wherein the tablets are intended for nonpharmaceutical uses.

Using starch A_p (pelletized bleached native cornstarch) described in example I as the binder-disintegrant ingredient and the tabletting procedure of example I, tablets that disintegrate rapidly in water and have excellent hardness and friability properties are prepared from the following formulations:

Plant Root-growth Stimulant Tablets	Parts by weight
Starch A_p	90
1-Naphthalene acetic acid	9
Colloidal silica (Cab-o-Sil)	1
Garlic Tablets	
Starch A_p	23
Powdered garlic (Dehydrated)	70
Colloidal silica (Cab-o-Sil)	2

Table 5 below contains comparative data showing that compaction of starch so as to impart the properties set forth above in table form on page 7 renders the starch powder useful in forming tablets by direct compression whereas the same starch, noncompacted, does not have this property. In the table the heading "Allis-Chalmers Compacter Conditions" refers to technique 3 set forth on page 22 above while the heading "Differential Roll Mill Conditons" refers to technique 2 set forth above on pages 21 and 22. The starch used in samples Nos. 1–10, 12 and 13 is ordinary powder native cornstarch bleached with sodium hypochlorite to make it whiter while the oxidized starch used in sample 11 is a corn starch oxidized by sodium hypochlorite under alkaline conditions until it has about 0.5 percent carboxyl groups.

The data in table 5 may be summarized as follows:

a. Sample 1, 2, 7, 8, 9 and 10, which were not compacted and which did not fall within the parameters set forth on page 7 with respect to at least two of cold-water solubility, swelling power, loose bulk density, and moisture content, could not be tabletted.

b. Samples 3, 4, 5, 6, 11, 12 and 13, which were compacted, could be tabletted. However, sample 3 had a cold-water solubility below the required minimum and the tablets formed therefrom were not satisfactory since they were not sufficiently hard and were excessively friable. Samples 4, 5 and 6 had values for cold-water solubility, loose bulk density and

swelling power within the range as set forth in the table on page 7.

c. Sample 13, which was compacted well beyond any of the others, had excess cold-water solubility and excess swelling power. While it could be tabletted, the tablets did not disintegrate in over 45 minutes, well beyond the requirements for a useful tablet binder-disintegrant.

d. In the Allis-Chalmers Compacter, increasing compaction is obtained by narrowing the gap, increasing the water content, increasing the speed of the feeder, increasing the bearing pressure or any combination of these. The data for samples 3, 4, 5 and 6 show that increasing the extent of compaction increased the tablet hardness and disintegration time while decreasing friability.

TABLE 5

Type of starch	H_2O in feed starch	Allis Chalmers compacter conditions: Roll gap, inches	Force feeder, r.p.m.	Bearing pressure, lbs.	Powder subjected to tabletting (<80 mesh): Percent cold water solubles	Loose bulk density gm./ml.	Swelling power	Percent H_2O	Tablet: Hardness (kg.)	Friability percent weight loss	Disintegration, minutes
Sample Number:											
1 Bleached starch	10.0				0.3	0.52	1.9	10.0	Unable to make tablets		
2 do	20.7				0.8	0.46	2.45	9.7			
3 do	18.2	0.05	5	1,000	2.9	0.49	2.97	11.9	3.0	1.93	0.5–1.5
4 do	18.2	0.05	16	1,300	7.4	0.50	5.02	11.9	7.3	0.32	5.0–5.5
5 do	21.6	0.05	15	1,000	11.6	0.59	7.17	11.9	14.7	0.10	9.0–9.5
6 do	21.6	0.02	10	1,000	13.3	0.55	9.04	11.9	12.2	0.05	18.0–19.5
7 do	11.6				0.4	0.51	2.01	11.6	Unable to make tablets		
8 do	9.1				0.4	0.45	2.23	9.1			
9 do	10.4				0.2	0.56	1.97	10.4			
10 do	7.4				1.3	0.44	2.06	7.4			
		Differential roll mill conditions: Roll gap, mils	Roll speeds, ft./min.	No. of passes							
11 Oxidized starch	31.0	12	50–70	2	10.2	0.56	3.64	11.7	14.0	0.12	6.5–7.0
12 Bleached starch	25.2	12	50–70	4	13.1	0.60	6.79	11.8	13.2	0.13	7.5–8.5
13 do	27.0	12	50–70	[1] 4	61.1	0.56	12.3	11.8	14.8	0.01	[2] >45

