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COMPRESSED ORAL DRUG TABLET GRANULATIONS CONTAINING ADMIXED THEREIN ABOUT 1% TO 15% OF POLYFLUOROCARBON TYPE POLYMER LUBRICANT POWDERS IN ABOUT 1 TO 150 MICRON PARTICLE SIZE

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The present invention relates to a process of manufacturing tablets, such as tablets for oral ingestion containing a physiologically active ingredient, especially a pharmacologically effective compound.

In the manufacture of tablets, the addition of lubricating agents is necessary (1) to facilitate the flow of the granulate mixture, (2) to reduce the friction between the granulate and the die during compression and ejection of the compressed tablets, and (3) to prevent the sticking of the compressed tablet to the faces of the punches.

Compounds useful as lubricants are required to have high melting points, be chemically inert and physiologically non-toxic, and should affect neither the physiologically active ingredient, nor, at least not to a great degree, the physical characteristics of the compressed tablet, such as its disintegration time, its hardness and the like.

While a great number of the lubricating agents used in the art meet the requirements of friction reduction during compression, or tablet ejection, and satisfactorily prevent the sticking of the compressed tablet to the punches, many lubricants tend to alter the characteristics of the tablets; specifically they prolong the disintegration time and decrease the hardness of the tablet. Thus, in tests carried out with granulation compositions containing a physiologically active ingredient, certain lubricants, such as the widely used salts of stearic acid, e.g. sodium stearate, magnesium stearate, calcium stearate and the like, as well as hydrogenated castor oil, sodium lauryl sulfate, polyethylene glycols, powdered edible vegetable oils, and the like, cause a marked and undesired increase of the disintegration time of the tablet. In addition, certain lubricants, particularly magnesium stearate, tend to soften the tablets.

Furthermore, lubricants have individual disadvantages. For example, while it was found to be a lubricant devoid of any significant effects on the disintegration time of the tablets, stearic acid, due to its acidic properties, has other disadvantages; for example, it cannot be used in tablets containing physiologically active materials which are easily hydrolyzed, such as reserpine, without impairing the stability of the drug. Even its metal salts are incompatible with certain ester compounds, e.g. aspirin, which is hydrolyzed in the presence of a metal stearate. Polyethylene glycol lubricants are, for example, not suitable for tablets containing syrosingopine.

The need for a lubricant, which satisfactorily fulfills the functions of a lubricating agent and does not unduly change the physical characteristics of the resulting tablet or affect the stability of the physiologically active ingredient, is, therefore, obvious.

It is an object of the present invention to provide the use of a new lubricating agent in the process of manufacturing tablets.

It is a further object of the present invention to provide the use of a lubricant in the process of manufacturing tablets which sufficiently reduces the friction between the granulation mixture and the die during compression, facilitates the ejection of the tablet after compression, and prevents the compressed tablet from sticking to the punch faces.

A further object of the present invention is to provide the use in the process of manufacturing tablets of a lubricating agent which is chemically inert and physiogically non-toxic, and which does not substantially alter the desired physical characteristics of the compressed tablet.

The primary object of this invention is in the process of manufacture of tablets, the step which comprises using a polymer of the polyfluorocarbon type or a mixture of polymers of the polyfluorocarbon type as the lubricating agent.

I have found that polymers of the polyfluorocarbon type (i.e. the so-called polyfluorocarbons or fluorocarbon polymers) have the characteristics necessary of the lubricating agents used in manufacturing tablets, i.e. they facilitate the flow of the granulation mixture, they reduce the friction between the granulation and the die during compression, they prevent the compressed tablet from sticking to the face of the punches, and they reduce the force necessary to eject it after compression. In addition, polymers of the polyfluorocarbon type have a sufficiently high melting point and are chemically inert; they are, therefore, compatible with tablet ingredients which are easily degraded in the presence of known lubricating material, and do not pose any physiologic and toxic problems.

