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(57) Abrégé/Abstract:
A tablet composition containing N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine and a disintegrator is rapidly disintegrated in the stomach speedily after administration and absorbed without being influenced by meals to inhibit the rise of the blood sugar levels of diabetics after meals.

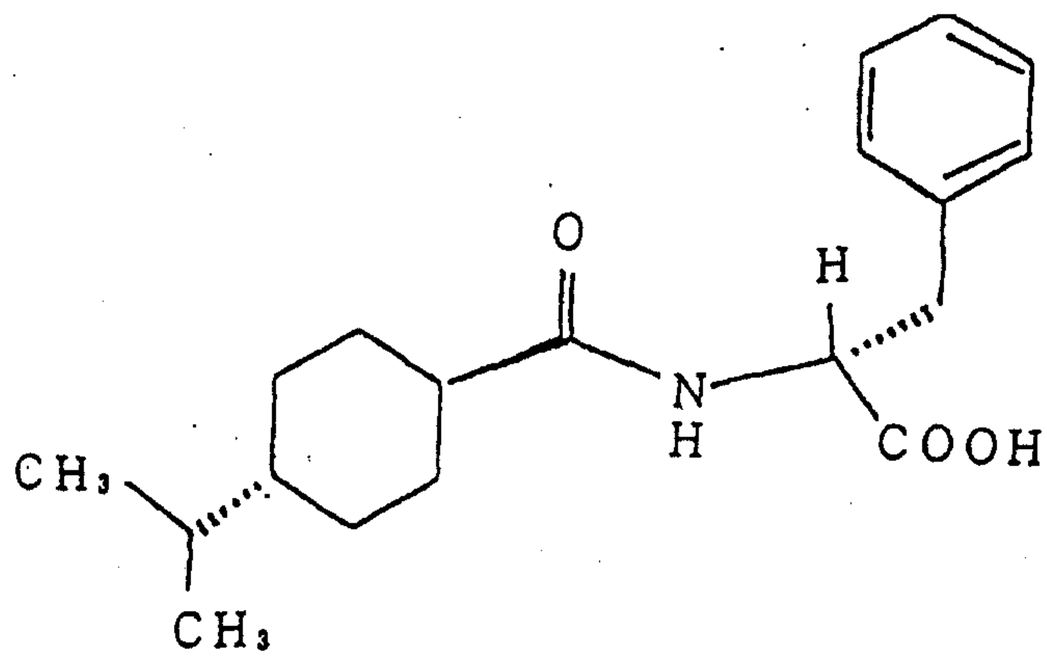
Abstract

A tablet composition containing N-(trans-4-isopropylcyclohexane-carbonyl)-D-phenylalanine and a disintegrator is rapidly disintegrated in the stomach speedily after administration and absorbed without being influenced by meals to inhibit the rise of the blood sugar levels of diabetics after meals.

TABLET COMPOSITION

The present invention relates to a tablet composition for controlling the blood sugar levels of diabetics.

It is known that N-(trans-4-isopropylcylohexanecarbonyl)-D-phenylalanine of the formula:



(I)

exhibits an excellent effect in respect of lowering the blood sugar level when it is taken orally, and is thus useful as a medicine for diabetes [Japanese Patent Publication for Opposition Purpose (hereinafter referred to as "J. R. KOKOKU") No. Hei 4-15221].

However, it was found that when the compound of formula (I) is taken orally before or after a meal for the purpose of preventing the blood sugar level after the meal from rising, the bioavailability of the compound is lowered.

It is, therefore, an object of the present invention to provide a tablet composition which can be rapidly absorbed without being influenced by the meals and without impairing the essential properties of the compound of formula (I) contained therein, which lowers the blood sugar level and has only a short

According to the present invention, there is provided a tablet composition for lowering blood sugar levels of diabetics, containing as active ingredient the compound of formula (I) and a disintegrator.

In a preferred embodiment, the tablet composition of the invention further includes a filler, preferably a filler containing lactose.

According to another preferred embodiment, the tablet composition of the invention further includes hydroxypropyl cellulose as a binder.

After administration, the tablet compositions according to the invention are rapidly disintegrated in the stomach and absorbed without being influenced by the meals, to prevent the blood sugar levels of diabetics after meals from rising.

In the accompanying drawings:

Fig. 1 is a graph showing the concentration of the compound of formula (I) in the blood plasma of patients fasting from food; and

Fig. 2 is another graph showing the concentration of the compound of formula (I) in the blood plasma of patients, which was administered before meals.

The active compound in the tablet composition of the present invention is N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine of the above formula (I). Processes for producing the compound of formula (I) are described in J. P. KOKOKU No. Hei 4-15221. This compound can be obtained by, for example, condensing 4-isopropylcyclohexanecarboxylic acid with D-phenylalanine or an ester thereof by, for example, an active ester method. Processes for obtaining stable crystals of this compound are described in Japanese Patent Unexamined Published Application (hereinafter referred to as "J. P. KOKAI") No. Hei 5-208943. For example, the compound of formula (I) can be obtained by crystallizing from a mixed solvent of ethanol, acetone or the like and water at a temperature of not lower than 10°C.

The amount of the compound of formula (I) is generally present in the tablet composition of the invention in an amount of 5 to 50 % by weight, preferably 10 to 40 % by weight, and more preferably 20 to 30 % by weight, based on the total weight of the composition.

The disintegrator is preferably a low substituted hydroxypropyl cellulose. The latter is a hydroxypropyl ether of cellulose which can be obtained by etherifying only a part of hydroxyl groups of the pyranose ring of a cellulose with propylene oxide. When the hydroxypropyl group content of dry low substituted hydroxypropyl cellulose is determined, it is generally between 5.0 and 16.0 % by weight (see Japanese Pharmacopeia, 13th Revision, D-885 to D-888 and U. S. Pharmacopeia, 23rd Revision, pages 2253 to 2254). Examples of the low substituted hydroxypropyl

cellulose include low substituted hydroxypropyl cellulose L-HPC (LH-11, LH-20, LH-21, LH-22, LH-30, LH-31 and LH-32; products of Shin-Etsu Chemical Co., Ltd.).

The disintegrator is generally present in the tablet composition of the invention in an amount of 5 to 50 % by weight, preferably 5 to 40 by weight, more preferably 10 to 40 % by weight, and most preferably 20 to 40 by weight, based on the total weight of the composition.

Sodium carboxymethyl cellulose, calcium carboxymethyl cellulose or sodium croscarmellose sodium can also be used as disintegrator. Although corn starch, sodium carboxymethyl starch, crystalline cellulose or partly pregelatinized starch having a low disintegrating property is not preferably used alone, the disintegrating property thereof is improved by combining each of them with low substituted hydroxypropy1cellulose.

The tablet composition of the present invention can further contain lactose, starch, crystalline cellulose, calcium monohydrogen phosphate, light anhydrous silicic acid, titanium oxide or magnesium aluminometasilicate as a filler, in addition to the above-described ingredients. Among these, lactose is preferred because it is compatible with the compound of formula (I). The amount of filler can constitute the balance in the tablet composition. It generally ranges from 10 to 90 % by weight, more preferably 20 to 80 % by weight and most preferably 30 to 60 % by weight, based on the total weight of the composition.

Further, it is desirable to incorporate 0.1 to 5 % by weight, preferably 0.5 to 2 by weight, of hydroxypropyl cellulose as a binder so as to facilitate the granulation in the manufacturing process. Hydroxypropyl cellulose used for this purpose is different from the above-described low substituted hydroxypropyl cellulose. The quantity of hydroxypropyl group in dry hydroxypropyl cellulose generally ranges from 53.4 to 77.5 % by weight (see the Japanese Pharmacopeia, 13th Revision, D-880 to D-885 and U. S. Pharmacopeia, 23rd Revision, page 2253). Such a hydroxypropyl cellulose is easily available as HPC-L, L (fine powder) or the like (products of Nippon Soda Co., Ltd.).

The tablet composition of the present invention can contain other additives usually incorporated into tablet compositions in addition to the above-described ingredients, as long as the effect of the present invention is not impaired. These additives include fillers such as crystalline cellulose, calcium monohydrogen

phosphate, starch, light anhydrous silicic acid, titanium oxide, magnesium aluminometasilicate and polyethylene glycol; disintegrators such as starch, crystalline cellulose, hydroxypropyl starch and partly pregelatinized starch; binders such as gelatin, acacia, ethyl cellulose and polyvinyl alcohol; lubricants such as stearic acid, magnesium stearate, calcium stearate, talc and hydrogenated oil; coating agents such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymers and polyvinyl acetate phthalate; colorants such as tar colorant and titanium oxide; corrigents such as citric acid, adipic acid, ascorbic acid and menthol; and surfactants such as glycerol monostearate, polysorbates, sodium laurylsulfate and sucrose esters of fatty acids.

