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**METHOD OF GRANULATING MATERIALS FOR
SUBSEQUENT FORMING INTO TABLETS**

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The present invention relates to a new granulation method, and more particularly to improvements in granulation processes for use in pharmaceutical and related industries to provide agglomerates of powdered material which can be used for tableting or other purposes.

Granulation is the process of agglomeration of dry powders or dry powder blends so as to make the powders suitable for compression into tablets and pills with, for example, conventional tablet-making machines.

Present methods now in use are known as the "wet process" and the "direct compression process." Although these processes are both quite extensively used in the field at the present time, there are limitations with respect to each of the processes which limit the use thereof, and which particularly have the effect of making the price thereof relatively high.

It is accordingly a primary object of the present invention to provide for a granulation method which substantially lowers costs as compared to presently known methods and which can be used quite extensively for various different products.

The process most widely used today is the "wet granulation process." This process requires four or more steps to prepare the dry powders for the tablet-making machines. These steps are:

- (1) Dry blending of ingredients;
- (2) Addition of liquids, pastes or solvents to the blender while continuing to mix;
- (3) Drying, and
- (4) Size reduction or screening.

In the first step, the dry ingredients, for example, of a pharmaceutical formulation, are charged into conventional blending equipment. After dry mixing for a period of time which is sufficient to assure a satisfactory blend, liquids or liquid binders, such as gelatin solutions, starch solutions, or pastes, are added to the blender and the mixing is continued, the object being to disperse the liquids and cause the particles of dry powder to become agglomerated and bound together by the starch, gelatin or similar binding material. This results in the formation of a wet paste or of wet granules. In some cases solvents are used which form pastes with the dry material. The steps are performed at room temperature. The blender is then discharged.

After agglomeration of the powder, the liquid such as the water or other solvent, is removed by drying. This may be done on trays in ovens, or by means of a fluidized bed drying process, which is accomplished by passing hot gases, such as air, through the material held in a porous container.

When dried, the pastes are then processed in a size-reduction machine to form granules. However, the granules which are obtained directly, or the granules obtained from size-reduction machines are usually of a non-uniform size and therefore must be screened to eliminate over-sized and under sized particles. The materials are then ready for compression in tablet making machines.

Among the disadvantages and limitations of this process are the difficulty of properly dispersing the relatively small amount of liquid throughout the total material of the blender, which would be necessary to form a uniform agglomerate. Poor agglomeration and granulation result in poor compression in the tablet machine and the possibility of friable tablets. In addition, drying consumes

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considerable production time. Using conventional dryers, the time required is about 8 to 12 hours, and using the fluidized bed dryers, the time required is 1 to 4 hours. Furthermore, from a production standpoint, a 3 to 4 man crew is necessary for the material handling between blender, dryer, size reduction machine and screens. Over-sized and undersized materials are returned for reprocessing, or they may be discarded. As a result, the cost of processing pharmaceutical formulations using the wet granulation process is about 15-25 cents per kilogram (2.2 lbs.).

The direct compression granulation method was developed to overcome the shortcomings of the wet process. The direct compression method requires at least three steps, namely:

- (1) Dry blending of ingredients;
- (2) Direct compression of dry powders; and
- (3) Size reduction or screening.

This process does not use liquids or binders to agglomerate the dry materials but relies on the physical property of the powder or powder blends to be compressed into a ribbon or cake. In some cases "slugs" are formed. Since all materials are not compressible, or not compressible to the degree required to satisfactorily make tablets, dry additives are blended into the powders; these additives improve the compressibility of the materials. The additives are usually of a very light bulk density and by themselves can be easily compressed.

Consequently, in direct compression all of the dry powder ingredients are blended, with compressible materials added if necessary. The blends are then processed in specialized machinery which compresses the material by passing the same through revolving rollers, rotating plates, reciprocating pistons or a variety of mechanical devices designed to apply work or force to the material, thereby compressing the powders into a cake. The cake is then broken apart and screened to provide granules of a satisfactory mesh size for tablet making.

This process is limited by the varying compressibility of the many dry formulations in use in pharmaceutical and related industries, the possible classification of blended ingredients tending to "unmix" them in the hoppers of the compressing machines, which results in changing the percentages of ingredients in the finished tablet, and the considerable labor required for material handling, size reduction and screening. The cost of processing using the direct compression process is about 15-22 cents per kilogram.

It is accordingly another object of the present invention to provide a process which offers the advantages of the direct compression process while being adapted for use with a substantially wider range of dry powders or blends, regardless of their physical characteristics such as solubility and compressibility, and which results in a final product which is always equal to or superior to the product which is produced by either the dry or wet process, and which is nevertheless produced in a more economical manner.

It is still another object of the present invention to reduce the cost of processing by as much as fifty percent (50%) of the cost of existing methods and to provide for reduction in labor costs, equipment and process steps.

It is yet another object of the present invention to provide a process which completely eliminates drying equipment and long drying periods used in the wet process, while at the same time providing the advantage of the wet process in being applicable for the widest possible range of materials.

As still another object, the present invention provides a method which minimizes possible contamination of pharmaceutical process by considerable reduction in material handling steps.

It is yet a further object of the present invention to provide a process which results in very uniform particle sizes of the finished granulation, thereby eliminating the necessity of screening, yet resulting in the production of tablets in available tableting machines, the tablets being produced being less friable than tablets made by existing methods.

Other objects and advantages of the present invention will be apparent from further reading of the specification and of the appended claims.

With the above and other objects in view, the present invention mainly comprises a granulation method wherein substantially dry particles of physiologically active material adapted to be ingested are uniformly mixed with dry particles of a physiologically compatible, ingestible thermoplastic material which softens below the temperature which would damage the physiologically active material, the mixing being carried out at a temperature below the softening point of the thermoplastic material, then heating the mixture to a temperature sufficiently high to soften the thermoplastic material but not high enough to cause damage to the physiologically active material, thus causing the thermoplastic material to agglomerate with the physiologically active material, and cooling the resulting mixture, thus forming uniform granules of the dry particles.

According to a preferred embodiment of the present invention, the above set forth method is carried out in a jacketed mixing device so that after the dry particles of the physiologically active material and of the thermoplastic material are thoroughly intermixed, a heated fluid such as steam or water is passed through the jacket of the jacketed mixing vessel to heat the contents thereof in the same vessel where the mixing took place, thereby causing the agglomeration of the particles due to the at least partial melting of the thermoplastic material, and then the cooling is accomplished either by removing the heated fluid or by passing the cold fluid through the jacketed vessel. Consequently, all of the operations up until the tableting step can be carried out in a single device, which, of course, results in considerable lowering of costs and economy of operation.

A most suitable mixing device that can be used for this purpose is the Littleford Lodige Mixer, manufactured by Littleford Brothers, Cincinnati, Ohio. The mixing devices of the type set forth in U.S. Patent No. 2,679,385 and 2,750,163 are particularly suitable for accomplishing the homogeneous mixing of the dry particles.

It is, of course, possible to carry out the method by mixing in one vessel, and heating and cooling in a second vessel, or by mixing in one vessel, heating in a second vessel, and cooling in a third vessel. However, the use of a mixing vessel which is highly efficient in transferring heat to the mixture of particles therein, so that the same can be heated and cooled in the same vessel provides advantages over and above the advantages which are achieved by the general method of this invention.

The ingredients which are mixed can include not only the physiologically active material and the thermoplastic material, but filler materials can also be mixed therewith, if it is desired to have some amount of filler. Any pharmaceutical or food filler can be used for this purpose. Of course, it is also possible to have no filler but to have only the physiologically active material and the thermoplastic material. The thermoplastic material can serve the dual purpose of binder and filler.

The amount of thermoplastic material with respect to the amount of other ingredients, namely the physiologically active material alone, or the physiologically active material plus filler, can vary within wide ranges, though generally between about 2-20% by weight of the thermoplastic material, and most preferably 6-12% by weight of the thermoplastic material is preferred. Larger amounts of thermoplastic material may be used as binder where

it is desired to produce sustained release tablets. The present invention is applicable to the economical and simple production of compositions containing any amount of thermoplastic material as binder. The advantages are obtained by mixing the components dry, then heating to a temperature high enough to soften or start to melt the thermoplastic material, but not so high as to destroy or damage the physiologically active material, thereby causing an agglomeration, and then cooling. The mixing is far more uniform than in the case of the addition of liquids or liquid pastes, or than can be achieved by the addition of thermoplastic material in already melted condition, so that the tablets which are finally produced from the granulates prepared as described herein are entirely uniform and satisfactory for all purposes.

The present invention is, of course, applicable to any and all solid physiologically active materials and to any and all physiologically compatible ingestible thermoplastic materials, provided only that the thermoplastic material melts at a temperature below the temperature which causes damage to the physiologically active material. Among the physiologically active materials, to which the invention is of course not limited, may be mentioned:

sulfadiazine
sulfanilimide
acetylsalicylic acid
ascorbic acid
thiamin hydrochloride
riboflavin
pyridoxine hydrochloride
niacinamide
penicillin
N-acetyl-p-aminophenol
aureomycin, etc.

It can be seen from the above that the list of solid, physiologically active materials that can be used in the method of the present invention is practically unlimited.

The list of physiologically compatible ingestible thermoplastic materials is likewise just about unlimited, this list including, but not being limited to:

solid polyethylene glycols
polyethylene glycol esters
polyethylene glycol ethers
propylene glycol esters
propylene glycol ethers
polyoxyethylene glycols
glyceryl mono-esters, such as glyceryl monostearate
glyceryl di-esters, such as glyceryl distearate
glyceryl tri-esters, such as glyceryl tristearate
ethoxylated lanolin
ethoxylated beeswax
polyoxyethylene glycol mono and di-esters
polyoxyethylene glycol mono and di-ethers
polyoxyethylene-polyoxypropylene copolymers
polyoxyethylene sorbitan mono esters
polyoxyethylene sorbitan mono ethers, etc.

It is preferred that the melting point of the thermoplastic material be between about 45° C. and 120° C., and most preferably between about 60° C. and 85° C.

In general, the method of the present invention can, for example, be carried out by charging a 2.8 cubic foot capacity Littleford Lodige Mixer at room temperature and normal pressure with 100 lbs. of dry physiologically active powder, e.g. aspirin, and adding about 8% of the physiologically compatible ingestible thermoplastic material such as glyceryl tristearate (8 lbs.). The mixer is started and permitted to blend the thermoplastic material and active ingredient for 30 seconds, after which steam is introduced into the steam jacket of the mixer. The temperature of the dry material is allowed to reach 70° C., which takes about five minutes. This time will vary with the temperature of the steam available.

After heating, the steam is shut off and clear water is

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introduced into the jacket for an additional five minutes. The product is then discharged from the mixture as very uniform granules and, when tested in the tablet press, produces an excellent table.

The above procedure completely eliminates the drying step and much material handling. Screening is also eliminated for most materials, though in some cases it may still be desirable to do some screening.

The cost of processing according to the present invention is about 50% of the cost of other methods, the total cost being between about 8 cents and 12 cents per kilogram. In addition to lower cost, the method of the present invention actually results in a better product.

The following examples are given to illustrate the production of specific compositions in accordance with this invention. However, it is to be understood that the invention is not meant to be limited to the specific details of these examples. In all of the examples, unless otherwise indicated, the parts and percentages given are by weight.

Example 1

Solid particles of the following:

	Parts
Ascorbic acid	82
Corn starch (low moisture)	10
Polyoxyethylene polypropylene copolymer (Pluronic F 68)	8

are blended together at about room temperature in a Littleford Lodge Mixer and then heated to 80° C. while continuing the blending operation for about five minutes. The resulting granules are then cooled to room temperature and can be directly compressed into satisfactory tablets.

The Littleford Lodge Mixer is particularly suitable for the method because the material is constantly thrown against the heat transfer surfaces of the drum container, so that the entire process of blending, heating and cooling takes a total of about 15 to 50 minutes. Other mixing devices can be used, but in general do not offer the complete blending, heating and cooling requirements of the single-unit described.

The granules which are produced by this method require little or no screening after the cooling operation and prior to tableting on a rotary press. The tablets produced are of high quality, with low friability, high hardness and good disintegration with rapid dissolution rates. The tablets remain white after prolonged periods of storage.

Example 2

The same process as described in Example 1 is carried out with:

	Parts
Thiamin HCl (B ₁)	92
Glyceryl tristearate (M.P. 69° C.)	2
Pluronic F68	6

The resulting granules are tableted to tablets of good quality on standard tablet machinery.

Example 3

The same process as described in Example 1 is carried out on the following components:

	Parts
Riboflavin (B ₂)	92
Glyceryl tristearate (M.P. 69° C.)	2
Pluronic F68	6

The resulting granules could be directly processed to tablets of high quality on standard tablet machinery. To a portion of the above granulation there is added 10% of corn starch and the result is a high quality tablet produced on standard tableting machinery.

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Example 4

The same process as in Example 3 is carried out on the following components:

	Parts
5 Pyridoxine HCl (B ₆)	92
Glyceryl tristearate (M.P. 69° C.)	2
Pluronic F68	6

The resulting tablets are of high quality.

Example 5

The same process are carried out in Example 3 using the following ingredients:

	Parts
15 Niacinamide	92
Glyceryl tristearate	2
Pluronic F68	6

Ten percent corn starch is added to a portion of the granulation and the tablets produced therefrom are of extremely high quality.

Example 6

Following the procedure of Example 2 and using the following ingredients:

	Parts
25 Ascorbic acid (C)	92
Glyceryl tristearate	2
Pluronic F68	6

and adding 10% corn starch to a portion of the granulation, tablets of high quality are produced.

Example 7

A composite multivitamin formulation is prepared from the basic 92% potent vitamin granulations produced in the previous examples, as follows:

	Mg./tablet	Mg./tablet
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Example 2 granules (Thiamin HCl, 92%)	5.433	10.866
Example 3 granules (Riboflavin, 92%)	5.433	10.866
Example 4 granules (Pyridoxine HCl, 92%)	5.433	5.433
Example 5 granules (Niacinamide, 92%)	10.866	5.433
Example 6 granules (Ascorbic Acid, 92%)	54.330	108.660
45 Corn starch (low moisture)	8.505	18.742
Total compression weight, mg.....	90.000	160.000

50 The equiparticle granules prepared from composite powder blends as described in Examples 2-6 are blended with the prescribed quantities of corn starch. The binder employed is sufficient to lubricate the tablets for rotary press runs. High quality tablets are produced in each instance with no punch shape or concavity limitations encountered, i.e. tablets are prepared on flat face, standard concave, deep concave, extra deep concave and modified ball punches.

It is apparent to those familiar with the pharmaceutical tablet art that:

60 (1) Granules containing high amounts of active ingredients can be prepared and tableted.

(2) Any admixture of the preformed granules that does not introduce chemical or physical incompatibilities is possible.

65 (3) In the preparation of multivitamin tablets or other tablets of multi active composition, it is a logical and practical expedient to prepare high potency granules for admixture to meet diverse demands and concomitantly produce tablets of the smallest possible size.

Example 8

75 Particles of N-acetyl-p-aminophenol (92% by weight) and polyoxyethylene glycol (8% by weight) are milled and then heated to 85° C. and subsequently cooled to

effect granulation. The granules are blended with corn starch as follows:

	Grams
N-acetyl-aminophenol granules (92%) -----	353
Corn starch -----	27

and the active starch blend is compressed to produce 380 mg. tablets of high pharmaceutical elegance. The resulting tablets can be used for their anti-pyretic action.

The foregoing describes specific and generic aspects of the present invention, and it is of course to be understood that modifications thereof may be made without departing from the spirit of this invention. Such modifications are intended to be comprehended within the range of equivalents of the following claims.

What is claimed is:

1. Granulation method, which comprises uniformly mixing substantially dry particles of a physiologically active material adapted to be ingested and being damaged at elevated temperatures with substantially dry particles of a physiologically inactive and physiologically compatible thermoplastic material which softens at a temperature below the temperature at which said physiologically active material is damaged, heating the thus formed mixture to above the softening temperature of said thermoplastic material and below the temperature at which said physiological active material is damaged so as to cause agglomeration of the particles of physiologically active material with the particles of thermoplastic material and thereby forming powdered agglomerates, and cooling the

resulting agglomerates to a temperature below the softening point of said thermoplastic material so as to form a granulate which can be directly pressed into tablets wherein said particles of active material and said particles of thermoplastic material are mixed throughout the steps of heating and cooling.

2. Method according to claim 1 in which the thermoplastic material has a melting point of from between about 45° C. and 120° C.

3. Method according to claim 1 in which the amount of thermoplastic material is between about 2% and 20% by weight of the composition.

4. Method according to claim 2 in which the amount of thermoplastic material is between about 2% and 20% by weight of the composition.

5. Method according to claim 1 in which a solid filler material is added to the physiologically active material and thermoplastic material.

6. Method according to claim 1 in which the mixing, heating and cooling steps are carried out in a jacketed vessel and in which the heating is accomplished by passing a heated fluid through the jacket and the cooling is accomplished by passing a cooled fluid through the jacket.

No references cited.

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