Furthermore, I have also found that the polymeric substances of the polyfluorocarbon type, when used as lubricating agents, affect the physical characteristics of the compressed tablet to a much smaller degree than the majority of the known lubricants. For example, the disintegration time of a tablet containing as a lubricant a polymer of the polyfluorocarbon type is smaller than that of a tablet containing as a lubricating agent a metal stearate lubricant, e.g. magnesium stearate and the like, or hydrogen castor oil. It has also been observed that, contrary to the results with known lubricants, such as those mentioned above, the disintegration time of a tablet containing, as a lubricant, a polymer of the polyfluorocarbon type is not significantly affected by various amounts of the latter. These types of lubricants also add coherent strength to the compressed tablets; this property appears to be in contrast with the effects of the known lubricating agents which tend to soften the compressed tablet.

Polymers of the polyfluorocarbon type (i.e. polyfluorocarbons) are a well-known group of polymeric and copolymeric substances made up of carbon and fluorine, which, in addition, may contain hydrogen and/or chlorine. Particularly useful as a lubricating agent is the polytetrafluoroethylene of the formula $(—CF_2—CF_2)_n$; other polyfluorocarbons, capable of being used as lubricants in the process of manufacturing tablets according to this invention, are the copolymer of tetrafluoroethylene and hexafluoropropylene of the formula

$$(—CF_2CF_2—CF_2\underset{\displaystyle CF_3}{\underset{|}{C}}FCF_3)_n$$

the polyvinylidene fluoride of the formula

$$(—CH_2—CF_2—)_n$$

the copolymer of vinylidene fluoride and hexafluoropropylene of the formula

$$(—CF_2CH_2—CF_2\underset{\displaystyle CF_3}{\underset{|}{C}}FCF_3)_n$$

the polytrifluorochloroethylene of the formula

$$(—CF_2CFCl—)_n$$

the copolymer of vinylidene fluoride and trifluorochloroethylene of the formula $(—CF_2CH_2—CF_2CFCl—)_n$, and the like. These polyfluorocarbons, their properties and manufacture are known and are described, for example, by Simonds and Church, A Concise Guide to Plastics, pages 45 to 52, and pages 137 to 138 (second edition, 1963, Reinhold Pub. Corp., New York).

The polymers of the polyfluorocarbon type for lubricating purposes are used in the form of powders having a particle size of from about 1 micron to about 150 microns, preferably of from about 1 micron to about 25 microns. The tablets manufactured with the help of such lubricating agent(s) have a content from about 1 percent to about 15 percent, preferably from about 2 percent to about 10 percent, of the polymer(s) of the polyfluorocarbon type.

Also included within the scope of this invention are tablets containing as the lubricating agent a polymer of the polyfluorocarbon type or a mixture of polymers of the polyfluorocarbon type.

Apart from any physiologically active ingredient(s) and the polymer(s) of the polyfluorocarbon type as lubricant(s), the tablets contain the usual bulking materials, such as sugars, e.g. lactose, glucose, sucrose and the like, inorganic salts, e.g. calcium phosphate, calcium sulfate, calcium lactate and the like, or any other suitable bulking materials, disintegrants, such as starches, e.g. corn starch, wheat starch, rice starch and the like, alginic acid or salts thereof, e.g. ammonium or calcium alginate and the like, microcrystalline cellulose and the like or any other suitable material enhancing the disintegration of a tablet, as well as any other ingredients facilitating the manufacture of a tablet or its use, such as water-repellents, coloring agents, and the like.

The tablets are prepared according to standard methods of tablet manufacturing, usually by forming a granulate mixture suitable for compression. The polymer(s) of the polyfluorocarbon type used as lubricant(s) is(are) added to the mixture of the tablet ingredients either before granulation or after the granulate has been formed. Usually the granulate is prepared by mixing the physiologically active product(s), the bulking material(s), the disintegrant(s), or any other ingredients, and, if desired, the polymer(s) of the polyfluorocarbon type used as the lubricant(s), if necessary, after sieving the ingredients to obtain uniform maximum particle sizes, and wetting the resulting mix with a liquid diluent or with a paste. The wet mass is then passed through a mill to reduce the particle size, dried to lower the moisture content, and, if necessary, again passed through a mill. Formation of the granules can also be achieved by the slugging method, i.e. by blending the physiologically active ingredient(s), the bulking agent(s), the disintegrant(s), or any other ingredients, and, if desired, the polymer(s) of the polyfluorocarbon type used as the lubricant(s), all having the desired particle size, in a suitable mixer, agglomerating the powder mass by slugging it or passing it through a compactor mill, and, if necessary, classifying the agglomerated mass or passing it through a grinder. In case the granulate does not yet contain the polymer(s) of the polyfluorocarbon used as the lubricant(s), the latter is(are) mixed with the granulate mixture, which is then compressed into the desired tablets.

The resulting tablets may be used as such, or, if desired, may be coated; coatings may have non-enteric (sugar, methylcellulose, sodium carboxy-methylcellulose coatings and the like) or enteric properties (cellulose acetate phthalate, polyvinyl acetate coatings and the like), and may be applied by the pan coating or compression coating method. In the latter procedure, in which a dry coating material is compressed around a preformed core, a coating granulate mixture may be utilized which has from about 1 percent to about 15 percent, preferably from about 2 percent to about 10 percent, of the lubricating agent(s).

The following examples illustrate the invention and are not intended to represent limitations thereon. Temperatures are given in degrees centigrade.

Example 1

Tablets, each containing 0.05 g. of 2-[N-benzyl-N-(2-N,N-dimethylaminoethyl)-amino] - pyridine hydrochloride as the active ingredient, and 0.01 g. of polytetrafluoroethylene of an average particle size of from about 5 microns to about 10 microns, as the lubricating agent, are prepared as follows (for 5,000 tablets).

Ingredients:	G.
2-[N-benzyl-N-(2-N,N - dimethylaminoethyl)-amino]-pyridine hydrochloride	250.0
Corn starch	50.0
Lactose	650.0
Polytetrafluoroethylene	50.0
Alcohol 3A, 50 percent, q.s.	

The 2 - [N - benzyl - N - (2-N,N-dimethylaminoethyl)-amino]-pyridine hydrochloride, the corn starch, the lactose and the polyetrafluoroethylene are passed through a 30 mesh screen, and the powders are blended in a suitable mixer for thirty minutes. The granulate is formed by adding the alcohol (3A, 50 percent); the wet mass is passed through a No. 12 mesh screen and then dried at 40°. The dried granules are broken through a 20 mesh screen and compressed into tablets weighting 0.2 g. using $^{19}/_{32}$ inch standard concave punches.

Example 2

Tablets each containing 0.005 g. of methyl α-phenyl-α-(2-piperidyl)-acetate hydrochloride as the physiologically active ingredient, and 0.005 g. of polytetrafluoroethylene of an average particle size of from about 5 microns to about 10 microns as the lubricating agent, are prepared as follows (for 10,000 tablets).

Ingredients:	G.
Methyl α-phenyl-α-(2-piperidyl)-acetate hydrochloride	50.0
Corn starch	30.0
Lactose	870.0
Polytetrafluoroethylene	50.0
Alcohol 3A, 50 percent, q.s.	

The methyl α - phenyl-α-(2 - piperidyl)-acetate hydrochloride, the corn starch, the lactose and the polytetrafluoroethylene are passed through a 30 mesh screen and the powders are blended in a suitable mixer for thirty minutes. The granulate is formed by adding the alcohol (3A, 50 percent); the wet mass is passed through a No. 12 mesh screen and then dried at 40°. The dried granules are broken through a 20 mesh screen and compressed into tablets weighing 0.1 g. using $^{9}/_{32}$ inch standard concave punches.

Example 3

Tablets, each containing 0.025 g. of 6 - chloro-7-sulfamyl-2H-3,4 - dihydro-1,2,4 - benzothiadiazine-1,1-dioxide as the physiologically active ingredient, and 0.01 g. of polytetrafluoroethylene of an average particle size of from about 5 microns to about 10 microns, as the lubricating agent, are prepared as follows (for 5,000 tablets).

Ingredients:	G.
6-chloro-7 - sulfamyl-2H - 3,4-dihydro-1,2,4-benzothiadiazine - 1,1-dioxide	125.0
Corn starch	50.0
Lactose	775.0
Polytetrafluoroethylene	50.0
Alcohol 3A, 50 percent, q.s.	

The 6 - chloro - 7 - sulfamyl - 2H - 3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, the corn starch, the lactose and the polytetrafluoroethylene are passed through a 30 mesh screen and the powders are blended in a suitable mixture for thirty minutes. The granulate is formed by adding the alcohol (3A, 50 percent); the wet mass is passed through a No. 12 mesh screen and then dried at 40°. The dried granules are broken through a 20 mesh screen and compressed into tablets weighing 0.2 g. using $^{19}/_{32}$ inch standard concave punches.

In the above examples, the polytetrafluoroethylene lubricant can be replaced by an equivalent amount of any

other polyfluorocarbon powder, such as the copolymer of tetrafluoroethylene and hexafluoropropylene, polyvinylidene fluoride, polytrifluorochloroethylene, and the like, as well as by an equivalent amount of a mixture of polytetrafluoroethylene and the copolymer of tetrafluoroethylene and hexafluoropropylene.

Example 4

Compression coated tablets, each containing 0.01 g. of 1-hydrazino-phthalazine hydrochloride as the physiologically active ingredient, and, as a lubricating agent, 0.005 g. of polytetrafluoroethylene in the core, the average particle size of the polytetrafluoroethylene being from about 5 microns to about 10 microns, are prepared as follows (for 10,000 tablets).

Ingredients for the core formulation:

	G.
1-hydrazino - phthalazine hydrochloride	100.0
Lactose, USP	800.0
Corn starch	50.0
Polytetrafluoroethylene	50.0
Ethanol 3A, 50 percent, q.s.	

The 1-hydrazino-phthalazine hydrochloride, the lactose, the corn starch and the polytetrafluoroethylene are sifted through a 20 mesh sieve and mixed for twenty minutes. The resulting mixture is granulated with the 50 percent ethanol 3A; the granulate is passed through a 12 mesh sieve, dried at about 38° C. and broken through a 20 mesh screen.

Ingredients for the coating formulation:

	G.
Lactose, USP	1760.0
Corn starch	100.0
Methylcellulose, 100 cps.	40.0
Ethanol 3A, 70 percent, q.s.	

The lactose, the corn starch and the methylcellulose are passed through a 20 mesh sieve and are mixed for twenty minutes. The mixture is granulated with the 70 percent ethanol 3A; the wet granulation mass is passed through a 12 mesh screen, dried at about 38° C., and broken through a 20 mesh screen.

The core formulation is compressed into a core tablet, weighing 0.1 g., and using $\frac{8}{32}$ inch standard concave punches. Around this core is compressed the coating formulation weighing 0.2 g., and using $\frac{11}{32}$ inch standard concave punches. The total weight of the tablet is 0.3 g.

What is claimed is:

1. The process of manufacturing tablets containing a pharmacologically active ingredient which comprises admixing in the tablet granulation as the lubricating agent about 1 to 15% of a member selected from the group consisting of a polymer of the polyfluorocarbon type and a mixture of polymers of the polyfluorocarbon type, said polyfluorocarbon type polymer having a particle size of about 1 to about 150 microns, compressing the granulation in a die to form compressed tablets and ejecting the compressed tablets from the die.

2. Process according to claim **1**, wherein polytetrafluoroethylene is admixed in the tablet granulation, as the lubricating agent.

3. A tablet containing a pharmacologically effective active ingredient having as a lubricating agent about 1 to about 15% of a member selected from the group consisting of a polymer of the polyfluorocarbon type and a mixture of polymers of the polyfluorocarbon type, said polyfluorocarbon type polymer having a particle size of about 1 to about 150 microns.

4. A tablet according to claim **3**, having polytetrafluoroethylene as the lubricating agent.

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