The tablet composition of the present invention can be prepared by an ordinary wet granulation method, wherein the above-described ingredients are thoroughly mixed and then granulated with water which may contain a lower alcohol such as ethanol or isopropanol, the granules thus obtained are dried and, if necessary, reduced in size and tableted with a tableting machine. The tablets thus obtained can be coated, if desired.

The following non-limiting Examples further illustrate the present invention.

Example 1

The ingredients shown in Table 1 were weighed and all the ingredients excluding magnesium stearate were mixed with a highshear mixer for 10 minutes. Purified water in an amount (15 to 75 parts by weight) such that granules having a diameter of 100 to 500 μm would be obtained was added thereto, and the resultant mixture was granulated with a highshear mixer for 10 minutes. The granules thus obtained were reduced in size with a mill and then dried. Magnesium stearate was added to the dry granules obtained, and the mixture thus obtained was blended with a V-shaped blender for 2 minutes and tableted to provide tablets having a diameter of 7 mm, thickness of 3 mm and weight of 100 mg. The disintegration time of the tablets thus obtained in water was determined according to a disintegration test of the Japanese Pharmacopeia. L-HPC(LH-31) (a product of Shin-Etsu Chemical Co., Ltd.) having a hydroxypropyl group content of 10 to 12.9 % by weight and an average

particle diameter of not larger than 30 μm was used as the low substituted hydroxypropyl cellulose. The results are shown in Table 1.

Table 1

	Comparative composition					Composition of invention				
	1	2	3	4	5	6	7	8	9	10
Compound of formula (I)	25	25	25	25	25	25	25	25	25	25
Lactose	74	49	44	54	64	54	44	44	34	44
Corn starch		20	10				20		10	
Na carboxy-methyl starch					10					10
Partly Pregelatinized starch				10					10	
Crystalline cellulose		5	20	10				10	10	
Low substituted hydroxypropyl cellulose						20	10	20	10	20
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Disintegration time(min)	>30	>30	>30	>30	11	0.8	3.1	3.1	3.0	3.8

As is apparent from Table 1, the tablets prepared by using a low substituted hydroxypropyl cellulose as the disintegrator were disintegrated more rapidly than tablets prepared by using another disintegrator.

Example 2

250 g of the compound of formula (I), 530 g of lactose and 200 g of low substituted hydroxypropyl cellulose (LH-31; a product of Shin-Etsu Chemical Co., Ltd.) having a hydroxypropyl group content of 10.0 to 13.0 % by weight and an

average particle diameter of not larger than 30 μm were thoroughly mixed with a highshear mixer. 10 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 500 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture thus obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 120 mg and containing 30 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

Comparative Example 1

250 g of the compound of formula (I), 440 g of lactose, 100 g of corn starch and 200 g of crystalline cellulose were thoroughly mixed with a highshear mixer. 3.0 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 360 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture thus obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 120 mg and containing 30 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

The influence of food on the oral absorption of the tablets obtained in Example 2 and Comparative Example 1 was examined. As controls, No. 3 hard gelatin capsules each containing 30 mg of the compound of formula (I) and 70 mg of lactose were used. The tablets or capsules were orally administered to beagles (n=8), and foods were given five minutes after. Blood samples were taken 0, 15, 30, 45, 60, 90, 120, 180, 240, 360 and 480 minutes after the administration and the concentration of the compound of formula (I) in the blood plasma was determined by HPLC. The time for attaining the maximum blood concentration (Tmax), the maximum blood concentration (Cmax) and the area under the curve of the blood concentration (AUC) were determined. For comparison, the same tests were repeated except that the tablets

or capsules were administered to the fasting beagles. The results are shown in Table 2 and Figs. 1 and 2.

Table 2

		Cmax (μg/ml)	Tmax (min)	AUC (μg・min/ml)
Tablets of Ex.2	Before meal	6.6±3.3	68± 30	1218±278
	Fasting	9.7±2.6	47± 36	1635±526
Tablets of Comp. Ex.1	Before meal	3.5±0.9	131± 96	1018±200
	Fasting	7.5±3.3	64± 41	1462±542
Capsules	Before meal	3.1±1.1	226±145	738±210
	Fasting	9.5±2.3	38± 36	1445±453

(Average ± standard deviation, n = 8)

It is apparent from Table 2 and Fig. 1 that when the tablet composition of the present invention was administered to the fasting beagles, the absorption thereof was equivalent to or slightly superior to that of the tablet composition and capsules of Comparative Example 1. In contrast, when the tablet composition of the present invention was administered before meals on the assumption that it is practically used in that way, it was rapidly absorbed without being influenced by foods and it could inhibit the rise of the blood sugar level of diabetics after meals. When the tablet composition or capsules of Comparative Example 1 were used in Comparative Example 1, the absorption of the compound of formula (I) was low and impractical.

