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Hanssen et al.

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[54] METHOD OF MANUFACTURING RAPIDLY DISINTEGRATING PHARMACEUTICAL TABLETS

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[21] Appl. No.: **89,120**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 779,269, Nov. 26, 1968, abandoned.

[52] **U.S. Cl.** **424/357,** 424/360, 424/361, 424/362, 424/363

[51] **Int. Cl.** **A01n 9/00**

[58] **Field of Search** 264/117, 121–123; 424/357–366

[56] **References Cited**

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[57] **ABSTRACT**

A method of compounding the inert pharmaceutical carrier ingredients and active drug ingredient of a pharmaceutical tablet composition, which circumvents the conventional granulation step prior to compression in the manufacture of pharmaceutical tablets and results in very rapidly disintegrating tablets; the method consists of

1. spray-drying, after inert gas foaming, a suspension of
   A. 1 – 20 percent by weight of very finely divided silicon dioxide or aluminum oxide and
   B. 60 – 98 percent by weight of at least one fine-grained, inert filler material chosen from the group consisting of selected from the group consisting of substantially water-insoluble rice starch and corn starch and alkaline earth metal phosphates, in an aqueous solution of
   C. 1 – 20 percent of a water-soluble binder,
2. adding the active drug ingredient to the resulting spray-dried, ungranulated tablet pre-mix, and
3. compressing the resulting composition together with the active agent and a tablet lubricant, into pharmaceutical tablets.

5 Claims, No Drawings

METHOD OF MANUFACTURING RAPIDLY DISINTEGRATING PHARMACEUTICAL TABLETS

This is a continuation-in-part of copending application Ser. No. 779,269, filed Nov. 26, 1968, now abandoned.

This invention relates to a novel method of compounding the inert pharmaceutical carrier ingredients and active drug ingredients of a pharmaceutical tablet composition, which circumvents the conventional granulation step prior to compression in the manufacture of pharmaceutical tablets and results in very rapidly disintegrating tablets exhibiting very desirable properties, especially with respect to oral administration of drugs to infants and small children.

BACKGROUND OF THE INVENTION AND STATE OF THE ART

Pharmaceutical tablets are usually prepared from a mixture which, in addition to one or more active drug ingredients, contains a number of therapeutically inert, physiologically compatible carrier components which serve as diluents, adsorbents, agglutinants, disintegration promoters, lubricants and the like. These ingredients are generally first intimately admixed with each other, the mixture is granulated, and the granulate is then compressed into tablets with the aid of a conventional tablet-making machine.

It is also known that the granulating step can be circumvented by subjecting the inert ingredients or a mixture thereof and the active ingredient to a spray-drying treatment [see Raff et al., J. Pharm. Sci. 50 (1961), 76; Gunsel and Lachmann, ibid. 52 (1963), 178; and U.S. Pat. No. 3,293,132]. However, since spray-drying is a relatively expensive procedure, this method has until now not displaced the conventional granulating step in the manufacture of pharmaceutical tablets.

THE INVENTION

We have discovered that by applying the spray-drying procedure to a very particular combination of inert pharmaceutical carrier ingredients it is not only possible to avoid the granulation step but also to produce pharmaceutical tablets having such uncommonly favorable properties that the application of this more costly procedure becomes justifiable for certain particular cases.

In heretofore conventional pharmaceutical tablet compositions the achievement of a satisfactory disintegration rate of the tablet is often predicated upon the incorporation of disintegration promoters which, upon coming in contact with water or aqueous liquids, channel the water as rapidly as possible into the center of the compressed tablet and then undergo swelling with the water and thus cause a bursting of the compacted bond of the tablet. However, due to the nature of the active ingredient, a satisfactory and rapid disintegration is sometimes difficult to achieve or not achievable at all; in some instances disintegration periods of up to half an hour or more must be accepted.

In accordance with the present invention we provide a pharmaceutical tablet composition which, when compressed into pharmaceutical tablets in conventional manner in a tablet-making machine, is capable of channeling the water toward the center of the tablet very rapidly and, in addition, producing extraordinarily good disintegration within a very short period of time.

The disintegration periods achieved thereby are generally less than one minute and in every case do not exceed the span of 2 or 3 minutes.

