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[54] **ENROBED SOLID HYDROPHOBIC TABLETING LUBRICANTS AND COMPOSITIONS**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 159,569, July 2, 1971, abandoned.

[52] **U.S. Cl.** **424/32;** 252/10; 264/300; 424/33; 424/34; 424/35; 424/37; 424/38; 424/357; 424/365

[51] **Int. Cl.²** **A61K 27/00**

[58] **Field of Search** 424/32–38, 424/357, 365; 264/300; 252/10

[56] **References Cited**

UNITED STATES PATENTS

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[57] **ABSTRACT**

Conventional solid hydrophobic tableting lubricants enrobed in a hydrophilic friable sheath are disclosed. The utilization of these enrobed lubricants with conventional tableting equipment makes possible the preparation of compacted tablets with improved dissolution times.

6 Claims, No Drawings

ENROBED SOLID HYDROPHOBIC TABLETING LUBRICANTS AND COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Patent application Ser. No. 159,569, filed July 2, 1971, now abandoned.

BACKGROUND OF THE INVENTION

It is a desirable characteristic of compacted pharmaceutical tablets, other than those specifically designed to release medication over a prolonged period of time, to yield rapid and complete effects of the active components. The disintegration of a compact is critical since it is this disintegration which exposes the contained active components to absorption by the recipient. The rate of disintegration of the compact should ideally not be impeded by the processing or additives required to convert the active constituents into a convenient, stable and easily ingestible oral dosage form. However, in practice, it is usually necessary to include in the tableting composition agents which impart physical characteristics essential for manufacture with existing compaction equipment, but having adverse effects on tablet disintegration and thus on the availability of the active components.

The conventional procedure for making compacts requires the addition of a lubricant to the mixture before compression. Compression is accomplished by subjection of the tablet mix to high pressures by moveable punches operating in a die wherein the tablet mix is confined. The lubricant, generally fine particles of solid material typified by such hydrophobic, antiadherent materials as metallic stearates, fatty acids, talc and natural and synthetic waxes, is necessary to allow the ready ejection of the formed compact and to prevent the binding of the punches in the die. Lubrication is required only at the tablet-die interface to prevent sticking of the newly formed compact to the die walls. However, existing practical approaches to tablet lubrication require homogeneous distribution of lubricant within the entire tablet granulation (see for example: Remington's Practice of Pharmacy, 12th edition, 1961, Mack Publishing Co., Page 448).

The inclusion of an anti-adherent lubricant between granules intended for compression and cohesion in a compact is a paradoxical reality of tableting. Cohesion of adjacent granules is desired to form a structurally adequate compact; however, when anti-adherent lubricant particles are interspersed between these granules, cohesion is reduced and a weak compact results. Similarly, the presence of hydrophobic lubricant particles in a compressed matrix surrounding active material which is intended for rapid dissolution and absorption is a negative design. The movement of fluid through intergranular passages is desired in order to initiate the disintegration of the compressed tablet thus allowing the active components to be absorbed by the host. The presence throughout the tablet of hydrophobic lubricant particles, however, impedes this distribution of solvent into the tablet interior, thus increasing disintegration time for the compact.

The desirability of providing lubrication only on the tablet sides or lands is indicated by prior efforts to obtain external lubrication of the die surfaces. Various methods and techniques of spraying or insufflating lubricants in solution or as small particle size solids have been used. These methods require elaborate mechanical components, do not precisely or uniformly deposit lubricant films where needed and are difficult to regulate and adjust for changes in tableting rates.

U.S. Pat. No. 3,158,111 discloses a timed spray to lubricate the punch and die surfaces, the lubricant being dispersed in and distributed by an aerosol propellant.

U.S. Pat. No. 3,042,531 teaches a dual cycle compression system in which a tablet containing only lubricant and carrier is first compressed within a die and then ejected leaving a residue of lubricant on the punch and die surfaces providing external lubrication for a second active granulation which is subsequently introduced and compressed.