[1] Minutes equivalent to 128 to 180 passes.
[2] Had not disintegrated in 45 minutes when test was halted.

We claim:

1. A directly compressed tablet requiring a disintegrant and a binder, having resistance to breaking and crumbling, and being capable of disintegrating in an aqueous medium, said tablet comprising (a) an active ingredient by which said tablet derives its utility and (b) a pulverulent cohesive binder for said active ingredient, said binder comprising as the only dual-function binder and tablet-disintegrant a directly compressible compacted starch powder in a concentration that provides substantial binding action and substantially accelerates disintegration of said tablet in an aqueous medium, said compacted starch powder being a superficially dry, free-flowing material in which the starch is in the form of a mixture of birefringent granules and nonbirefringent fragments of granules, in which some aggregates of granules and fragments are present and having a cold-water solubility in the range of from about 4 to about 40 percent by weight, dry substance basis, a swelling power in the range of from about 2.5 to about 12, a loose bulk density in the range of from about 0.50 to about 0.70 gram per milliliter, a moisture content in the range of from about 9 to about 16 percent, total weight basis, and a particle size distribution such that said powder is essentially free of +40 mesh size material and that on a total weight basis, at least 90 percent of said powder is −80 mesh size, at least about 10 percent of said powder is +270 mesh size, and from about 30 to about 90 percent of said powder is −270 mesh size said powder being adapted to function as the essential, bifunctional disintegrant and binder in the direct compression method of tablet manufacture.

2. The compressed tablet according to claim 1 wherein said active ingredient is a pharmaceutically active compound.

3. The compressed tablet according to claim 1 wherein said active ingredient is a nonpharmaceutically active compound.

4. The compressed tablet according to claim 1 wherein said compacted starch powder constitutes at least about 50 percent of the total weight amount of binder in said tablet.

5. The compressed tablet according to claim 1 wherein the amount of said active ingredient in said tablet is in the range of from about 5 percent to about 90 percent dry substance weight basis.

6. The compressed tablet according to claim 1 wherein said compacted starch powder constitutes at least about 50 percent of the total weight amount of binder in said tablet, has a cold-water solubility in the range of from about 6 to about 20 percent, dry substance weight basis, and a swelling power in the range of from about 3.5 to about 10, and contains, on a total weight basis, from about 45 to about 75 percent of material which is −270 mesh.

7. The compressed tablet according to claim 6 wherein said compacted starch is a compacted granular cornstarch raw material.

8. The compressed tablet according to claim 7 wherein said granular cornstarch raw material is bleached native cornstarch and said compacted starch powder has a cold-water solubility in the range of from about 6 to about 15 percent, dry substance weight basis, and a swelling power in the range of from about 5 to about 8.

* * * * *

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,622,677 Dated November 23, 1971

Inventor(s) Rolland W. P. Short and Frank Verbanac

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 3, line 41, "powers" should be --powders--.

Column 9, line 17, "formations" should be --formulations--.

Column 11, line 36, "a" should be --and--.

Column 11, Table 2, last column, next to last entry reading as "2.0" should be --2.5-- and last entry reading as "90-105" should be --90-100--.

Column 13, Table 3, third column, line 5, "roll-minded" should be --roll-milled--.

Column 15, line 7, "g." should be --gm.--

Column 15, line 26, "an" should be --and--.

Column 16, line 57, "Conditons" should be --Conditions--.

Signed and sealed this 9th day of January 1973.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents

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