The method according to the present invention has the further advantage that it may be employed for the manufacture of rectal tablets and of tablets which, upon addition of a small amount of water, rapidly form a smooth and homogeneous slurry or, upon addition of somewhat larger amounts of water, rapidly form a potable suspension. The employment of a tablet containing an exact dose of an active ingredient as a means which immediately yields a slurry that is tolerated by infants and small children upon being admixed with a small amount of water or a potable suspension upon being stirred with somewhat more water, represents a substantial broadening of the spectrum of application of drugs. Thus, a so-called slurry-tablet must fulfill the following requirements:

1. It must, upon being brought in contact with a small amount of water (about twice the volume of the tablet), spontaneously and promptly disintegrate, i.e., within a few seconds or no more than a minute.
2. The slurry must be uniform, easily spreadable and smooth-tasting.
3. Upon further dilution with a little more water, so that the total volume does not exceed a few child's swallows, the slurry must be capable of being stirred into a substantially homogeneous and free-flowing suspension.
4. In place of with water, the slurry should also be dilutable or freely miscible with fruit juice, milk, baby cereal, cream of wheat or the like.

The above requirements are fully met by pharmaceutical tablets manufactured by the method according to the present invention.

More particularly, the method of making pharmaceutical tablets pursuant to the present invention consists of

1. spray-drying, after inert gas foaming, a suspension of
   - A. 1 – 20 percent by weight of very finely divided silicon dioxide or aluminum oxide and
   - B. 60 – 98 percent by weight of at least one fine-grained, inert filler material chosen from the group consisting of starches selected from the group consisting of substantially water-insoluble rice starch and corn starch, and alkaline earth metal phosphates, in an aqueous solution of
   - C. 1 – 20 percent of a water-soluble binder,
2. adding the active ingredient to the resulting spray-dried, ungranulated tablet pre-mix, and
3. compressing the resulting composition, together with the active agent and a tablet lubricant, into pharmaceutical tablets.

The disintegration properties of pharmaceutical tablets prepared by the method according to the present invention may be further improved by employing the spray-dried three-component mixture described in the preceding paragraph in combination with a spray-dried two-component mixture obtained by spray-drying a suspension of component (A) in an aqueous solution of component (C). The quantity of the spray-dried two-component mixture may amount to between 5 and 50 percent by weight, based on the total weight

of the finished pharmaceutical tablet inclusive of the active ingredient.

The silicon dioxide or aluminum oxide used as component (A) in the spray-drying step of the method according to the present invention should be provided in highly dispersed to colloidal form with a particle size of 10 – 100 mμ or a surface area of about 10 to 500 m^2/gm. Colloidal silicic acid sold under the name "Aerosil" is a particularly suitable example.

Component (B) is preferably provided in fine-grained form with a particle size between 10 and 20 μ.

Examples of water-soluble binders suitable for use as component (C) are water-soluble cellulose derivatives, such as hydroxyethylcellulose or carboxymethylcellulose, water-soluble starches such as amylum pectinum solubile, water-soluble plant gums such as gum arabic or tragacanth, alginates, gelatin and polyvinylpyrrolidone.

Of course, all of the components of the spray-dried tablet pre-mix must be chemically inert with respect to each other and therapeutically inert as well as physiologically compatible.

The size of the individual particles obtained from the spray-drying procedure lies generally between 10 and 70 μ. The spray-dried, ungranulated tablet pre-mix according to the present invention is admixed with one or more active ingredients as well as with other optional adjuvents, and the mixture is then pressed into pharmaceutical tablets in conventional fashion. If the spray-dried tablet pre-mix composition according to the present invention is used as the disintegration-promoting component in pharmaceutical tablets, the composition should advantageously constitute about 10 to 70 percent by weight of the finished tablet. In the case of so-called slurry-tablets the spray-dried three-component tablet pre-mix composition, possibly in combination with the spray-dried two-component composition previously referred to, forms the major constituent of the tablet composition to which, in most cases, only the active ingredient needs to be added prior to making the tablet.

The preparation of the tablet pre-mix composition according to the present invention is, as indicated above, effected by subjecting a suspension of components (A) and (B) in an aqueous solution of component (C) to spray-drying. The water-soluble binder (C) should preferably be soluble in cold water and capable of swelling; particularly suitable is soluble starch (amylum pectinum solubile). In accordance with an illustrative embodiment of the process, the suspension of (A) and (B) in an aqueous solution of (C) is adjusted to a suitable viscosity, then foamed with an inert gas such as carbondioxide, and then spray-dried. The spray-drying may be effected in conventional spray-drying towers. The solids content of the suspension to be spray-dried lies advantageously between 15 and 50 percent by weight, and if the suspension is foamed with the inert gas the solids content is preferably from 15 to 30 percent by weight.

