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SELF-LUBRICATING GRANULATION

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This invention relates to a new and improved method for preparing tablet granulations.

In the manufacture of compressed tablets, two methods are generally used. The most common is the so-called wet granulation process. This is a long and tedious operation requiring many steps. It includes moistening a mixture consisting of the therapeutic component, excipients and binder with a suitable moistening agent, passing the wet mass through a screen to form granules, drying and rescreening the granules in order to reduce them to a size suitable for use in a tableting machine. At this point a lubricating agent is homogeneously admixed with the granulation in order to facilitate its passage through various orifices in the tableting machine.

Another method for the preparation of compressed tablets is one commonly referred to as "slugging." This method includes mixing the active ingredients with suitable excipients, compressing the dry powdered mass into large tablets or slugs, reducing the slugs to granules by forcing them through a screen of appropriate mesh size and recompressing the granules on a tableting machine.

Thus, in the case of the wet granulation process, it has heretofore been thought necessary to include in the wet mass only the drug, excipients and binder and to add the lubricant to the dried granulation in a separate step. If the slugging method is used, the lubricant can be added in the initial mixing step but it is necessary to recompress the slugs after they have been granulated. It is also customary to add an additional lubricant before recompression to the final tablet shape.

Contrary to the teachings of the art at the present time, we have found that the lubricant can be added to the initial powdered mixture and can be subjected to wet granulation. The incorporation of the lubricant in the initial mixture, as well as the wetting and drying of it, in no way detract from its lubricating properties. This is an unexpected and surprising observation, inasmuch as it has been though that the dry free-flowing consistency of the lubricant can be retained only if its contact with moistening agents is completely avoided. Our discovery that the lubricating properties of lubricants are not affected by moisture and drying, not only eliminates a step which heretofore has been considered essential in the preparation of tablet granulations, but affords a considerable saving in time in the overall tableting process.

An additional advantage in incorporating the lubricant in the initial pre-granulated mixture resides in the efficacy of the tableting operation. Where, as before, it was necessary to subject the granulation to an additional mixing step, thus reducing the control over the accuracy of dosage per unit and increasing the probability of error, contamination and loss, it is now possible to make tablets by a process which is more accurate, more efficient, and less time-consuming. Tablets prepared in accordance with our process do not vary in hardness, have optimal disintegration time, are smooth and readily extrudable by the machine. Pitting and jamming, because of lack of lubricant in the granulation, have not been observed.

Lubricants considered to be suitable in the operation of our process are talc, stearic acid, salts of this acid, preferably magnesium stearate and mixtures thereof. The amount of lubricant in relation to the total weight of the tablet depends largely upon the nature of the lubricant employed, and for this reason may vary within certain prescribed limits. For example, if talcum is employed, it is preferable to use about 5% to 10% of the lubricant. If magnesium stearate is used, the limits are somewhat narrower in range, being from 0.5 to 2%. In the case of stearic acid one may use a quantity varying from about 2% to about 5%. If mixtures of these are used, the proportions will vary in accordance with the respective quantities employed.

The method we have described here may be advantageously applied to a wide variety of tableting formulations wherein the use of a lubricating agent is mandatory. Therapeutically active compounds which may be formulated in accordance with our improved method include tripelennamine, methyl-phenidylacetate, phenobarbital, aspirin, reserpine, glutethimide, hydrocortisone, cortisone and other substances usually administered in tablet form.

Excipients suitable for use in our process are milk sugar, corn starch or other therapeutically inert substances commonly employed for this purpose. As binders, to insure adequate cohesive properties, may be used sucrose, gelatin, acacia or tragacanth. If desired, a water-soluble polyethylene glycol such as Carbowax 6000 may be added to provide added binding properties. Water, a lower alkanol such as methyl, ethyl, propyl or isopropyl alcohol, acetone, or mixtures thereof may be advantageously used as moistening agents in our process.

The following examples are intended to illustrate this invention but are not intended to be limitative upon the scope thereof.

Example 1

100 grams of methyl phenidylacetate hydrochloride, 30 grams of tragacanth, 987 grams of milk sugar, 225 grams of confectioner's sugar, 75 grams of talcum and 7.5 grams of magnesium stearate are mixed in a suitable container until homogeneous. 75 grams of polyethylene glycol 6000 are dissolved in 100 ml. water and the mixture is diluted with 100 ml. anhydrous 3A alcohol, heating, if necessary, to a temperature of about 45° C. to effect solution. The mixed powders are granulated with the polyethylene glycol solution, additional 50% 3A alcohol being added when necessary. The moist mass is pressed through a No. 10 sieve and is dried. The resultant granules are passed through a No. 16 mesh screen and compressed into tablets.

Example 2

884 grams of lactose, 20 grams of tragacanth, 20 grams of acacia and 25 grams of talcum are mixed in a suitable container to a homogeneous mixture. 50 grams of polyethylene glycol 6000 are dissolved in a solution containing 60 cc. of distilled water and 20 cc. of anhydrous 3A alcohol. The mixture of powders is granulated with the polyethylene glycol solution, passed through a No. 10 mesh screen, air-dried, passed through a No. 20 mesh screen and compressed into tablets.

Example 3

About 780 grams of calcium sulfate dihydrate, 100 grams of mannitol, 20 grams of tragacanth, 50 grams of talcum and 20 grams of magnesium stearate are thoroughly mixed and moistened with 150 ml. of 20 percent mucilage acacia, with addition of a sufficient quantity of 50 percent alcohol to complete the granulation. The mass is passed through a No. 10 sieve and air-dried. The

resultant granules are passed through a No. 20 sieve and compressed into tablets.

What is claimed is:

1. In a method for preparing granules of therapeutically active substances, the improvement which comprises the steps of adding a lubricating agent, in an effective amount up to and including about 10%, by weight, of the resulting granules to a dry, powdered mixture of a therapeutic compound and an excipient, moistening said mixture with a solvent containing a binding agent and forming the resulting mass into granules.

2. In a method for preparing granules of therapeutically active substances, the improvement which comprises the steps of adding a lubricating agent, in an effective amount up to and including about 10%, by weight, of the resulting granules to a dry, powdered mixture of a therapeutic compound and an excipient, moistening said mixture with a solvent containing a binding lubricating agent, and forming the resulting mass into granules.

3. In a method for preparing granules of therapeutically active substances, the improvement which comprises the step of moistening a dry, powdered mixture of a therapeutic compound and an excipient with a mixture of a solvent containing a binding-lubricating agent, said agent having an effective amount of lubricant up to and including about 10% by weight, of the resulting granules, and forming the resulting mass into granules.

4. In a method for preparing granules of therapeutically active substances, the improvement which comprises the steps of moistening a dry, powdered mixture of a therapeutic compound, an excipient and a lubricating agent, in an effective amount up to and including about 10%, by weight, of the resulting granules with a solvent containing a binding agent, and forming the resulting mass into granules.

5. In a method for preparing granules of therapeutically active substances, the improvement which comprises the steps of moistening a dry, powdered mixture of a therapeutic agent, an excipient and an effective amount up to and including about 10%, by weight, of the resulting granules a member selected from the group consisting of talc, stearic acid, magnesium stearate and mixtures thereof with a solvent containing a binding agent, and forming the resulting mass into granules.

6. In a method for preparing granules of therapeutically active substances, the improvement which comprises the steps of moistening a dry, powdered mixture of a therapeutic compound, an excipient and an effective amount up to and including about 10%, by weight, of the resulting granules, a member selected fro mthe group consisting of talc, stearic acid, magnesium stearate and mixtures thereof with an aqueous solvent containing a member of the group consisting of sucrose, gelatin, acacia and tragacanth and forming the resulting mass into granules.

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