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# PROCESS FOR THE UNIFORM DISTRIBUTION OF A DRUG ON A GRANULATED BASE

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## ABSTRACT OF THE DISCLOSURE

A method for making tablets containing a solid biologically active compound in non-granular form fixed to the external surface of a granular base material by:

(a) combining a predetermined amount of said biologically active compound with an inert volatile liquid,
(b) contacting said liquid and said active compound with an agitated mass of said granular base, and
(c) removing said voltaile liquid,
(d) directly compressing the coated granular base to form a tablet.

## BACKGROUND OF THE INVENTION

In the pharmaceutical processing industry, very few crystalline or powdered pharmaceutically active materials are directly convertible into tablet form. Generally, the flow characteristics and other compressibility factors of powdered organic and inorganic substances are such that they will not efficiently fill a die cavity for mechanized tablet production and/or they incorporate sufficiently large quantities of air so that compression of the solid material causes breakage at the minute surface contact points of the crystalline solid material and elastic deformation at other solid interfaces leading to decreased particle size of the compound and, upon release of the compression force, splitting of the "slug" or "tablet" matrix as a result of the relaxation of the highly strained pressure bonded (cold bonded) interparticulate adhesive forces.

To overcome these problems, it is conventional in the pharmaceutical manufacturing industry to granulate the pharmaceutically active material with or without a substrate or base material of inert nature. The granulation process affords a coarse particle which is desireably of such free-flowing character that it will readily fill the tablet die cavity in a tableting machine without the formation of trapped air pockets. Excessively large granulated particles may present a relatively intractible fused surface which affects the dissolution properties of the drug and, during the fabrication stages of manufacture, require the presence of a filler material to fill voids in a tablet die during compression. Thus, the desired particle for drug processing is free-flowing, presenting a non-fused surface, and of a size that air is not entrapped although a tablet die is adequately filled while readily cold bonding during compression. The use of an inert material as a base for a free-flowing granule with which an active drug may be mixed and directly compressed into a tablet is conventional. The techniques employed today generally involve either wet or dry granulation processes.

The wet granulation process commercially employed today involves the performance of eight distinct processing steps, which are:

(1) blending of dry ingredients;
(2) milling the dried blended solid material to the desirable particle size;
(3) the preparation of a binder solution;
(4) mixing the blended milled dry ingredients in the binder solution;



(5) after drying the solution the material is screened to afford a desired granule size;
(6) the still moist material is thoroughly dried;
(7) the dried agglomerated material is re-screened to break up any mass which is too large for subsequent handling; and
(8) blending of the thus formed granules with a lubricant or other desired external coating material.

The commercially practiced "double compression" or "slugging" procedures followed in the pharmaceutical industry, involve several distinct processing steps in which either all or a portion of the granular substrate needed for a given recipe is milled and mixed with the active ingredients in the dry state, followed by compaction of the mixture to form a slug which is ground, sieved to separate fines, the fines being reslugged and converted to granules by repeating the same sequence of steps, followed by blending of the granules so produced. Where only a portion of the original granular substrate was mixed with the active ingredients, additional steps are necessary to blend the "concentrate" with the rest of the granular substrate material after assay of the "concentrate."

Following any of the known techniques for the combination of pharmaceutical compounds with filler materials to produce compressible granules a substantial amount of equipment, labor, floor space and time is involved. The "double compression" (slugging) method was formerly believed to be indispensible where unique problems existed requiring the production of granulated material for tablets in the complete absence of water or abnormal temperatures. To date, the inherent problems attending dry compaction of crystalline or powdered materials, e.g. the production of an inordinate amount of fines and loss of uniformity of product concentration still plague the industry.

## BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided a process for the uniform distribution of small quantitites of solid, powdered ingredients upon a directly compressible granular base material which comprises combining a predetermined amount of a biologically active compound with an inert volatile liquid, contacting the resulting mixture with a mass of granular base material in an agitated state, followed by removal of the volatile liquid from the mixture, thereby depositing the active ingredient upon the surface of the granular base without changing the characteristics of the granulated base material. Thus, the process of the instant invention provides for the direct addition of active ingredients; e.g. active drug substances, etc. to a base material while retaining the free-flow characteristic, the direct compression characteristic and the original particle size distribution of the granular substrate. Thus, by the process of the instant invention, the direct production of a drug tablet may be performed in the operative steps of (1) preparation of a solution or suspension of the pharmaceutical material, (2) distribution of the solution or suspension of the active pharmaceutical material over the granular substrate, and (3) removal of the solvent or diluent from the mixture followed by direct compression of the so produced composition.

Following the process of the instant invention, production costs in drug manufacture, tablet manufacture are significantly reduced as a result of the elimination of several milling steps, slugging steps, grinding steps, concentrate assay and final blending procedures which are essential to the production of tablets employing the dry "compaction" method of granulation. Furthermore, the various apparatuses formerly needed in the production

of granulated material are no longer essential to the production of a more uniformly distributed pharmaceutical material than was heretofore obtainable. Moreover, a tablet mixture employing the external method of drug addition to the granular base can provide tablets with improved dissolution rates over tablets made from mixtures using the slugging method of preparation.

Other and equally important advantages afforded by the external method of drug application provided by the process of the instant invention, is the improved distribution of the drug over the base material. In the case of dry blending of drug and substrate materials, replication of drug content uniformity is difficult if not unachievable in batch operations. This is especially true where repeated blending and reblending as well as multiple milling and grinding steps produces a relatively large quantity of fines. The inordinate concentration of active drug materials in the fines of any given granulation batch is believed to result from the initial poor mixing properties of a fine crystalline or powdered material with a large granulated substrate material, or, in the case of the wet granulation procedure, it is generally considered that upon drying, the solvent as it leaves the granule matrix carries with it the soluble drug material and leaves an uneven deposit on the surface of the granule base, which upon blending with additional amounts of inert granular material tends to be eroded and appear in relatively high percentages in the composition fines.

In the "concentrate" method of granule preparation in which the active ingredient is uniformly mixed with a portion of the granular base material followed by various slugging and reslugging steps and an ultimate blending with the rest of the inert base recipe, the "concentrate" granules and the granule substrate are of similar dimension, but differ in appearance. The granular substrate is oft times uniformly rough on all surfaces whereas the concentrate exhibits one surface which is flat and smooth. The flat surface of the concentrate granule is believed to represent a portion of the slug surface which was fractured during grinding. The achievement of uniform drug distribution throughout the composition produced by the "concentrate" method is poor as a possible result of the fact that the "concentrate" particle presents one flat surface whereas the granular substrate does not.

## DETAILED DESCRIPTION OF THE INVENTION

The instant invention is based on the discovery of a means for preparing pharmaceutical compositions suitable for tableting by combining active drug ingredients with a granular substrate. The granular substrate may range in particle size from about 10 to 200 mesh (U.S. Standard Sieve), preferably about 12 to 50 mesh. The percentage by weight of granular substrate lies in the range from about 60 to 99.9 percent, preferably within the range of about 80 to 99.9 percent. The percentage by weight of the externally added drug material based upon the weight of the particulate substrate granule may be from approximately 0.1 percent to about 40 percent, preferably up to 20 percent.

To achieve uniform distribution of the drug on a granular substrate, any inert volatile solvent or diluent may be employed which is not a solvent for the granular substrate, such as a lower alcohol containing from 1 to 3 carbon atoms, chloroform, methylene chloride, acetone, and the like. Generally, it has been found that from about 5 to 33 percent by weight, preferably from 10 to about 20 percent by weight based upon the weight of the granular substrate, is a suitable quantity of solvent for dissolution or dispersion of the drug without providing an excessive amount of liquid for subsequent removal. It is preferred that a solvent be selected in which the drug is soluble. However, a fine dispersion of the drug in a diluent provides acceptable results. If additional additives are desired to be added to the granular substrate, such as one or more active pharmaceutical compounds, a dye or pigment, a disintegrant, an absorbent, a sweetener, or a lubricant, it is preferred that these components be introduced simultaneously with the application of the desired drug material all in combination with the same solvent or diluent. It is not necessary that each additive component be completely dissolved in the volatile material, some may be dissolved while the others appear in a dispersed state.

The dissolved or suspended drug and/or other additional ingredients, may be sprayed or poured by suitable means onto the mixing or agitated mass of granular substrate material. Mixing of the granular substrate during the addition of the active drug material in its liquid carrier, should be maximized while maintaining a very low rate of attrition of the granular substrate material. To achieve this it is preferred to employ a twin cone or twin shell blender or a single blade sigma mixer in which the mixing function may be optimized by sealing the mixing chamber and providing jacketed heating and/or cooling means as well as a vacuum system for removal of the volatile solvent. The preferred mixer is a twin shell blender fitted with a water jacket, vacuum system, condenser and a liquid/solid dispersion device.

In practice, the granular substrate is charged in the mixer and the unit is sealed. The drug to be distributed on the substrate material is dissolved or suspended in the solvent of choice. The granular substance is blended and the drug/solvent mixture is added through a liquid/solid dispersion device. When all of the drug/solvent mixture has been added to the blending substrate, the vacuum system is activated and solvent is stripped from the mixture. After complete solvent removal, the dry product mixture is discharged from the mixer. The resultant granulated material exhibits very little change in particle size distribution from that of the originally charged substrate and may be directly transferred to a tablet press for compression into tablets.

The following specific examples are presented for the purpose of illustrating the method for preparing one layer of a two layer tablet or a tablet existing as a single entity by external addition of an active drug material to a granular substrate. These examples are not to be construed as limitations on the scope of the invention, since it is apparent that the production of compressible granular particles containing externally applied drug material may form the basis for uniform, reproducible readily dissolvable pharmaceutical compositions for encapsulation rather than tableting.

In the following examples the expressions U.S.P. means United States Pharmacopeia Grade Reagents, the quantities expressed are in terms of weight percent of the named compenent to the whole, N.F. means National Formulary, the measurements of pressure are given in inches of mercury, absolute, the expression F.D. and C. stands for an approved Food, Drug and Cosmetic and the amount of diluent or solvent employed was that sufficient to suspend or dissolve the material to be applied to the granular base material.

### EXAMPLE I

Tablet Composition

| | Percent |
|---|---|
| 10-(2-dimethylaminopropyl)phenothiazine | 5–6 |
| Aspirin | 94–95 |
| Chloroform, N.F. | |

Transfer the aspirin in granular form to a single blade sigma mixer. Dissolve the phenothiazine in chloroform. While mixing the aspirin granulation, add the drug chloroform mixture through a perforated tube. Dry the granulation with vacuum of 30 inches Hg. Discharge the granulation and compress.

## EXAMPLE II

Following the procedure of Example I, with the exception that a diluent (acetone) is substituted for the solvent, the tablet is produced as follows: Transfer the aspirin granulation to a single blade mixer. Add the phenothiazine to the acetone and stir to susupend. Add the susupension to the aspirin granulation while mixing, then dry. Discharge the granulation and compress.

## EXAMPLE III

| | Percent |
|---|---|
| 10-(2-dimethylaminopropyl)phenothiazine | 0.5–1.5 |
| Sodium Saccharin, N.F. | 1.0–5.0 |
| Aspirin | 93.5–98.5 |
| Methanol Alcohol. | |

Add the aspirin granules to a twin shell blender. Dissolve the phenothiazine in the methyl alcohol, then add and suspend the sodium saccharin in the methyl alcohol solution. Add the solution/suspension to the blending aspirin granules, then dry in vacuum. Discharge the granulation and compress.

## EXAMPLE IV

| | Percent |
|---|---|
| *dl* - 13-β-ethyl-17-α-ethinyl-17-β-hydroxygon-4-en-3-one | .05–5.0 |
| Pigment, yellow | .10–1.0 |
| Cellulose Binder | 10.0–40.0 |
| Lactose | 50–90 |
| Tablet Disintegrant | .5–2.0 |
| Lubricant | .1–1.0 |
| Chloroform. | |

Transfer the lactose and cellulose binder to a twin shell blender. Dissolve the progesterone in the chloroform then add and suspend the yellow dye. Add the drug/dye/solvent mixture to the lactose and cellulose binder. Dry in vacuum, add the disintegrant lubricant and blend. Discharge the granulation and compress, using conventional feeding systems.

## EXAMPLE V

A tablet containing more than one pharmaceutical is readily produced, for example, by reducing the amount of the progesterone in Example IV to from about 0.05 to about 1.5 percent and using, in manner otherwise identical to the technique employed with progesterone, from 15 to about 35 percent by weight estrogen (19-nor-17-α-pregna-1,3,5,(10)-trien-20-yne-3,17-diol) as follows:

Transfer the cellulose binder and lactose to a twin shell blender. Dissolve the progesterone and estrogen in the chloroform and add it to the cellulose/lactose mixture. Dry in vacuum, then add the binder and lubricant and blend. Discharge the granulation and directly compress into tablets.

The following tabular comparison of an externally added drug combined with a granular substrate versus granular products produced by the "concentrate" or total "slugging" method shows the improved distribution characteristics obtained by the process of the instant invention.

Table II illustrates the screen analysis of granulated compositions prepared by the "concentrate" slug, the "total" slug method and external application method of the instant invention. In each case, the active ingredient and the same additional granular substrate material was employed.

TABLE II

Screen analysis of a granular substrate and an externally added active ingredient vs. slugging method.

[Screen analysis: percent retained (U.S. standard Sieve)]

| | Granular substrate | Granular substrate external adds | Concentrate slug method | Total slug method |
|---|---|---|---|---|
| Mesh No.: | | | | |
| 16 | 0.05 | 0.53 | 13.34 | 1.08 |
| 40 | 99.25 | 90.49 | 61.46 | 70.43 |
| 80 | 0.51 | 5.8 | 21.27 | 14.60 |
| 100 | 0.06 | 0.58 | 0.91 | 1.62 |
| 140 | 0.07 | 1.09 | 1.03 | 3.09 |
| 200 | 0.02 | 0.73 | 0.78 | 2.87 |
| Pass 200 | 0.01 | 0.60 | 1.20 | 5.89 |

In each example above, 10 gm. samples were randomly selected from final granulations and tested in a Sonic Sifter.

From this analysis, it is clear that the particle size remains substantially constant in the process of this invention as opposed to the "slugging" method of particle preparation.

Since the dissolution rate of a drug substance from a dosage form is a measure of the rate of solution of the drug, this rate is often considered to be the critical attribute of a specific dosage form for presentation of that specific drug to the gastrointestinal fluids of the host. The following Table III presents comparative dissolution rates in water of a specific drug formulation produced by the method of the instant invention as well as the "concentrate" slug method and the "total" slug method. As may be clearly seen from the data presented, the dissolution rate of the granules formed in the slugging methods was slow, possibly because the drug was tightly bound in the compacted aggregate and rapid and/or total release or dissolution was thereby inhibited.