A preferred tablet pre-mix composition according to the present invention contains, for example, 12 – 18 percent by weight of colloidal silicic acid, 3 – 15 percent by weight of water-soluble binder, and 67 – 85 percent by weight of water-insoluble rice starch or corn starch.

Analogous to the above-described process, a two-component spray-dried composition, which is advantageously added to the three-component spray-dried composition for the manufacture of slurry-tablets, is obtained by suspending finely dispersed silicon dioxide or aluminum oxide in an aqueous solution of a swellable, water-soluble binder, such as a hydrophilic cellulose derivative, and thereafter spray-drying the suspension. A preferred two-component spray-dried composition consists, for example, of 90 percent by weight of colloidal silicic acid and 10 percent by weight of water-soluble binder.

The combination of the three-component spray-dried composition with the two-component spray-dried composition produces a particularly advantageous tablet pre-mix composition for inclusion in pharmaceutical slurry-tablets.

The following examples further illustrate the present invention and will enable others skilled in the art to understand it more completely. It should be understood, however, that the invention is not limited solely to the particular examples given below. The parts are parts by weight.

EXAMPLE 1

Rapidly disintegrating pharmaceutical tablets were prepared from the following ingredients:

		Parts
Penicillin V potassium		145
Sulfadimethoxine		150
Spray-dried composition I		558
Talcum		40
Colloidal silicic acid		20
Magnesium stearate		12
	conventional	925

The spray-dried composition I was prepared in the following manner from the following ingredients:

	Parts
Substantially water-insoluble rice starch	70
Colloidal silicic acid	15
Soluble starch	15
Total	100

The soluble starch was dissolved in hot water, the resulting solution was cooled to about 40° C., and then the silicic acid and the rice starch were stirred in. The suspension thus obtained was spray-dried in a conves-spray-drying tower with an entrance temperature of about 200° C. and an exit temperature of about 75° C.

The tablets were made in the following manner:
The penicillin V potassium and the sulfadimethoxine were passed through a fine screen, thoroughly admixed with the other ingredients, and the resulting mixture was pressed into 925 mgm tablets with a diameter of 15 mm with the aid of a conventional tablet making machine. Each tablet contained 145 mgm of penicillin V potassium and 150 mgm of sulfadimethoxine and completely disintegrated within 2 to 3 minutes after coming in contact with water or an aqueous liquid.

EXAMPLE 2

Slurry-tablets were prepared from the following ingredients:

	Parts
Aspirin	300.0
Spray-dried composition I	88.0

Spray-dried composition II		10.0
Magnesium stearate		1.0
Cyclamate		0.6
Saccharin		0.4
	Total	400.0

Spray-dried composition I was the same as that in Example 1. Spray-dried composition II was obtained from 90 parts of colloidal silicic acid and 10 parts of hydroxyethyl cellulose by dissolving the hydroxyethyl cellulose in water at about 50° C., accompanied by vigorous stirring, incorporating into the solution the colloidal silicic acid by stirring, and spray-drying the resulting suspension in a spray-drying tower having an entrance temperature of about 220° C. and an exit temperature of about 80° – 100° C.

The two spray-dried compositions were thoroughly admixed with each other as well as with the other tablet ingredients, and the mixture was pressed into 400 mgm-tablets. Each tablet contained 300 mgm of aspirin and, in contact with about twice its volume of water, disintegrated within less than a minute to form a smooth aqueous slurry.

EXAMPLE 3

Antibiotic slurry-tablets were prepared from the following ingredients:

		Parts
Spray-dried composition I		1193.0
Spray-dried composition II		150.0
Penicillin V potassium		133.0
Magnesium stearate		15.0
Cyclamate/saccharin (2:1)		10.0
	Total	1500.0

The spray-dried compositions I and II were the same as those in Examples 1 and 2, respectively. The ingredients were thoroughly admixed with each other, and the mixture was pressed into 1,500 mgm-tablets. Each tablet contained 132 mgm of penicillin V potassium and, in contact with about twice its volume of water, disintegrated within less than a minute to form a smooth aqueous slurry.

EXAMPLE 4

The same results were obtained as in Examples 1, 2 and 3 when the spray-dried composition I therein was replaced by one prepared from the following ingredients:

		Parts
Substantially water-insoluble rice starch		74
Colloidal silicic acid		15
Soluble starch		10
Tragacanth		1
	Total	100

The tragacanth and the soluble starch were dissolved in water and, while stirring, the colloidal silicic acid and the rice starch were incorporated into the solution. The resulting suspension was spray-dried in a conventional spray-drying tower having an entrance temperature of about 180° – 200° C. and an exit temperature of about 70° – 80° C.

EXAMPLE 5

The same results were obtained as in Examples 1, 2 and 3 when the spray-dried composition I therein was replaced by one prepared according to Example 4 from the following ingredients:

		Parts
Corn starch		73.5
Colloidal silicic acid		15.0
Soluble starch		10.0
Gum arabic		1.5
	Total	100.0

EXAMPLE 6

The same results were obtained as in Examples 1, 2 and 3 when the spray-dried composition I therein was replaced by one prepared from the following ingredients:

		Parts
Calcium hydrogen phosphate, fine		85
Colloidal silicic acid		10
Carboxymethyl cellulose		5
	Total	100

The carboxymethyl cellulose was dissolved in warm water, while vigorously stirring. After the carboxymethyl cellulose was thoroughly wetted throughout, the colloidal silicic acid and the finely divided calcium phosphate were stirred in, and the resulting aqueous suspension was spray-dried in customary fashion.

It should be understood that the physical properties of the active drug ingredient have no bearing upon the operativeness of the present invention. Thus, it is immaterial, for example, whether the active ingredient is water-soluble or not; the only criterion is that it must lend itself to incorporation into a pharmaceutical tablet. In other words, any active ingredient which is normally administered in tablet form may be combined with the spray-dried, ungranulated tablet pre-mix composition according to the present invention.

While the present invention has been illustrated with the aid of certain specific embodiments thereof, it will be readily apparent to others skilled in the art that the invention is not limited to these particular embodiments, and that various changes and modifications may be made without departing from the spirit of the invention or the scope of the appended claims.

We claim:

1. The method of manufacturing pharmaceutical tablets which spontaneously and completely disintegrate in water or in a potable aqueous liquid within 2 or 3 minutes by a process wherein the conventional granulation step prior to the compression in the manufacture of pharmaceutical tablets is circumvented or displaced by subjecting the inert ingredients or a mixture thereof with one or more active ingredients to a spray-drying treatment, said process consisting of the steps of

a. spraying-drying, after inert gas foaming, in a conventional spray-drying tower (A) as hereinafter defined and (B) as hereinafter defined in an aqueous solution of (C) as hereinafter defined, and then

b. compressing the resulting composition, together with the active agent and a tablet lubricant, in a conventional tablet-making machine, into a quickly-disintegrating pharmaceutical compressed tablet consisting essentially of one or more active ingredients added prior to compression of the tablet, without granulation, to an ungranulated tablet pre-mix consisting essentially of

(A) 1 – 20 percent by weight of finely divided silicon dioxide or aluminum oxide,

(B) 60 – 90 percent by weight of at least one fine-grained inert filler material selected from the group consisting of substantially water-insoluble rice starch or corn starch and alkaline earth metal phosphates, and

(C) 1 – 20 percent by weight of a water-soluble binder selected from the group consisting of hydroxyethyl cellulose, carboxymethyl cellulose, water-soluble starch, gum arabic, tragacanth, alginates, gelatin and polyvinylpyrrolidone.

2. The method according to claim 1, wherein component (A) has a particle size of 10 – 100 mμ and a surface area of 10 – 500 m^2/gm.

3. The method according to claim 1, wherein said component (A) is colloidal silicic acid.

4. The method according to claim 1, wherein said component (C) is substantially water-insoluble rice starch.

5. The method according to claim 1, wherein said binder (C) is a water-soluble cellulose derivative, a water-soluble starch, a water-soluble plant gum or a mixture of two or more of these.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,725,556 **Dated** April 3, 1973

Inventor(s) DIETER HANSSEN and ADOLF KNECHT

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

Insert --[73] Assignee: BOEHRINGER INGELHEIM GmbH
Ingelheim/Rhein, Germany

In line 14 of the ABSTRACT - insert --starches-- before "selected"

Col. 4, lines 48-49 - correct "conves-pray" to read
--conventional spray--.

Col. 6, line 53 - correct "spraying" to read --spray--.

Signed and sealed this 23rd day of April 1974.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents.