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(57) Abstract

A particulate co–processed composition that includes a botanical plant, microcrystalline cellulose and calcium carbonate. The botanical plant is selected from the group consisting of grains, plants, roots, and mixtures thereof. The co–processed composition is particularly useful in the manufacture of vitamins and food supplements. The co–processed composition is prepared by forming a slurry of the botanical plant, microcrystalline cellulose, and calcium carbonate and then spray drying the slurry to yield a particulate product.

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PLANT MATERIAL COMPOSITION

The present invention relates to a particulate co-processed plant composition that includes a botanical plant, microcrystalline cellulose, and calcium carbonate. The composition is particularly useful in vitamin and nutritional supplement formulations. The present invention is an improvement on the known co-processed microcrystalline cellulose formulations. In the present invention, the botanical plant, microcrystalline cellulose, and calcium carbonate are processed together in an aqueous medium and dried to yield a particulate product.

BACKGROUND OF THE INVENTION

It is desirable to provide vitamin and/or nutritional supplement formulations that contain a substantial amount of natural products such as botanical plants. One such product is marketed under the Nutrilite brand name as Double XX or Triple XXX. These products are generally tablets and contain a substantial amount of the botanical plant, alfalfa. A benefit resulting from the use of a botanical plant in such tablets is that they can provide phytonutrients, phytochemicals, and other substances beneficial to human health.

In general, these products are made by a wet granulation tabletting process. In this process, the ingredients are granulated, mixed with a solution, milled, dried, mixed with processing aids and compressed to form cores. The cores are then stored for a period of time after which they are coated and packaged. Although this process provides suitable tablets, it can be improved. One such desired improvement would be to increase the initial hardness as well as the hardness both before coating and after coating. It is known that tablets made according to a wet granulation process have a suitable initial hardness but that they relax or soften both

before and after coating. As a result, the tablets may be more susceptible to breaking during further processing and shipping.

Microcrystalline cellulose finds widespread use as a pharmaceutical excipient because it possesses desirable compressibility characteristics. Microcrystalline cellulose is a purified, partially de-polymerized cellulose that is prepared by treating alpha cellulose, in the form of a pulp manufactured from fibrous plant material, with mineral acids. It is a white, odorless, tasteless, relatively free flowing powder that is insoluble in water, organic solvents, dilute alkalis and dilute acids. U.S. Pat. Nos. 2,978,446 issued to Battista et al. and 3,146,168 issued to Battista describe microcrystalline cellulose and its manufacture; the latter patent concerns microcrystalline cellulose for pharmaceutical applications. Both are incorporated herein by reference in their entirety.

Unfortunately, microcrystalline cellulose is relatively costly to manufacture. This limits its use in price-sensitive formulations like vitamins and nutritional supplements. Thus, a lower cost replacement that has tabletting characteristics similar to those of microcrystalline cellulose is desired.

One solution is proposed by U.S. Pat. No. 5,585,115, which describes a particulate agglomerate of microcrystalline cellulose and from about 0.1-20% silicon dioxide. Another solution is proposed by U.S. Pat. No. 4,744,987, which describes a particulate co-processed microcrystalline cellulose and calcium carbonate in a ratio of 75:25 to 35:65.

Although these proposed solutions may be cheaper than simply using microcrystalline cellulose alone, each still requires a major amount of microcrystalline cellulose. Thus, there is still a need for a product that is suitable for

tabletting and that has acceptable compressibility characteristics but contains less microcrystalline cellulose than the co-processed microcrystalline cellulose products in the prior art.

The present invention solves the above needs by providing a composition that includes three components: a botanical plant, microcrystalline cellulose, and calcium carbonate, each of which are co-processed in a manner that produces a particulate product having unexpectedly good performance characteristics. For example, the product provides excellent compressibility, flow properties, hardness properties, and rapid disintegration. Moreover, the composition of the present invention provides advantages not found in tablets made according to a wet granulation method.

SUMMARY OF THE INVENTION

In accordance with the present invention, a novel composition is provided that is useful for nutritional supplements and vitamins. In other words, in one aspect of the present invention, a nutritional supplement or vitamin tablet that contains the novel composition according to the present invention is provided.

The composition is a particulate co-processed composition that includes a botanical plant, microcrystalline cellulose, and calcium carbonate, with the botanical plant being present in an amount from about 1% to about 75%, the microcrystalline cellulose being present in an amount from about 1% to about 50%, and the calcium carbonate being present in an amount from about 1% to about 75%. The composition may be combined with other ingredients and compressed to form a tablet. Alternatively, the composition may be directly compressed to provide a botanical plant tablet.

