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TABLETS CONTAINING L-DOPA

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ABSTRACT OF THE DISCLOSURE

Improved tablets containing L-DOPA and a binder comprising amylopectin admixed with, polyvinylpyrrolidone, a lubricant and a tablet disintegrant are described.

BACKGROUND OF THE INVENTION

L-3,4-dihydroxyphenylalamine, hereinafter referred to as L-DOPA, is an important tool in the therapeutic treatment of Parkinsonism. In the therapeutic treatment of Parkinsonism utilizing L-DOPA, the patients, in most instances, must consume inordinately large quantities of the drug, i.e. on the average of from 3 to 8 grams daily. The quantities of L-DOPA which must be consumed remain large even when other compounds, such as decarboxylase inhibitors are utilized to potentiate its action. It is therefore readily apparent that it is advantageous to incorporate large quantities of L-DOPA into small convenient dosage forms so that the expense and inconvenience of administering many tablets or capsules each day is avoided. Due to the low bulk density and other physical characteristics of L-DOPA, No. 0 and larger gelatin capsules are required for dosages of 500 mg. and above per capsule. Additionally, pregranulating L-DOPA to increase its bulk density prior to encapsulation, although allowing larger amounts to be encapsulated, is an inefficient, expensive process and not satisfactory for commercial purposes.

Attempts to formulate L-DOPA into pharmaceutically elegant tablets of acceptable size prior to this invention encountered problems which resulted in unsatisfactory tablets. Direct compression techniques as recognized in the art of pharmaceutical compounding, usually produce a smaller tablet. L-DOPA tablets produced using direct compression excipients commonly recognized in the art, however, were unsatisfactory as an unusually high percentage of excipient material was required and the tablets had a tendency to "pick," i.e. break off pieces which cling to the tabletting molds, and "cap," i.e. split a small longitudinal section of the tablet in normal handling. Among the direct compression excipients which were unsatisfactory were direct compression grade lactose, microcrystalline cellulose, monocalcium phosphate and Sta-Rx, a commercially available fine grade of starch.

Other methods of tabletting L-DOPA such as the conventional tabletting technique known as slugging and the technique of forming a melt of L-DOPA and a substance such as, for example, stearic acid were unsatisfactory mainly due to inferior compressibility of the tablets and poor flow characteristics of the bulk mixtures. Another method which was unsatisfactory for forming L-DOPA tablets due to inferior compressibility of the tablets and capping was the technique known in the art as placebo granulation. In this method a granulation is formed from such conventional tabletting materials as mannitol, dicalcium phosphate and the like. This granulation is then mixed in at least equal proportions with the drug and compressed into tablets. In addition to the other disadvantages mentioned, the tablets found by these methods also were disadvantageous since they were too large.

Still another method of tabletting L-DOPA, the conventional tabletting practice of wet granulation, utilizing

gelatin, acacia, pre-gelatinized starches and the like was unsatisfactory due to poor compressibility and capping.

It is therefore quite unexpected and surprising that tablets of suitable size containing large amounts of L-DOPA could be formulated in accordance with the present invention by the wet granulation method utilizing as a binder a combination of amylopectin and polyvinylpyrrolidone.

BRIEF SUMMARY OF THE INVENTION

In accordance with the present invention, pharmaceutically excellent tablets containing large quantities of L-DOPA, e.g., 500 mg. or more are prepared by the wet granulation method utilizing a formulation comprising L-DOPA and no more than 10% of the total tablet weight of a binder composed of amylopectin and polyvinylpyrrolidone.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, tablets containing L-DOPA are prepared by the conventioal wet granulation method utilizing a binder material comprising amylopectin and polyvinylpyrrolidone.

More particularly the L-DOPA tablets of the present invention contain from 1% to 10% of the total tablet weight of binders and not more than 35% by weight inert ingredients. Preferably, the tablets contain from about 1% to about 2% by weight binders based on the total tablet weight and between about 20% and 25% by weight of a tablet disintegrant, between from about 1% to about 2% lubricants and the remainder other inert ingredients, such as dyes, and the like.

It is contemplated that the L-DOPA tablets of the present invention may contain up to 750 mg. It is preferred, however, to produce tablets according to the invention which contain either 250 mg. of 500 mg. of L-DOPA. In any event, L-DOPA constitutes from about 60 to about 80% and preferably from about 70% to about 73% by weight of the tablets of the present invention.

The binder component of the novel L-DOPA tablets of the present invention is composed of amylopectin, polyvinylpyrrolidone or mixtures thereof. Although either of these two substances will form an acceptable tablet without the other, it is preferred to have both components present. In the preferred composition the ratio of the two components may vary from 1:9 to 9:1. It is, however, especially preferred to use equal quantities of each. The amylopectin utilized in the practice of the present invention is a soluble fraction derived from commercial starches. It has a molecular weight of from one million to about ten million with a preferred mean molecular weight of one million. The preferred amylopectin is a white powder, water dispersible and of sufficiently low viscosity that a 20% weight to volume dispersion in water is pourable at room temperature. The polyvinylpyrrolidone utilized in the practice of the present invention meets the specifications of the National Formulary. A suitable commercial product is Plasdone K by the GAF Corporation.

In addition to the binder component, the tablets of the present invention contain from 0.5 to 3.0% by weight preferably from 1% to 2% by weight of a tabletting lubricant conventional in the art. The lubricant is comprised of talc and a substance such as stearic acid, calcium stearate, magnesium stearate or a commercial product consisting of di- and tri-glycerides of certain fatty acids such as stearic and palmitic acid, e.g. Sterotex, by Capital City Products, Inc. Of these, magnesium stearate is preferred. While the two lubricant components may generally be used in a ratio of from 1:9 to 9:1 it is preferred to utilize equal quantities of each. The function of the talc lubricant component is to promote the

flow of the granulation while at the same time preventing "picking" when the tablets are removed from the molds. The second lubricant component functions to improve the overall flow properties and mold release of the granulation.

In addition to the binder and lubricants set forth above, the L–DOPA tablets of the present invention contain a tablet disintegrant. This class of substance includes, for example, cellulosic products such as methyl cellulose, hydroxy ethyl cellulose and the like, certain commercially available chemically modified starch fractions such as Sta-Rx 1500 by A. E. Staley and Company, and the like. It is preferred to utilize a disintegrant which possesses some tabletting properties. A preferred example of such a substance is microcrystalline cellulose such as that commercially available under the trademark Avicel by the American Viscose Corporation. The tablets of the present invention contain from about 1% to about 40% by weight of the disintegrating agent, preferably from about 20% to about 25% by weight.

The process of tablet making by wet granulation is well known in the pharmaceutical arts. It involves basically the intimate blending of the active ingredient and some or all of the inert ingredients with a suitable solvent, such as water, alcohol, methylene chloride, and the like. The granulation thus formed is then dried, such as, by placing it in shallow lined pans in an oven. The resulting dry mixture, which may be intimately mixed with other tabletting ingredients, is then compressed into tablets.

It is further within the purview of the present invention to include in the tablets other therapeutically active ingredients such as compounds which potentiate the action of L–DOPA. It is further within the purview of the present invention to combine into the tablets negligible amounts of standard ingredients, such as FDA certified colors.

In accordance with the present invention it has been found that tablets containing L–DOPA can be prepared, utilizing the ingredients set forth herein, that are stable, pharmaceutically elegant, and approximately twenty percent smaller than tablets prepared by other tabletting methods known in the art. The small tablet is important in the treatment of Parkinsonism as the disease strikes many elderly individuals who ordinarily have some difficulty in swallowing a large tablet. In addition, the tablets prepared according to the present invention are free from problems such as capping and poor compressibility inherent in other methods of preparation and methods utilizing other binder materials. Finally, and most surprising, the tablets of the present invention have been found to possess a dissolution rate in the body not only far superior to tablets made by other methods and containing other binders as described herein, but superior to standard gelatin capsules. This property was demonstrated in simulated gastric fluid utilizing tablets prepared in accordance with the present invention containing 500 mg. L–DOPA. Such tablets were found to be 47% dissolved in 2 minutes after exposure to the simulated gastric fluid and 90% dissolved after four minutes. In contrast, a group of tablets prepared by direct compression and film coated had 21% dissolved in 2 minutes and 90% dissolved only after 60 minutes had elapsed. Gelatin capsules containing the same amout of L–DOPA and talc were 1% dissolved after 2 minutes and 90% after 8 minutes. Similar capsules filled with a combination of talc and corn starch and L–DOPA in the unmilled state had 27% dissolution in 2 minutes and 90% in 10 minutes. Milling the L–DOPA before filling the capsules produced rates of 55% in 2 minutes but took 9 minutes for 90% dissolution.

The relative dissolution of the tablet or capsule is critical as it is theorized that high initial blood levels of L–DOPA are required for the drug to be effective. This theory is based on the fact that the drug is metabolized by enzymes in the blood and the drug must be intact to pass the blood brain barrier where its therapeutic action is exerted. Therefore, the L–DOPA tablets of the present invention, due to their rapid dissolution are superior to L–DOPA tablets and capsules made by other methods and with other inert ingredients.

The following examples are illustrative of the invention.

EXAMPLE 1

One thousand tablets containing 250 mg. L–DOPA were produced as follows. Using a 1% excess in accordance with standard pharmaceutical practices 252.5 grams of L–DOPA were passed through a suitable comminuting mill and admixed with a certified coloring agent. The resulting powder was granulated with an aqueous suspension prepared by suspending 2.5 grams amylopectin and 2.5 grams polyvinylpyrrolidone in 12.5 ml. distilled water. The resulting wet granulation was dried on lined trays at 120° F. The dry powder was milled on a suitable milling machine utilizing a No. 12 screen and medium speed. The granulation was then blended with 84.7 grams microcrystalline cellulose and some additional coloring material. A preblended lubricant comprising 2.5 grams talc and 2.5 grams magnesium stearate was intimately admixed with the granulation and tablets having a diameter of 9.6 mm., a thickness of approximately 3.8 mm., and a weight of approximately 348 mg. were produced therefrom on suitable conventional tabletting machinery.

EXAMPLE 2

One thousand tablets containing 500 mg. L–DOPA were produced as follows. Using a 1% excess in accordance with standard pharmaceutical practices 505.0 grams of L–DOPA were passed through a suitable comminuting mill and admixed with a certified coloring agent. The resulting powder was granulated with an aqueous suspension prepared by suspending 5.0 grams amylopectin and 5.0 grams polyvinylpyrrolidone in 25.0 ml. distilled water. The resulting wet granulation was dried on lined trays at 120° F. The dry powder was milled on a suitable milling machine utilizing a No. 12 screen and medium speed. The granulation was then blended with 169.5 grams microcrystalline cellulose and some additional coloring material. A preblended lubricant comprising 5.0 grams talc and 5.0 grams magnesium stearate was intimately admixed with the granulation and tablets having a diameter of 18 mm., a thickness of approximately 6 mm., and a weight of approximately 695 mg. were produced therefrom on suitable conventional tabletting machinery.

We claim:

1. A method of producing a stable tablet containing L–DOPA which comprises wet granulating drying and compressing into tablets a formulation comprising:

(a) from about 60.0% to about 80.0% by weight L–DOPA;

(b) from about 1.0% to about 10.0% by weight of a binder comprising amylopectin admixed with, polyvinylpyrrolidone;

(c) from about 1.0% to about 40.0% by weight of a tablet disintegrant; and

(d) from about 0.5% to about 3.0% by weight of a tabletting lubricant.

2. The method in accordance with claim **1** wherein said ingredient (a) is present in from about 70.0% to about 73.0% by weight, said ingredient (b) is present in from about 1.0% to about 2.0% by weight, said ingredient (c) is present in from about 20.0% to about 25.0% by weight and said ingredient (d) is present in from about 1.0% to about 2.0% by weight.

3. The method in accordance with claim **1** wherein said tablet disintegrant is microcrystalline cellulose and said lubricant is a mixture of equal parts of talc and magnesium stearate.

4. The method in accordance with claim **1** wherein said binder comprises from about 10% to about 90% by

weight amylopectin and from about 90% to about 10% by weight polyvinylpyrrolidone.

5. The method in accordance with claim 1 wherein said binder comprises equal quantities of amylopectin and polyvinylpyrrolidone.

6. The method in accordance with claim 1 wherein L-DOPA is present in a quantity of about 250 mg.

7. The method in accordance with claim 1 wherein L-DOPA is present in a quantity of about 500 mg.

8. A pharmaceutical tablet compresed from a direct wet granulation comprising.

(a) from about 60% to about 80% by weight L-DOPA;

(b) from about 1.0% to about 10.0% by weight of a binder comprising amylopectin admixed with, polyvinylpyrrolidone;

(c) from about 1% to about 40% by weight of a tablet disintegrant; and

(d) from about 0.5% to about 3.0% by weight of a tabletting lubricant.

9. A tablet in accordance with claim 8 wherein said ingredient (a) is present in from about 70.0% to about 73.0% by weight, said ingredient (b) is present in from about 1.0% to about 2.0% by weight, said ingredient (c) is present in from about 20.0% to about 25.0% by weight and said ingredient (d) is present in from about 1.0% to about 2.0% by weight.

10. A tablet in accordance with claim 8 wherein L-DOPA is present in a quantity of about 250 mg.

11. A tablet in accordance with claim 10 wherein L-DOPA is present in a quantity of about 500 mg.

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SHEP K. ROSE, Primary Examiner

U.S. Cl. X.R.

264—117; 424—80, 358, 361

PO-1050
(5/69)

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,632,778 Dated January 4, 1972

Inventor(s) Sheth and Katz

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 6, line 1 of claim 11 "10"

should be 8

Column 4, line 52 of claim 1

a comma should be added after "granulating"

Column 4, line 57 of claim 1

delete comma after "with"

Column 5, line 10 of claim 8

"compresed from a direct" should be

compressed from a dried

Column 5, line 15 of claim 8

delete comma after "with"

Signed and sealed this 20th day of June 1972.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents