

1

3,084,104 PROCESS OF PREPARING GRANULATION OF MEDICINAL AGENTS

Paul A. Tuerck and Edwin D. Carkhuff, Cincinnati, Ohio,
assignors to Richardson-Merrell Inc., New York, N.Y.,
a corporation of Delaware
No Drawing. Filed June 28, 1961, Ser. No. 120,192
7 Claims. (Cl. 167-82)

This invention relates to a process of preparing granulations of medicinal agents, suitable for high speed, automatic tableting.

The formation of granules of medicinal agents for compression into tablets is a very important part of the preparation of drugs for dispensation. Many medicinal agents cannot be compressed into tablets with high speed tablet-making machinery without previously processing the material to obtain free-flowing lubricated granules having binding properties of exacting characteristics. When drugs are not properly prepared they may not feed easily into the tablet-making dies, and great variations in weight and other physical properties may result. Some such tablets tend to break up or dust during subsequent handling. Other materials simply will not hold together in the shape of a tablet without the aid of a binder. Some medicinal agents tend to segregate from other components of the tablet, and this results in variations in potency in the finished tablet.

The natural tendency of some medicinal agents to resist compression into satisfactory tablets is usually overcome by forming granules containing the drug. These granules also contain other substances such as binding agents, diluents, dyes and other tablet-forming aids so that they can be compressed into good-looking tablets of uniform weight and physical properties.

One method of pre-treating medicinal agents prior to tableting is called "slugging." In this operation the dry components of the tablet are thoroughly mixed together and compressed into slugs which are subsequently ground and screened to the desired particle size. This material is then treated with a lubricating agent and compressed into tablets. Many medicinal agents can be processed in this manner to obtain granulations suitable for pressing into tablets but others cannot.

An alternative method of preparing granules is the "wet" method. In this method some of the final components of the tablet are ground to a fine powder and then treated with solutions of binding agents to obtain a mass which is forced through a screen having openings of a predetermined size. This wet material is then dried on trays, re-ground and re-screened to obtain granules of a size suitable for compression into tablets. The wet granulation method cannot be used with some medicinal agents.

The "slugging" and "wet" methods of preparing pharmaceutical granules involves a number of different steps requiring considerable labor and time and requires various kinds of machinery which occupy a large amount of space. Principal objects of the invention are to provide a process of preparing granulations of drugs, where active ingredients comprise the major portion of the granulation, suitable for compression into satisfactory tablets by a process which reduces the number of steps, the machinery, the labor and time ordinarily required.

The objects of the present invention are attained in a very simple manner. According to the process of the invention, the medicinal agent, fillers, binders and other excipients are ground to a fine powder in any one of several types of micropulverizing apparatus, such as an Abbe impact grinder, a roller mill, a Fitzpatrick comminuting machine, ball mills or other micropulverizing apparatus which will yield particle sizes ranging from 400 to 80 mesh. The thoroughly blended powders are

2

then placed in a conventional coating pan, preferably fitted with baffles, and adapted to be driven at variable speeds. At the beginning of the process, the pan is rotated at a relatively high speed, about five to thirty revolutions per minute. These pans should be made of stainless steel or some material inert to the medicinal components of the mixture. Water, or an aqueous solution of a binding agent, is then sprayed into the rotating pan in the form of a very fine mist, the particle size of the droplets preferably being uniform and no larger than about 0.2 mm. in diameter. Air guns, such as are used in spraying paint, may be used providing they are fitted with a nozzle and have an air pressure suitable to yield the fine type of spray that is necessary. Spray nozzles which do not require air pressure may also be used. A predetermined amount of water based on the weight of the dry solids in the pan is added in this manner. This amount will vary depending upon the ingredients comprising the granulation. The speed of rotation should be such that there is a continuous tumbling of material in the pan. About 15-30 revolutions per minute are usually required to produce tumbling in pans having a diameter up to four feet. About 5-15 revolutions per minute will produce satisfactory tumbling in pans having a diameter of six feet due to the increased peripheral speed of the pan. As water is added, granules commence to form. The time required for spraying in the critical amount of water is usually about ten minutes for batches of 100 to 400 kg., although in smaller batches a shorter time is all that is necessary, whereas in larger batches a longer period of time would be required.

When the pulverized powders in the rotating coating pan contain a sufficient amount of water soluble binding agent, the above described process is very effective in developing granules of a suitable size which can be readily dried and pressed into tablets. However, when the therapeutically effective agents comprise a major proportion of the mixture, and particularly where these components are water insoluble or lack adhesive or binding characteristics of their own when wetted and dried, it is necessary to follow particular procedures and observe certain conditions in finishing the granulation. When the amount of the water soluble binding components of the mixture is relatively small because of the necessity for a large proportion of drug in the mixture, the binding action may be inadequate and a large proportion of "fines" will tend to develop as a result of the tumbling action of the material in the rotating coating pan. We have discovered, however, that satisfactory granules can be prepared from powdered mixtures in which the therapeutically effective component comprises the major proportion of the granulation if the tumbling action is discontinued or reduced to a minimum as soon as granules of a desired size are formed and the drying action is completed without excessive agitation of the moist granules.

In accordance with the present invention a fine spray of water, or a granulating solution, is directed onto the tumbling powder mixture in the rotating tablet coating pans as described above until granules of a desired size commence to form. If too much water is added and the tumbling action is continued too long, large balls may result. If insufficient water is applied or if the tumbling action is continued too long, an unduly large proportion of "fines" results. To avoid the development of large balls of medicament and the development of "fines," the spraying and the rapid tumbling action are discontinued as soon as granules of a desired size and moisture content are obtained. It is preferred that the largest proportion of the granules be of such size as to pass through a 12 mesh screen but be retained on a 200 mesh screen. After suitable granules are formed, the tumbling action is reduced to not more than about three revolutions

per minute and may in fact be discontinued completely with intermittent rotation of the pan at the rate of about once every minute. During this time a gentle current of hot air is blown over the tumbling granules. Care should be taken that the current of air be not too strong, otherwise small particles of the material may be blown from the pan. If desired, the pan may be heated from the outside by blowing a stream of hot air on it, or by using a heat-jacketed pan. The tumbling and heating operations are continued until the material in the pan contains a satisfactory amount of moisture to provide proper compression characteristics. The residual moisture content will vary with tablet ingredients and diluents used, but may vary from about 0.4% up to 8% by weight.

At this point, a suitable lubricant, such as starch or magnesium stearate, is dumped into the revolving pan and the granules are thoroughly coated with the material. The dried granules may then be screened and delivered directly to a tableting machine.

To illustrate the invention in greater particularity and demonstrate its advantages over conventionally used methods of preparing granules, a number of granulations were prepared. In one series of experiments the powdered mixture was granulated by the conventional wet granulation method whereas in the other series, the material was granulated by the processes of the present invention.

EXAMPLE I

Granulations were prepared with the following formulae:

Granulation "A"—For A.P.C. Tablets

	Wet method, kg.	Spray method, kg.
Acetophenetidin.....	2.52	2.52
Caffeine.....	0.5	0.5
Corn starch.....	0.72	0.72
Soluble starch.....		

The wet method granules were prepared by granulating the acetophenetidin, caffeine and corn starch in a Day mixer with a solution of ten percent corn starch paste and sixteen percent gelatin. The granulation was passed through a 6 mesh screen while wet, spread on trays and dried overnight at 120° F. They were then dry screened through a 12 mesh screen.

The spray method granules were prepared by placing the powdered ingredients in a tablet coating pan and spraying the powders with a fine spray of water while they tumbled in the pan. When small granules of the material were formed, the speed of the pan was reduced to about one revolution per minute and hot air between the temperatures 400–600° F. was blown over the damp granules until they were dry. After the granules were dried, 4.6 kg. of a commercially available pre-prepared aspirin granulation containing 16 percent starch was added together with additional starch to bring the total weight of the granulation to 8.7 kg. These ingredients

were mixed by slowly rotating the coating pan after which four percent of corn starch was added as a lubricant.

To the granules prepared by the conventional wet processes there was also added 4.6 kg. of the pre-prepared aspirin granulation, and enough corn starch to bring the total weight up to 8.7 kg. was added as a lubricant. The mix was then dry screened through a 12 mesh screen. Compress on $\frac{7}{16}$ inch standard punches and dies to form tablets weighing 518 mg. Similarly, sulfadiazine granulations were prepared with the following formulae:

Granulation "B"—For Sulfadiazine Tablets (500 mg.)

	Wet method, kg.	Spray method, kg.
Sulfadiazine.....	3.0	3.0
Corn starch.....	0.34	0.3
Corn syrup solids.....		0.075
Soluble starch.....		0.15

One batch of the material was granulated in a Day mixer with an aqueous solution containing 5 percent starch paste and 5 percent glucose. The wet mass was then passed through a 6 mesh screen and dried overnight on trays at 120° F. The material was then dry screened through a 12 mesh screen and lubricated with one percent magnesium stearate.

The granules prepared by the spray method were granulated with a fine spray of water, dried as before, lubricated in the pan with one percent of magnesium stearate and screened. Compress on standard $\frac{7}{16}$ inch punches and dies to form tablets weighing 616 mg.

Ascorbic acid granules were also prepared with the following compositions:

Granulation "C"—For Ascorbic Acid Tablets (250 mg.)

	Wet method, kg.	Spray method, kg.
Ascorbic acid, powdered.....	1.605	1.605
Sugar, powdered.....	0.54	0.54
Lactose.....	0.816	0.816
Acacia, U.S.P. white powder.....	0.018	0.018
Corn starch.....	0.093	0.093
Soluble starch.....		

The wet method granules were prepared by granulating in a Day mixer with 16 percent gelatin solution, wet screened, dried, screened again and lubricated with one percent magnesium stearate as above.

The wet spray granules were granulated with water as above and dried and lubricated in the pan and screened. Compress on $\frac{7}{16}$ inch standard punches and dies to form tablets weighing 544 mg.

Each of the granules described above was pressed into tablets on a Model RB-2 Stokes single rotary tableting machine.

The granules and tablets described above were then examined with the following results.

TABLE I

Granulation	Granulations					Tablets			
	Method	Granulating solution, ml.	Percent moisture in wet granulation	Drying time (hours)	Percent moisture in dry granulation	Compression characteristics	Hardness (Mon-santo)	Disintegration U.S.P. method (minutes) 37° C.	General appearance
A.....	Spray H ₂ O.....	450	9.4	0.5	2.19	1	10	0.25	1
B.....	Wet.....	1,600	26.4	18	1.91	1	8.5	0.7	2
B.....	Spray H ₂ O.....	1,200	22.4	0.7	1.8	1	13	15	1
C.....	Wet.....	1,600	22.4	18	1.4	1	13	13	1
C.....	Spray H ₂ O.....	200	6	0.25	3.8	1	12	6	1
C.....	Wet.....	225	8.5	18	4	2	9	8	2

NOTE.—Key: Compression characteristics—(1) Good; (2) Capping tendency. General appearance—(1) Good; (2) Spotty, chipping tendency on edges.

5

To illustrate the saving in time and labor made by practicing the processes of the present invention as contrasted with the conventional wet granulation method,

mesh. These granulations were compressed on a single rotary tableting machine as were the wet granulation products. The results are shown in the following table:

TABLE III

Granulation	Method	Percent moisture in wet granulation	Drying times (hours)	Percent moisture in dry granulation	Compression characteristics	Hardness (Mon-santo)	Disintegration U.S.P. method (minutes) 37° C.	General appearance
A-----	Spray-	3.06	0.25	0.42	1	9	5.5	1
A-----	Wet---	6.9	18	0.52	2	8	5	4

NOTE.—Key: Compression characteristics—(1) Good; (2) fair; (3) poor (capping). General appearance—(1) Excellent; (2) Good; (3) fair (slightly mottled); (4) poor (badly mottled and spotted).

the following table illustrates comparative times involved in preparing A.P.C. tablets:

TABLE II

	Wet method (Day mixer)		Spray method	
	Labor time (hours)	Total mfg. time (hours)	Labor time (hours)	Total mfg. time (hours)
Loading and granulating-----	1.5	1.5	0.5	0.5
Wet screening-----	2.0	2.0	-----	2.0
Drying-----	-----	16	-----	0.4
Dry screening-----	1.0	1.0	0.4	0.5
Lubrication-----	1.25	1.25	0.5	0.5
Total clean up-----	0.75	0.75	0.25	0.25
Total-----	6.5	22.5	1.65	3.65

Similar savings are made in the preparation of other granulations.

EXAMPLE II

Powdered sugar, phenobarbital and water soluble dye, D and C Green No. 5, were mixed at a concentration of 0.5 gram of the dye and 37.5 grams of the phenobarbital per kilogram of powder and micropulverized in a Raymond mill. This color was chosen because it usually causes difficulty in producing smoothly colored tablets when granulated by ordinary methods. 2.5 kilograms of the micropulverized powders were granulated by the conventional wet granulation method. The granulations were made by adding water as the granulating agent to the powder in a small Day mixer. The wet granulations were forced through a six mesh screen and dried overnight on trays in a hot air oven at 120° F. Dried granulations were ground through a twelve mesh screen, lubricated with one percent magnesium stearate and compressed on a Model RB-2 Stokes single rotary tableting machine using 1 3/32 inch standard cup punches and dies at a tablet weight of 400 mg.

2.5 kilogram portions of the micropulverized powders were placed in 18 inch stainless steel coating pans having baffles mounted on the inner periphery. The speed of the pans was controllable from 0 to 30 revolutions per minute by means of a variable speed control mechanism. At the start of the granulation procedure, the pans were rotated at relatively high speed, about 20 to 30 revolutions per minute, and water was sprayed over the tumbling powders from a paint gun for a period of about ten minutes. As the powders were wetted, small granules formed and the speed of the pan was gradually reduced to prevent impaction on the periphery due to centrifugal force. Rotation was continued at such rate that a tumbling of the powders resulted and small round granules were formed. A gentle stream of heated air at a temperature of about 375° F. was blown over the tumbling granules and the speed was further reduced to about three revolutions per minute. The dry granulated material was lubricated with one percent of magnesium stearate and then screened to the desired size, about 12

Similarly, granulations were prepared using various binding agents including such mixtures as: powdered sugar, 90%, corn starch, 10%; lactose, 90%, corn starch, 10%; mannitol, 98%, powdered gelatin, 2%; mannitol, 88%, powdered gelatin, 2, corn starch, 10%; powdered sugar, 50%, lactose, 25%, corn starch, 25%; powdered sugar, 90%, corn syrup solids, 10%. In each case, the granules had better compression characteristics and the tablets had a better general appearance than did those prepared from similar powdered mixtures which were granulated by the conventional wet granulation method.

400 milligram tablets were prepared from granulations made by the process of the present invention in which thiamine hydrochloride (10 mg. per tablet) or ascorbic acid (50 mg. per tablet) were incorporated in the micropulverized powders. In each case the same superior results and savings in labor and processing time were obtained.

The process of the present invention also has a number of other important advantages. For instance, it is particularly adapted to the preparation of granules containing moisture sensitive therapeutic agents. The conventional wet granulation process uses a considerable amount of moisture in preparing the granules and requires a protracted drying time to remove the moisture from the granules to condition them for compressing on conventional tableting machinery. Moisture sensitive therapeutic agents often suffer from this treatment. In contrast thereto, the low amount of moisture applied to the material by the process of the present invention during formation of the granules and the rapid drying time reduce losses due to degradation of moisture sensitive materials.

Even though the stream of air used to dry the tumbling granules may be as high as 500° F., the high rate of evaporation of the moisture or other granulating liquid from the granules and the tumbling action during the drying process, maintains the temperature within the granulation within safe limits. Also the time of exposure of the sensitive material to moisture is greatly reduced.

The granulations of the present invention may be colored by micropulverizing pigments, lakes or dyes along with the other tablet ingredients before they are introduced into the pan. Alternatively, water soluble dyes may be distributed on the material in the tumbling pan as the granulations are being formed. Also, solutions of dyes in volatile solvents such as alcohol or chloroform, may be added to the powdered material either prior to granulation or during the granulation process.

The granules may be lubricated with conventional lubricating agents such as magnesium stearate or other stearate, starch, talc or the like, by simply mixing these materials with the formed granules in the rotating pan. This avoids a step which is commonly performed as a separate step in the wet granulation procedure. The application of a final spray of 0.25 percent to 0.5 percent of a light mineral oil to the granules tends to eliminate further dusting and provides a gloss to the tablet.

This application is a continuation-in-part of applica-

tion Serial No. 17,490, filed March 15, 1960, and now abandoned, and of application Serial No. 17,491, filed March 25, 1960, and now abandoned.

We claim:

1. In a method of preparing granulations suitable for compressing into tablets on automatic high speed pharmaceutical tableting machines the improvement which comprises the steps of preparing a micropulverized mixture of a medicinal agent and a solid, non-toxic, orally acceptable, binding agent, the said mixture having particle sizes within the range 400 to 80 mesh, placing the mixed powders in a tablet coating pan and rotating the pan at speeds within the range 5 to 30 revolutions per minute, whereby the powdered mixture is caused to tumble, spraying the surface of the tumbling powders with a fine spray of solvent for said binding agent, the particles of said spray being less than 0.2 mm. in diameter, until granules are formed by adhesion of the tumbling solid particles, and when the granules have developed to a particle size within the range 200 to 12 mesh reducing the rate of rotation of the coating pan to 1 to 5 revolutions per minute and drying the granules to a moisture content of 0.4 to 8 percent by weight by contacting the surface of the slowly tumbling granules with a stream of heated dry air.
2. In a method of preparing granulations suitable for compressing into tablets on automatic high speed pharmaceutical tableting machines the improvement which comprises the steps of preparing a micro-pulverized mixture of a small amount of a medicinal agent and at least 60 percent by weight of a sugar, the said mixture having particle sizes within the range 400 to 80 mesh, placing the mixed powders in a tablet coating pan and rotating the pan at speeds within the range 5 to 30 revolutions per minute, whereby the powdered mixture is caused to tumble, spraying the surface of the tumbling powders with a fine spray of water, the particles of said spray being less than 0.2 mm. in diameter, until granules are formed by adhesion of the tumbling solid particles, and when the granules have developed to a particle size within the range 200 to 12 mesh reducing the rate of rotation of the coating pan to 1 to 5 revolutions per minute and drying the moist granules to a moisture content of 0.4 to 8 percent by weight by contacting the surface of the slowly tumbling granules with a stream of heated dry air.
3. In a method of preparing granulations suitable for compressing into tablets on automatic high speed pharmaceutical tableting machines the improvement which comprises the steps of preparing a micro-pulverized mixture of a small amount of a medicinal agent and at least 60 percent by weight of lactose, the said mixture having particle sizes within the range 400 to 80 mesh, placing the mixed powders in a tablet coating pan and rotating the pan at speeds within the range 5 to 30 revolutions per minute, whereby the powdered mixture is caused to tumble, spraying the surface of the tumbling powders with a fine spray of water, the particles of said spray being less than 0.2 mm. in diameter, until granules are formed by adhesion of the tumbling solid particles, and when the granules have developed to a particle size within the range 200 to 12 mesh reducing the rate of rotation of the coating pan to 1 to 5 revolutions per minute and drying the moist granules to a moisture content of 0.4 to 8 percent by weight by contacting the surface of the slowly tumbling granules with a stream of heated dry air.
4. In a method of preparing granulations suitable for compressing into tablets on automatic high speed pharmaceutical tableting machines the improvement which comprises the steps of preparing a micro-pulverized mixture of a small amount of a medicinal agent and at least 60 percent by weight of mannitol, the said mixture having particle sizes within the range 400 to 80 mesh, placing the