Furthermore, Table III presents comparative disintegration data, the latter being the time required for a tablet to break down into particles sufficiently small to pass a ten mesh screen. In operation, the testing of a tablet for disintegration is performed by placing the tablet in a small cylinder having a ten mesh screen at the bottom. The cylinder is moved up and down in water at 37° C. to simulate *in vivo* agitation. The disintegration time is assumed to be the time in which the tablet would break apart in the stomach of a host. In these experiments, the granular material used as a substrate was also

TABLE I

Assay results of granulations prepared by externally added active ingredients vs. slugging methods

| | Externally added drug | | | | Concentrate slug method | | | Total slug method | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Trial No | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Content uniformity of drug (C.V. ± percent) | 1.3 | 0.6 | 0.9 | 1.0 | 4.8 | 10.7 | 8.8 | 2.4 | 1.5 | 1.8 |
| Mean assay of drug percent of claim | 100.1 | 99.9 | 99.1 | 100.6 | 97.6 | 104.7 | 96.7 | 99.0 | 100.0 | 99.0 |

In each trial, 10 samples were randomly removed from the finished bulk material and assayed. The content uniformity is indicated as a coefficient of variation (C.V.). The percent of Claim is based upon the theoretical amount of the drug that should be present based upon the amount used (percent of theory).

an active ingredient which was combined with B a second active ingredient.

In Table III, the expressions T50 and T80 represent the times in minutes in which 50% and 80% of the drug from the tablets dissolved. Likewise the percent of each compound dissolved in thirty and sixty minutes is presented.

TABLE III

| | Externally added drug | | | | Concentrate slug method | | | | Total slug method | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | A | B | A | B | A | B | A | B | A | B |
| Trial No. | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | |
| Dissolution: | | | | | | | | | | | | |
| T50 | 5 | 5 | 5 | 5 | 12 | 5 | 6 | 5 | 11 | 10 | 13 | 13.5 |
| T80 | 9 | 11.5 | 7 | 6.5 | 40 | 10 | 25 | 22 | 23 | 20 | 42 | 25.5 |
| Percent 30 minutes | 95 | 93 | 97 | 92 | 76 | 101 | 88 | 89 | 88 | 95 | 76 | 91 |
| Percent 60 minutes | 97 | 95 | 97 | 95 | 88 | 103 | 91 | 99 | 93 | 98 | 86 | 9 |
| Disintegration Ags.: | | | | | | | | | | | | |
| W./disks, minutes | 8 | | 6 | | 14 | | 13 | | 12 | | 15 | |
| Hardness, kg | 22-24 | | 20-24 | | 23 | | 25 | | 20-24 | | 20-24 | |

Disintegration Time in Artificial Gastric Solution W/D, U.S. Pharmacopoeia XVIII, Sept. 1, 1970 pp. 932–934.

What is Claimed is:

**1.** A process for preparing medicament containing tablets consisting essentially of:

(a) providing a granulated base material which is free flowing and of a character that it will readily fill a tablet die cavity on a tabletting machine without the formation of trapped air pockets while readily cold bonding during compression;

(b) combining a predetermined amount of a biologically active compound with an inert volatile liquid which liquid is not a solvent for the granular base;

(c) contacting said liquid and biologically active compound with an agitated mass of said granular base material to externally deposit said active compound on said base material;

(d) removing said volatile liquid to obtain a coated granulated base material containing from 0.1 to about 40 percent by weight of said biologically active compound;

(e) directly compressing said coated base material to form a tablet.

**2.** The process of Claim **1** in which said inert volatile liquid is a solvent for said biologically active compound.

**3.** The process of Claim **1** in which said mass of granular base is mechanically agitated while said mixture of volatile liquid and biologically active compound is applied thereto as a spray.

**4.** The process of Claim **1** in which said volatile liquid is removed from the particulate granular base by vacuum distillation.

**5.** The process of Claim **1** in which said biologically active compound is a solid crystalline powder.

**6.** The method of Claim **1** in which the biologically active compound is 10-(2-dimethylaminopropyl)phenothiazine hydrochloride.

**7.** The method of Claim **1** in which the biologically active compound is *dl*-13-$\beta$-ethyl-17$\alpha$-ethinyl-17-$\beta$-hydroxygon-4-en-3-one.

**8.** The method of Claim **1** in which the biologically active compound is 3,17$\beta$-diol 17$\alpha$-ethynyl-1,3,5-estratriene-3,17$\beta$-diol.

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