SUMMARY OF THE INVENTION

The invention sought to be patented in a principal composition aspect resides in the concept of finely divided particles of solid hydrophobic tableting lubricant, a substantial proportion of the particles of said lubricant being enrobed in a hydrophilic friable sheath.

The tangible embodiments of the principal composition aspect of the invention possess the applied use characteristic of supplying necessary lubrication at points of high shear when present in a tableting formulation subject to compression according to standard methods for compact formation. The hydrophilic envelope will selectively rupture at points of high shear such as the compact-die wall interface thus releasing the entrapped lubricant where it is needed. The enrobed solid hydrophobic lubricant particles in the interior of the compact as well as on the top and bottom surfaces will remain intact and present none of the antiadherent, hydrophobic characteristic properties of conventional, unprocessed lubricants.

The invention sought to be patented in a second composition aspect resides in the concept of a solid compact comprising finely divided particles of solid hydrophobic tableting lubricant, a substantial proportion of the particles of said lubricant being enrobed in a hydrophilic friable sheath.

The tangible embodiments of the second composition aspect of the invention possess the applied use characteristic of being compacts with improved disintegration characteristics capable of formation by standard tableting procedures known in the art.

The invention sought to be patented in a principal process aspect resides in the concept of a process for the production of a compact which comprises incorporating in a mixture to be compacted finely divided particles of solid hydrophobic tableting lubricant, a substantial proportion of said particles being enrobed in a hydrophilic friable sheath, and applying thereto a sufficient compressive force.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention a method is now provided whereby conventional tableting equipment and standard tableting procedures are utilized to prepare compacted tablets having improved disintegration characteristics.

The conventional tableting excipients such as binders, fillers, glidants, disintegrants, flavors and colorants may be mixed with a specially prepared enrobed solid hydrophobic lubricant before compaction. This solid hydrophobic lubricant has previously been treated to

enclose it within a non-hydrophobic, friable sheath or envelope. This relatively inelastic envelope is designed to selectively rupture only at areas of high shear during compaction, such as the tablet-die wall interface, and remain intact in the interior of the tablet. Thus, the entrapped solid hydrophobic lubricant released from the ruptured enrobed lubricant particle functions only where actually required. The enrobed lubricant particles in the interior of the tablet remain intact and present none of the anti-adherent, hydrophobic properties of conventional, unprocessed lubricants. Thus, dispersal of fluids within the tablet interior is facilitated and the availability of the contained active ingredient is improved. The enrobed particles on the top and bottom of the tablet also remain substantially intact, thus providing free entry of the dissolution fluid. These surface particles, while subjected to high compressive forces during compaction are not ruptured, because no true shearing or sliding forces are exerted on these areas. Shear, in this context, is considered as stress resulting from applied forces that cause two contiguous surfaces to slide relatively to each other in a direction parallel to their plane of contact. The designed mechanical function of this method may be visually indicated by dye tracers incorporated in the envelope surrounding the lubricant particle. The sides or lands of the otherwise uncolored compressed tablets show dye streaks parallel to the path of ejection, while examination of bisected tablets show intact unchanged enrobed particles in the tablet interior.

The enrobed solid hydrophobic lubricants of the present invention can be prepared by a variety of processes, such as:

Dispersion of solid hydrophobic tableting lubricant particles in molten mannitol, polyethylene glycol 4,000, 6,000 and 20,000, or other thermostable hydrophilic materials whereby milling or other methods of particle size reduction, after solidification, results in substantial entrapment of lubricant particles in a solid non-hydrophobic matrix;

Coating of the solid hydrophobic tableting lubricant particles with a hydrophilic material by spray drying or spray chilling technique;

Formation of hydrophilic micropellets from geletin, gum arabic, methyl cellulose, polyvinyl, alcohol, or the like, said micropellets containing solid hydrophobic tableting lubricant particles. The technique for preparation of micropellets containing particulate material is described in N. Tanaka, S. Takino, and I. Utsumi, J. Pharm. Sci., 52, 664 (1963).

Any of the various solid hydrophobic tableting lubricants may be used in this invention. Among these are magnesium stearate, calcium stearate, talcum, fatty acids, stearic acid, and powdered vegetable stearine. Other suitable tableting lubricants will readily suggest themselves and the utilization in the practice of the invention of any of a vast number of substances suitable as lubricants is well within the skill of the art.

Many hydrophilic substances may be utilized as the coating materials in the present invention. Among the hydrophilic materials contemplated by the present invention are such substances as gelatin, gum arabic, methyl cellulose, carboxymethylcellulose, polyvinyl alcohol, mannitol, polyethylene glycol 4,000, 6,000, and 20,000, and other hydrophilic materials which will be obvious to those skilled in the art. There is no criticality in the use of any particular lubricant or hydrophilic substance. The thickness of the enrobing material which surrounds the lubricant particles is not critical. The shearing forces generated during compaction are extremely large and are more than sufficient to rupture the various sheath thicknesses which may be applied by the methods described in this invention and other methods known in the art. The optimal thickness of the friable sheath will vary with the particular substances utilized, or the particular coating procedures used; however, the optimal thickness, or optimal range of thicknesses for a particular combination of lubricant and sheathing material may be readily determined by those skilled in the art.

It will be apparent to those skilled in the art that the compacts prepared utilizing the present invention may be multilayer compacts and have various different shapes and sizes. Further, that these compacts once formed may be coded and/or coated by a variety of procedures well-known to those skilled in the art. Still further, they may be subjected to a polishing procedure or other routine processes which have been carried out on compacts prior to this invention.

While it is the main object of this invention to provide an improved method of preparation of pharmaceutical compacts which possess an improved dissolution rate, it will be obvious to those skilled in the art that this improved method may be applied to compacts other than those which contain a medicament. Thus, compacted coloring and flavoring materials, spices, detergents, and even placebo tablets may be prepared utilizing the improved method of this invention.

Additional advantages of this invention include the improvement of physical properties of compressed tablets even where availability of the actives is not a factor. As an example, harder, less friable and more rapidly disintegrating tablets may be obtained with the enrobed solid hydrophobic lubricant particles of the invention than with an equivalent quantity of unprocesses lubricant.

The following non-limiting examples illustrate the best mode contemplated by the inventor of carrying out the processes of the invention.

EXAMPLE I

10% Magnesium Stearate Enrobed in Polyethylene Glycol 4000, U. S. P.

Polyethylene glycol 4000 (90 g.) is heated until molten (60°–65° C.), and dry, finely powdered magnesium stearate U.S.P. (10 g.) is added with mechanical stirring. This stirred dispersion is cooled to room temperature (ca. 25° C.) and chilled further with solid carbon dioxide. The solid is milled through a U.S. No. 30 screen producing the enrobed tableting lubricant which is suitable for use in conventional tableting procedures.

EXAMPLE II

33% Magnesium Stearate Enrobed in Gelatin

To a suspension of gelatin (40 g.) in water (200 g.) is added finely powdered magnesium stearate U.S.P. (20 g.) with rapid stirring. This mixture is warmed on a steam bath to form a solution and poured into mineral oil (600 g.) heated to ca. 55°–60° C. The total mixture is stirred at 18–22 r.p.m. for 5 minutes and quickly cooled to ca. 5° C. producing gelatin micropellets containing magnesium stearate. The micropellets are washed with isopropanol and dried. The dried micro-

pellets produced in this manner are suitable for use as a lubricant in conventional tableting procedures.

EXAMPLE III

Calcium Stearate Enrobed in Gelatin by Spray Drying

Dry powdered calcium stearate (10 g.) is suspended in a 1% gelatin solution (500 cc.) and the suspension is spray dried to remove the water. In this manner gelatin coated calcium stearate particles are obtained which are suitable for use as a tableting lubricant in a conventional tableting procedure.