- mixed powders in a tablet coating pan and rotating the pan at speeds within the range 5 to 30 revolutions per minute, whereby the powdered mixture is caused to tumble, spraying the surface of the tumbling powders with a fine spray of water, the particles of said spray being less than 0.2 mm. in diameter, until granules are formed by adhesion of the tumbling solid particles, and when the granules have developed to a particle size within the range 200 to 12 mesh reducing the rate of rotation of the coating pan to 1 to 5 revolutions per minute and drying the moist granules to a moisture content of 0.4 to 8 percent by weight by contacting the surface of the slowly tumbling granules with a stream of heated dry air.
5. In a method of preparing granulations suitable for compressing into tablets on automatic high speed pharmaceutical tableting machines the improvement which comprises the steps of preparing a micro-pulverized mixture of a small amount of a medicinal agent and at least 60 percent by weight of sucrose, the said mixture having particle sizes within the range 400 to 80 mesh, placing the mixed powders in a tablet coating pan and rotating the pan at speeds within the range 5 to 30 revolutions per minute, whereby the powdered mixture is caused to tumble, spraying the surface of the tumbling powders with a fine spray of water, the particles of said spray being less than 0.2 mm. in diameter, until granules are formed by adhesion of the tumbling solid particles, and when the granules have developed to a particle size within the range 200 to 12 mesh reducing the rate of rotation of the coating pan to 1 to 5 revolutions per minute and drying the moist granules to a moisture content of 0.4 to 8 percent by weight by contacting the surface of the slowly tumbling granules with a stream of heated dry air.
6. In a method of preparing granulations suitable for compressing tablets in automatic high speed pharmaceutical tableting machines the improvement which comprises the steps of tumbling a finely divided mixture of solids having a particle size within the range of 400 to 80 mesh said mixture containing a medicament in a tablet coating pan rotating at speeds within the range 5-30 revolutions per minute, spraying the surface of said tumbling powders with a fine spray having a particle size not in excess of 0.2 mm. of an aqueous solution containing a non-toxic, orally acceptable, water soluble binding agent whereby the fine particles of solids are caused to adhere and form granules of a size within the range of 200 to 12 mesh, reducing the speed of rotation of the coating pan when granules of the desired size are formed to a rate of less than three revolutions per minute but sufficient to maintain a tumbling action of the granules in the coating pan and blowing a stream of hot air over the tumbling granules until the granules are dried.
7. In a method of preparing granulations suitable for compressing into tablets on automatic, high speed, pharmaceutical tableting machines the improvement which comprises preparing a micro-pulverized mixture having a particle size within the range 400 to 80 mesh of at least 60 percent by weight of a medicament and a one to 40 percent by weight of a non-toxic, orally acceptable, water soluble binding agent, placing the mixed powders in a tablet coating pan and rotating the pan at speeds within the range 5 to 30 revolutions per minute, sufficient to cause the powdered mixture to tumble, subjecting the surface of the tumbling powders to a fine spray of water, the particle size of which is less than 0.2 mm. in diameter, until granules having an average particle size of less than 12 mesh but greater than 200 mesh are formed, reducing the rate of rotation of the coating pan and the tumbling action in the pan to an extent that the surface of the granulation is renewed only about once in one minute, and blowing air at 400° F. to 600° F. on the granules, whereby the granules are dried to a moisture

content suitable for compression, discontinuing the rotation of the pan before substantial disintegration of the granules occurs, and thereafter passing the granules through a 12 mesh screen to obtain free flowing granules suitable for tableting on automatic machinery.

5

References Cited in the file of this patent

UNITED STATES PATENTS

2,851,364	Peebles -----	Sept. 9, 1958
2,877,159	Lachman et al. -----	Mar. 10, 1959
2,914,797	Cavanaugh -----	Dec. 1, 1959
2,977,203	Sienkiewicz et al. -----	Mar. 28, 1961