The botanical plant is preferably a natural ingredient suitable for oral ingestion by a human. Preferably, the botanical plant is selected from the group consisting of edible grains, plants, roots, and mixtures thereof. More preferably, the botanical plant is selected from the group consisting of alfalfa, wheat, oat, barley, rice, corn, watercress, parsley, brassica and umbelliferous plants, spinach, spirolina, and mixtures thereof.

The microcrystalline cellulose may be derived from any source. The term "microcrystalline cellulose" as used in the foregoing specification and the appended claims means both the wet cake from a conventional microcrystalline cellulose process and the dried or finished product. The wet cake is material that has not yet been dried and is oftentimes referred to as hydrocellulose. The dried or finished product is commercially available under the trade name EMCOCEL® from Edward Mendell Co. or as Avicel® from FMC Corp.

The calcium carbonate can be derived from any source such as by precipitation, mining, and harvesting (e.g., from oyster shells).

Each of the three components are intimately associated in the co-processed product and may be present as agglomerates of the three components. The particulate co-processed composition is preferably a spray dried material. Preferably, the particle size of the co-processed product is such that substantially all particles are less than No. 60 sieve (250 μm) and preferably have an average particle size in the range of from 20 μm to 150 μm.

The particulate co-processed composition is prepared by forming a well-dispersed aqueous slurry of the botanical plant, microcrystalline cellulose, and calcium carbonate and then drying by removing water resulting in the particulate co-

processed product. The aqueous well-dispersed slurry of the three components is preferably formed by introducing the microcrystalline cellulose, calcium carbonate, and botanical plant into an aqueous medium, with their addition being in the order mentioned, in amounts that yield a relatively concentrated slurry of at least 1% solids. The aqueous slurry is preferably dried by spray drying to yield the particulate co-processed product.

It is therefore an object of the present invention to provide an oral solid dosage form for one or more active ingredients that is economical to manufacture, maintains its integrity during storage, and possesses excellent disintegration and dissolution properties when exposed, e.g., to gastrointestinal fluid. Advantageously, the composition according to the present invention has a hardness after storage for two days (i.e. a retained hardness) that is within the range of 0 to about 15% less than the initial hardness, preferably within the range of 0 to about 10% less than the initial hardness.

The present invention is further directed to a mixture of an active ingredient(s) and the particulate co-processed composition of the present invention. The ratio of active ingredient to the co-processed composition is from about 1:99 to about 99:1, by weight.

The present invention is further directed to a compressed solid dosage form comprising an active ingredient(s) and the novel co-processed composition described herein, wherein the active ingredient(s) and the co-processed composition have been directly compressed into the solid dosage.

It is to be noted that, unless otherwise stated, all percentages stated in this specification and appended claims refer to percentages by weight.

These and other objects, advantages, and features of the present invention will be better understood upon review of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a ternary diagram of various embodiments of the co-processed composition of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The particulate co-processed composition of this invention contains three essential components; a botanical plant, microcrystalline cellulose, and calcium carbonate. Referring to FIG. 1, several areas have been labeled and depict the ranges for each component that may be useful for preparing compositions according to the present invention. The areas labeled A and B depict useful and preferred combinations of each ingredient, respectively. Area C depicts a preferred combination of each ingredient where the calcium carbonate is precipitated or mined. Area D depicts a preferred combination of each ingredient where the calcium carbonate is supplied from oyster shells. It will be apparent that those areas correspond with the following ranges:

Component	A (wt. %)	B (wt. %)	C (wt. %)	D (wt. %)
Botanical plant	1-75	10-60	30-50	35-55
Microcrystalline cellulose	1-50	10-30	15-25	15-25
Calcium carbonate	1-75	10-60	30-50	25-45

Other ingredients may also be incorporated into the particulate product during its preparation. These are ordinarily present in relatively small amounts, representing less than 20%, and preferably less than 10%, of the total particulate

product weight. Such additives may be incorporated to facilitate the co-processing procedure, particularly during the drying step, or to provide enhanced properties for resulting finished products. Examples of additives in these categories are binders, e.g., water-soluble gums like hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, etc.; lubricants, e.g., long chain fatty acid esters or salts thereof like palmitic and stearic acids; disintegrants like cross-linked carboxymethylcellulose, starch, etc.; and non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, celluloses, cellulose ethers, cellulose esters and mixtures thereof.

Desirably, however, these other ingredients are added to the resulting co-processed composition. In this regard, it is preferred that the co-processed composition consists essentially of the botanical plant, the calcium carbonate, and the microcrystalline cellulose.

The particulate co-processed product of this invention possesses desirable performance attributes that are not achieved by the corresponding wet granulation of botanical plant, microcrystalline cellulose, and calcium carbonate. The mechanism that occurs during the co-processing procedure required in this invention is not fully understood but appears to yield a particulate product in which the three essential components are in intimate association with each other. This intimate association or admixture of the botanical plant, microcrystalline cellulose, and calcium carbonate requires that they be co-processed as an aqueous slurry or mixture.

This intimate association of the three components apparently manifests itself in the appearance of particles, containing the botanical plant, microcrystalline cellulose, and calcium carbonate that result after drying of the slurry.

In simple terms, the process for preparing the particulate product of this invention involves forming a well-dispersed aqueous slurry of the botanical plant, microcrystalline cellulose, and calcium carbonate. The relative amounts of the three components are adjusted in the slurry to yield the specific weight ratio desired in the recovered co-processed product. Since the weight ratio of the three components in the particulate co-processed product corresponds closely to that in the precursor well-dispersed slurry, this ratio adjustment is relatively straightforward.

The process of this invention next involves drying the aqueous slurry by removing water from it to yield the particulate co-processed product. Spray drying is the preferred drying means but other drying methods, e.g. flash drying, freeze drying, fluidized bed drying, ring drying, micron drying, tray drying, vacuum drying, radio-frequency drying, or microwave drying, may also be adapted for use in this co-processing step.

The three components used in forming the well-dispersed aqueous slurry are the botanical plant, microcrystalline cellulose, and calcium carbonate. The source and nature of these components is not particularly critical.

For example, the botanical plant can be a natural ingredient suitable for oral ingestion by a human. Preferably, the botanical plant is selected from the group consisting of edible grains, plants, roots, and mixtures thereof. More preferably, the botanical plant is selected from the group consisting of alfalfa, wheat, oat, barley, rice, corn, watercress, parsley, spinach, brassica and umbelliferous plants, spirolina, and mixtures thereof. In a preferred embodiment, the botanical plant consists of alfalfa.

The botanical plant material should be finely ground so that substantially all, e.g., greater than about 95%, passes through a 100 mesh screen (i.e., about 250 μm).

The co-processed composition includes from about 1% to about 75% of the botanical plant, preferably from about 10% to about 60%, with amounts greater than 20%, such as 25% being a more preferred minimum. The botanical plant is preferably included in an amount from about 30% to about 50%, most preferably about 40%, when the calcium carbonate source is mined or precipitated. The botanical plant is preferably included in an amount from about 35% to about 55%, most preferably about 45%, when the calcium carbonate is derived from oyster shells.

The microcrystalline cellulose used in the composition of the present invention can be the so-called wet-cake or the dried finished product. Wet cake is material that has not yet been dried, to yield a conventional microcrystalline cellulose free-flowing powder product. The wet cake is sometimes referred to as "never dried" or hydrocellulose.

The dried finished microcrystalline cellulose may be prepared by partially depolymerizing cellulose obtained as a pulp from fibrous plant material with dilute mineral acid solutions. Following hydrolysis, the hydrocellulose thereby obtained is purified via filtration and the aqueous slurry may be spray dried to form dry, white odorless, tasteless crystalline powder of porous particles of a broad size distribution. Another method of preparing microcrystalline cellulose is disclosed in U.S. Pat. No. 3,141,875. This patent discloses subjecting cellulose to the hydrolytic action of hydrochloric acid at boiling temperatures so that amorphous cellulosic material can

be removed and aggregates of crystalline cellulose are formed. The aggregates are collected by filtration, washed with water and aqueous ammonia and disintegrated into small fragments, often called cellulose crystallites by vigorous mechanical means such as a blender.

The particle size of the microcrystalline cellulose used in the aqueous slurry is ordinarily that which is encountered in conventional microcrystalline cellulose product, or in its precursor wet cake. No matter how made, microcrystalline cellulose is commercially available in several grades that range in average particle size from 5 to 200 microns. The particle size is desirably such that substantially all particles are less than No. 60 sieve (250 μm) in size.

Specific size requirements for fine particle sizes, if desired, can be met through screening off unwanted coarse material or through conventional wet or dry attrition procedures. Such attrition may also be accomplished with the microcrystalline cellulose in the aqueous slurry. These size reduction procedures are ordinarily not required with microcrystalline cellulose as is now commercially produced.

The microcrystalline cellulose is present in the co-processed composition in an amount less than about 50%, typically from about 1% to about 50%, preferably from about 10% to about 30%, more preferably from about 15% to about 25%, and most preferably about 20%.

The calcium carbonate ($CaCO_3$) used in this invention may be from any known source. For example, without limitation, the calcium carbonate can be from a precipitated material, mined material, or harvested material such as oyster shells. Precipitated calcium carbonate may be desirable since it is ordinarily more pure than

ground calcium carbonate and typically has a finer particle size. Ground calcium carbonate may nevertheless be used as a source with satisfactory results. To provide a more natural end product, calcium carbonate from oyster shells is preferred.

The particulate calcium carbonate is preferably finer in particle size than the particulate microcrystalline cellulose with which it is co-processed. Extremely fine particle size calcium carbonate is more readily combined in intimate association with the microcrystalline cellulose during co-processing of the three components.

Calcium carbonate sizing is preferably such that substantially all particles are less than about 150 μm, preferably less than about 105 μm in size.

The calcium carbonate may be included in the co-processed composition of the present invention in an amount from about 1% to about 75%, preferably from about 10% to about 60%. When the calcium carbonate source is mined or precipitated, it is preferably included in an amount from about 30% to about 50%, most preferably about 40%. When the calcium carbonate is derived from oyster shells, the botanical plant is preferably included in an amount from about 25% to about 45%, most preferably about 35%.

Both microcrystalline cellulose and calcium carbonate are substantially insoluble in water. Consequently, the particle size of the material present in the well dispersed aqueous slurry is directly related to the sizing of the two components introduced to the slurry; i.e., there is no appreciable dissolution of either of these two components in the aqueous slurry.

The aqueous slurry of these three components may be prepared in any of several ways. The three components may both be introduced into a single aqueous

medium, or each may be introduced separately into separate aqueous media that are then combined, or other analogous procedures may be devised.

One procedure involves dispersing the microcrystalline cellulose alone into an aqueous solution, preferably water. Once the microcrystalline cellulose is well dispersed in the aqueous slurry, the appropriate amount of calcium carbonate may be added, in dry form, with mixing being continued during its addition. The exact amount of calcium carbonate to be added depends on the microcrystalline cellulose content of the slurry, the amount of botanical plant to be added, and the ratio of the three components desired in the co-processed product.

Once the microcrystalline cellulose and calcium carbonate are well dispersed in the aqueous slurry, the desired amount of botanical plant may be added, with continued mixing. The amount of botanical plant to be added depends on the microcrystalline cellulose and calcium carbonate content of the slurry and the ratio of the three components desired in the co-processed product.

Water may also be added if a more dilute slurry is desired, but this is usually not required. The aqueous slurry containing the three components should be well mixed to assure uniform dispersion of the components throughout the aqueous medium. This is necessary to provide for a uniform, consistent component ratio in the particulate product, prepared by drying the aqueous slurry.

The total solids content of the aqueous slurry should be at least 1%, based on the total slurry weight, and preferably should be at least 20% solids, more preferably. 35% solids. The higher solids content levels are desirable since the amount of water that must be removed during the drying step is accordingly reduced. Consequently, the solids content of the aqueous slurry will be as high as can be achieved and yet

allow efficient processing conditions. The upper limit on solids content in the aqueous slurry is typically determined by the operating constraints of the drying apparatus used.

The temperature of the aqueous slurry is not critical. Ambient temperatures, of from about 10-25° C., are generally preferred. Higher slurry temperatures may be used, and these may be desirable with certain types of drying equipment.

The drying of the well-dispersed aqueous slurry is preferably accomplished by spray drying of the slurry. Conventional spray drying equipment may be used, and operating procedures that are familiar to those experienced in the spray drying art are applicable to the spray drying step of this process. Drier (drier gas) outlet temperature is ordinarily used to control the residual moisture level obtained in the co-processed particulate product. In a spray drying procedure, drier outlet temperatures are ordinarily in the range of about 40-100° C. Corresponding drier inlet temperatures are higher, ordinarily in the range of about 90-300° C.

Moisture levels of about 0.5% to about 10% water are desired in the co-processed dried composition and moisture levels of about 1% to about 8% are preferred, with a level of from about 1.5% to about 4% being more preferred and about 1.8% being most preferred.

The co-processed product recovered from the drying operation is a free-flowing particulate solid, that typically has a fine granular powder appearance. The particle size of the product is a function of the particle size of the botanical plant, microcrystalline cellulose, and calcium carbonate in the aqueous slurry and, more importantly, of the drying conditions employed for removing water from the slurry. The particulate co-processed product should have a particle size such that

substantially all are less than No. 60 sieve (250 μm). The average particle size of the particulate material is preferably in the range of from about 20 μm to 150 μm and more preferably is in the range of from about 30 μm to 100 μm with a range of about 50 μm to about 90 μm being most preferred.

The exact relationship of the components of the composition after co-processing is not presently understood; however, for purposes of description the co-processed particles are described herein as including an agglomerate of microcrystalline cellulose, calcium carbonate and botanical plant in intimate association with each other. By "intimate association," it is meant that each component has in some manner been integrated with the other components, as opposed to a chemical interaction of the ingredients. The term "intimate association" is therefore deemed for purposes of the present description as being synonymous with "integrated" or "united." The co-processed particles, however, are not necessarily uniform or homogeneous.

The bulk density (loose) of the co-processed product is typically in the range of about 0.4 to about 0.6 g/cm^3. Microcrystalline cellulose ordinarily exhibits a loose bulk density of about 0.28-0.30 g/cm^3.

The particulate co-processed product of this invention, besides being economical, has several desirable properties that make it particularly well-suited for use in direct compression tabletting applications such as those typically used in making vitamins and nutritional supplements. For example, the compressibility of this co-processed product compares favorably with that of commercially available microcrystalline celluloses. Compressibility is typically measured as the profile, or shape, of the plot of tablet hardness vs. tablet compression force.

Importantly, the co-processed product and products incorporating the co-processed product of the present invention show excellent initial hardness values. In fact, the average initial hardness of the compositions according to the present invention is on average about 5% to 20% greater than tablets made according to a wet granulation process. More importantly, these products retain a substantial amount of their initial hardness over time. In general, these products exhibit a hardness after storage for two days within the range of 0 to 15% of the initial hardness. In other words, tablets incorporating the co-processed composition retain at least 85% of the initial hardness of the tablet

The novel co-processed composition of the invention is free-flowing and directly compressible. Accordingly, the co-processed composition of the present invention may be mixed in the desired proportion with an active agent and optional lubricant, and then directly compressed into solid dosage forms.

The active agent(s) that may be combined with the novel co-processed composition into solid dosage forms include herbs, herbal extracts, fruits, vegetables, extracts from fruits and/or vegetables, vitamins, antioxidants, proteins, minerals, fatty acids, lecithin, honey, therapeutic agents, and the like.

The solid formulations of the invention may also include other locally active agents, such as flavorants and sweeteners. Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing,* pub 1274 by the National Academy of Sciences, pages 63-258 may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, FD & C and D & C dyes; see the Kirk-Othmer

Encyclopedia of Chemical Technology, Vol. 5, pp. 857-884, hereby incorporated by reference), stabilizers, binders, odor controlling agents, and preservatives.

The following examples illustrate, but do not limit, the present invention. Unless otherwise indicated, all parts and percentages are by weight.

EXAMPLE 1

Tablets were prepared by blending a co-processed alfalfa composition according to the present invention with other excipients and compressing the blend to form tablets. An iron dissolution test was performed according to USP 23-NF 18 on a tablet. It was found that the tablet exhibited 100% iron dissolution after 60 minutes and exhibited 90% iron dissolution after 10 minutes.

Commercially available tablets under the brand name Triple X from Nutrilite contain an alfalfa base together with calcium carbonate and microcrystalline cellulose and are made using a wet granulation process. An iron dissolution test was performed according to USP 23-NF 18 on a Triple X tablet. It was found that the tablet exhibited 56% iron dissolution after 60 minutes.

These results demonstrate that a tablet that incorporates the co-processed botanical composition of the present invention not only achieves complete dissolution but does so much more rapidly than a tablet prepared using a conventional wet granulation process.

EXAMPLE 2

The following was conducted to determine the tableting performance based on Hiestand's indices of tableting performance of alfalfa and a co-processed composition according to the present invention. A square faced compact was prepared under triaxial compression using 100 mesh dried alfalfa powder (the

"alfalfa compact"). The compact was about 19 mm x 19 mm x 10 mm. Another square faced compact was prepared under triaxial compression using the co-processed composition according to the present invention. This compact had the same size as the alfalfa compact and contained about 45% by weight of 100 mesh alfalfa, 35% by weight of calcium carbonate (from oyster shells), and 20% by weight of microcrystalline cellulose.

The following Hiestand indices were calculated: the strain index (SI), the worst case bonding index (WBI), and the brittle fracture index (BFI). The strain index is calculated from the dynamic indentation hardness and the reduced elastic modulus of the compacts at a given porosity (P_d/E') and it indicates the strain energy that could develop during decompression and elastic recovery following compression. In general, a higher SI associated with a low WBI would increase the likelihood of tablet cracking, capping, and lamination.

The worst case bonding index is calculated as the ratio of tensile strength and dynamic indentation hardness (P_d). The brittle fracture index is calculated according to $0.5(T/T_0 - 1)$ where T is the tensile strength of an intact compact and T_0 is the tensile strength of the compact with a hole. The brittle fracture index provides a measure of stress concentration and thus, the propensity for crack development and brittle fracture. Fracture problems are severe when BFI > 0.8.

Table 1 presents the average of the results obtained for the alfalfa compact and for the co-processed composition.

Table 1

Compact	Hiestand's Indices		
	SI (x 100)	WBI (x 100)	BFI
Alfalfa	2.30	2.56	0.123
Co-Processed	1.53	3.36	0.003

The results indicate that the use of alfalfa alone may tend to produce a tablet having a propensity to develop cracks and brittle fracture. The use of the co-processed composition would be expected to provide good tableting performance.

EXAMPLE 3

The following was conducted to demonstrate the advantageous hardness levels of the co-processed compositions according to the present invention. Tablets were made according to a wet granulation process using alfalfa, calcium carbonate, and microcrystalline cellulose. The initial hardness of the tablets was measured and average hardness was 27.1 SCU. The tablets were stored. After three to five days, the average hardness was 22 SCU, representing an 18.8% decrease in initial hardness. After nine to ten days, the average hardness was 21.6 SCU, representing a 20% decrease in initial hardness.

The tablets made according to the wet granulation method were allowed to sit from three to four days before coating. After the tablets were coated, they were stored. The hardness of the stored coated tablets was measured after two days, three days, and six days. After two days, the average hardness was 20.5 SCU, representing a 24% decrease from the initial hardness. After three days, the average hardness was 20.1 SCU, representing a 25.8% decrease from the initial hardness. After six days, the average hardness was 19.3 SCU, representing a 28.8% decrease from the initial hardness.

Compressed tablets were made using the co-processed composition according to the present invention. The co-processed composition contained 45% by weight alfalfa, 35% by weight calcium carbonate, and 20% by weight microcrystalline cellulose and it was made by spray drying the ingredients. The

initial hardness was measured the average was 36.3 SCU, which is about a 36% increase in initial hardness as compared to the wet granulation process.

The tablets were stored for seven days and the hardness was measured. The average hardness was 33 SCU, which is only a 9.15 decrease in initial hardness. The tablets were coated after seven days and then their hardness was measured. The average hardness after coating was 31.6 SCU, which is a 14% decrease in the initial hardness.

A comparison of the results of the hardness measurements of the tablets incorporating the co-processed composition according to the present invention with the hardness measurements of tablets made according to wet granulation shows that the co-processed compositions according to the present invention retain a greater amount of the initial hardness as compared to the wet granulation tablets.

These results also demonstrate that a tablet containing the spray-dried co-processed composition which includes a botanical plant, a calcium carbonate, and microcrystalline cellulose has an initial hardness greater than 30 SCU as well as has a hardness after seven days of storage that is within the range of 0 to 15% less than the initial hardness. In other words, after seven days of storage, the tablet containing the co-processed composition retains at least 85% of the initial hardness of the tablet.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention. It is intended to claim all such changes and modifications that fall within the true scope of the invention.

What is claimed is:

1. A composition comprising dried particulates of co-processed botanical plant, microcrystalline cellulose, and calcium carbonate, the three components being intimately associated with each other.

2. The composition of claim 1, wherein the particulate is a spray-dried co-processed botanical plant, microcrystalline cellulose, and calcium carbonate.

3. The composition of claim 1 wherein the botanical plant is present in an amount from about 1% to about 75% by weight , the microcrystalline cellulose is present in an amount from about 1% to about 50% by weight and the calcium carbonate is present in an amount from about 1% to about 75% by weight.

4. The composition of claim 1 wherein the botanical plant is selected from the group consisting of grains, plants, roots and mixtures thereof.

5. The composition of claim 4 wherein the botanical plant is selected from the group consisting of alfalfa, wheat, oat, barley, rice, corn, watercress, parsley, spinach, brassica and umbelliferous plants, spirolina, and mixtures thereof.

6. The composition of claim 1 wherein the particulates have a particle size less than about 250 μm.

7. The composition of claim 1 wherein the particulates have an average particle size in the range of from 20 μm to 150 μm.

8. The composition of claim 1 wherein the particulate has a moisture content of from about 1% to about 10%.

9. The composition of claim 1, wherein the composition has a bulk density from about 0.4 g/ml to about 0.6 g/ml.

10. The composition of claim 1, wherein the particles have an initial hardness greater than 30 SCU.

11. The composition of claim 10, wherein the particles have a hardness after seven days of storage that is at least 85% of the initial hardness.

12. The composition of claim 1, wherein the composition further comprises an additive selected from the group consisting of non-silicon metal oxides, starches, starch derivatives, surfactants, polyalkylene oxides, celluloses, cellulose ethers, cellulose esters and mixtures thereof, wherein the additive is present in an amount less than about 20% by weight.

13. The composition of claim 1 further comprising from about 99% by weight to about 1% weight of an active ingredient.

14. The composition of claim 11 wherein the active ingredient is different than the botanical plant and is selected from the group consisting of herbs, extracts of herbs, fruits, fruit extracts, vegetables, vegetable extracts, vitamins, minerals, antioxidants, proteins, therapeutic agents, and mixtures thereof.

15. The composition of claim 12 wherein the active ingredient is selected from the group consisting of minerals and vitamins.

16. A process for preparing a particulate composition that comprises

a. forming a well-dispersed aqueous slurry that includes a botanical plant, microcrystalline cellulose, and calcium carbonate, and

b. drying the aqueous slurry by removing water.

17. The process of claim 15 wherein the aqueous slurry is dried by spray drying.

18. The process of claim 16 wherein the botanical plant is selected from the group consisting of alfalfa, wheat, oat, barley, rice, corn, watercress, parsley, spinach, brassica and umbelliferous plants, spirolina, and mixtures thereof.

19. The process of claim 17 wherein the botanical plant is present in an amount from about 1% to about 75%, the microcrystalline cellulose is present in an amount from about 1% to about 50% and the calcium carbonate is present in an amount from about 1% to about 75%.

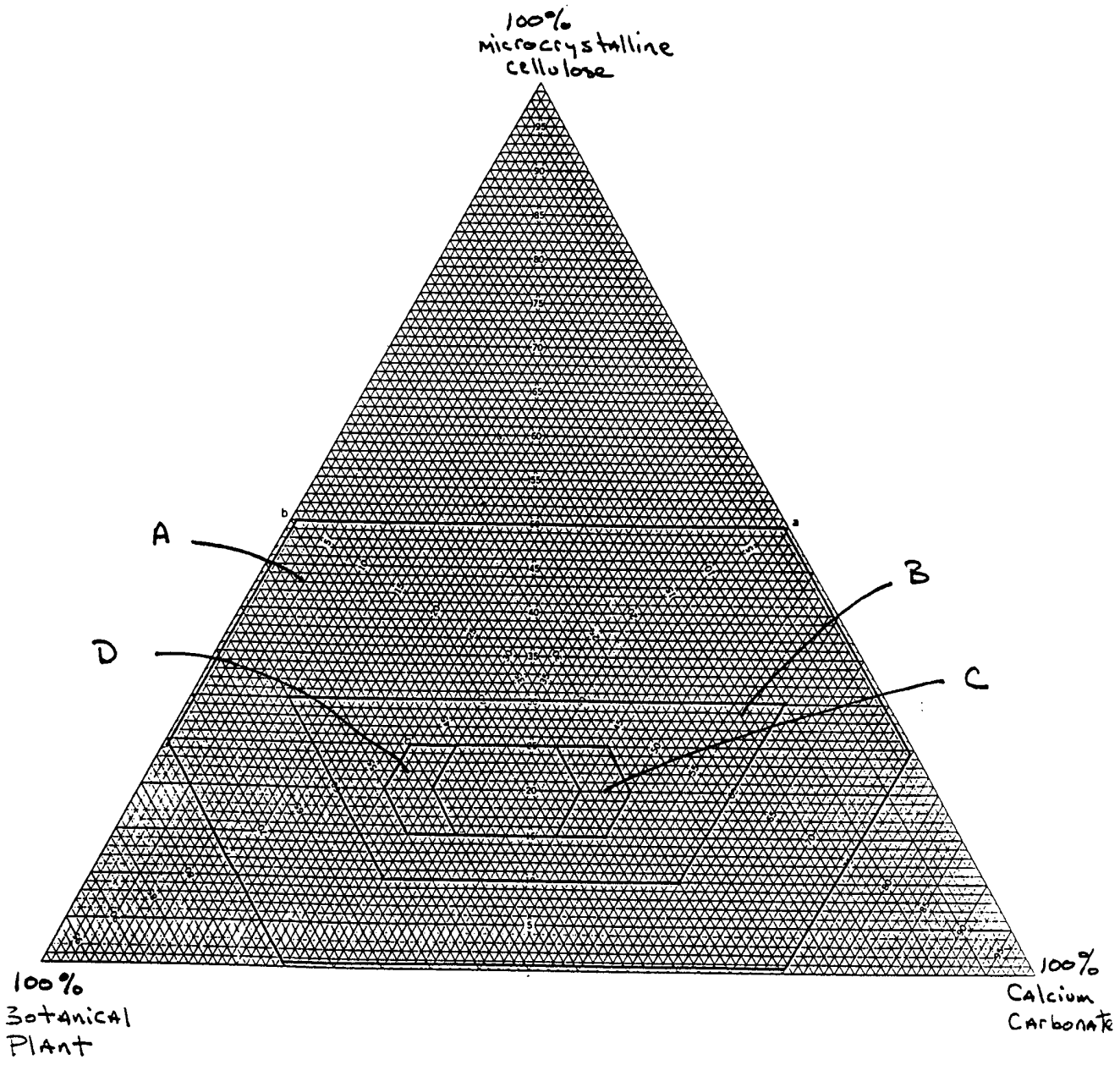
100% microcrystalline cellulose
A
B
C
D
100% Botanical Plant
100% Calcium Carbonate

FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11382

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/78 A23K1/00 A23L1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A23K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	US 4 744 987 A (MEHRA DEV K ET AL) 17 May 1988 (1988-05-17) cited in the application the whole document	1-19
Y	WO 97 41741 A (PALICKA JOSEF) 13 November 1997 (1997-11-13) the whole document	1-19
Y	US 3 600 189 A (RAYNAL ARMANDO R) 17 August 1971 (1971-08-17) the whole document	1-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 1999	06/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fischer, W

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/11382

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 006, no. 227 (C-134), 12 November 1982 (1982-11-12) & JP 57 129655 A (ONODA KAGAKU KOGYO KK), 11 August 1982 (1982-08-11) abstract	1-19
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INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims relate to an extremely large number of possible products/methods. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible; in particular the claims relate to products/methods defined (inter alia) by reference to the following parameter(s):

P1: " Botanical plant " (which - appearently jury rigged - generic term is obviously intended to encompass more than plants, parts thereof and/or materials derived therefrom on the one hand (viz. e.g. claim 4), but not all plants, parts thereof and/or material derived therefrom on the other one (viz. e.g. claim 14) and is exemplified in the specification only by alfalfa powder;

P2: "co-processed "(appearently intended to cover more than products obtained according to the process of claim 17, but not any composition comprising an intimate admixture of the three mandatory components of claim 1 obtained by drying an aqueous dispersion thereof;

P3: (loss of)" hardness upon storage" (in claim 11; a typical "desideratum").

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.
Consequently, the search has been restricted to:

Solutions of the problem set forth in the specification (viz. e.g. page 2, line 25 - page 3, line 3),
i.e. providing excipients for low priced actives having the favorable properties of pure microcrystalline cellulose but being cheaper (because microcrystalline cellulose has been partly substituted by a low- price mineral powder) and compositions containing such excipients in intimate admixture with the only
exemplified "botanical plant", i.e. (powdered) alfalfa.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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National Application No
PCT/US 99/11382

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