EXAMPLE IV

Talc Enrobed in Polyethylene Glycol 6000 by Spray Chilling

Dry powdered talc (25 g.) is suspended in molten polyethylene glycol 6,000 (250 g.) and stirred until homogeneous. This suspension is sprayed into a chilled chamber with cold air causing the polyethylene glycol 6,000 to solidify about the talc particles. In this manner talc particles coated with polyethylene glycol 6,000 may be obtained which are suitable for use as a tableting lubricant in a conventional tableting procedure.

EXAMPLE V

Tablets having the following composition are prepared with conventional tableting equipment:

Ingredient	mg. per tablet
Meprobamate, U.S.P.	400.
Methylcellulose, U.S.P., 400 cps.	32.4
Enrobed Solid Lubricant (10% Magnesium Stearate, U.S.P. in Polyethylene Glycol 4000, U.S.P.)	49.
Starch, U.S.P.	42.2
Total Weight	523.6

Tablet disintegration time was reduced from 23 minutes for a control tablet containing a conventional lubricant to 17 minutes for a tablet containing an equivalent amount of the enrobed lubricant.

EXAMPLE VI

Antibiotic tablets having the following composition and showing the superior dissolution characteristics tabulated are prepared as follows:

Ingredient	mg. per tablet
Potassium Penicillin G, U.S.P.	166.0
Gelatin Enrobed Lubricant (33% Magnesium stearate, U.S.P.)	18.0
Calcium Carbonate, U.S.P.	222.0
Silicon Dioxide	22.0
Methylcellulose, U.S.P., 400 cps.	40.0
Total Weight	468.0

The penicillin availability is indicated by continuously recorded fluorometric assay. T_{50} and T_{80} is time in minutes necessary for dissolution of 50% and 80%, respectively, of the total potassium penicillin per tablet.

	T_{50}	T_{80}	% in sol'n in 30 mins.	% in sol'n in 60 mins.
Control Tablet (containing unprocessed lubricant)	25	56	57	82
Tablet (made with equivalent amount of enrobed lubricant)	19	37	60	95

The dissolution test method and equipment is described in Poole, J. W., Drug Information Bull. 3, 8–16 (1969).

The subject matter which the applicant regards as his invention is particularly pointed out and distinctly claimed as follows:

1. A tableting lubricant composition consisting essentially of micropellets of finely divided particles of solid hydrophobic tableting lubricant selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, talcum, and powdered vegetable stearine, a substantial proportion of the particles of said lubricant being enrobed in a hydrophilic friable sheath, said sheathing material being selected from the group consisting of mannitol, polyethylene glycol 4,000, **6,000,** and 20,000, gelatin, methyl cellulose, carboxymethylcellulose, gum arabic, and polyvinyl alcohol; said enrobed tableting lubricant imparting a reduction in dissolution time to a compacted pharmaceutical dosage form when incorporated in said compacted pharmaceutical dosage form, as compared to said lubricant when not enrobed.

2. The composition of claim **1** wherein the solid hydrophobic tableting lubricant is magnesium stearate and the hydrophilic friable sheathing material is polyethylene glycol 4000.

3. The composition of claim **1** wherein the solid hydrophobic tableting lubricant is magnesium stearate and the hydrophilic friable sheathing material is gelatin.

4. The composition of claim **1** wherein the solid hydrophobic tableting lubricant is calcium stearate and the hydrophilic friable sheathing material is gelatin.

5. The composition of claim **1** wherein the solid hydrophobic tableting lubricant is talc and the hydrophilic friable sheathing material is polyethylene glycol 6,000.

6. A compressed pharmaceutical medicament tablet containing as tableting lubricant a tableting lubricant composition consisting essentially of micropellets of finely divided particles of solid hydrophobic tableting lubricant selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, talcum, and powdered vegetable stearine, a substantial proportion of the particles of said lubricant being enrobed in a hydrophilic friable sheath, said sheathing material being selected from the group consisting of mannitol, polyethylene glycol 4,000, 6,000, and 20,000, gelatin, methyl cellulose, carboxymethylcellulose, gum arabic, and polyvinyl alcohol; said tablet having imparted, by said enrobed lubricant, reduced disintegration time compared to said lubricant if not enrobed.

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