Example 3

330 g of the compound of formula (I), 450 g of lactose and 200 g of a low substituted hydroxypropyl cellulose (LH-31; a product of Shin-Etsu Chemical Co., Ltd.) were thoroughly mixed with a highshear mixer. 10 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 500 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 121 mg and containing 40 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

The influence of food on the oral absorption of the coated tablets obtained as described above was examined. The coated tablets had an absorption superior to that of the tablets or capsules of Comparative Example 1, like the coated tablets of Example 2, when they were administered during fasting or before meals. In particular, the coated tablets could inhibit the rise of the blood sugar level of diabetics after meals.

Example 4

125 g of the compound of formula (I), 655 g of lactose and 200 g of low substituted hydroxypropyl cellulose (LH-31; a product of Shin-Etsu Chemical Co., Ltd.) were thoroughly mixed with a highshear mixer. 10 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 500 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture thus obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 120 mg and containing 15 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

The influence of food on the oral absorption of the coated tablets obtained as described above was examined. The coated tablets had an absorption superior to that of the tablets or capsules of Comparative Example 1, like the coated tablets of Example 2, when they were administered during fasting or before meals. In particular, the coated tablets could inhibit the rise of the blood sugar level of diabetics after meals.

Example 5

250 g of the compound of formula (I), 430 g of lactose, 100 g of crystalline cellulose and 200 g of low substituted hydroxypropyl cellulose (LH-31; a product of Shin-Etsu Chemical Co., Ltd.) were thoroughly mixed with a highshear mixer. 10 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 570 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture thus obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 120 mg and containing 30 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

The influence of food on the oral absorption of the coated tablets obtained as described above was examined. The coated tablets had an absorption superior to that of the tablets or capsules of Comparative Example 1, like the coated tablets of Example 2, when they were administered during fasting or before meals. In particular, the coated tablets could inhibit the rise of the blood sugar level of diabetics after meals.

Example 6

250 g of the compound of formula (I), 320 g of lactose, 100 g of corn starch, 100 g of crystalline cellulose, 100 g of partly pregelatinized starch and 100 g of hydroxypropyl cellulose (LH-31; a product of Shin-Etsu Chemical Co., Ltd.) were thoroughly mixed with a highshear mixer. 10 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 450 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules

thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture thus obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 100 mg and containing 30 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

The influence of food on the oral absorption of the coated tablets obtained as described above was examined. The coated tablets had an absorption superior to that of the tablets or capsules of Comparative Example 1, like the coated tablets of Example 2, when they were administered during fasting or before meals. In particular, the coated tablets could inhibit the rise of the blood sugar level of diabetics after meals.

Example 7

250 g of the compound of formula (I), 430 g of lactose, 100 g of sodium carboxymethyl starch and 200 g of low substituted hydroxypropyl cellulose (LH-31; a product of Shin-Etsu Chemical Co., Ltd.) were thoroughly mixed with a highshear mixer. 10 g of hydroxypropyl cellulose (HPC-L; a product of Nippon Soda Co., Ltd.) dissolved in 640 g of purified water were added thereto and the mixture obtained was granulated with a highshear mixer. The granules thus obtained were reduced in size and dried. 10 g of magnesium stearate were added to the powder and the mixture thus obtained was tableted to provide tablets having a diameter of 7 mm, thickness of 3.7 mm and weight of 120 mg and containing 30 mg of the compound of formula (I). The tablets were spray-coated with a coating liquid comprising 8 g of hydroxypropylmethyl cellulose, 1.5 g of polyethylene glycol 6000, 2.4 g of talc, 0.5 g of titanium oxide and 87.6 g of purified water to obtain the coated tablets.

The influence of food on the oral absorption of the coated tablets obtained as described above was examined. The coated tablets had an absorption superior to that of the tablets or capsules of Comparative Example 1, like the coated tablets of Example 2, when they were administered during fasting or before meals. In particular, the coated tablets could inhibit the rise of the blood sugar level of diabetics after meals.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A tablet composition for lowering blood sugar levels of diabetics, comprising as active ingredient N-(traps-4-isopropylcyclohexanecarbonyl)-D-phenylalanine and a disintegrator.

2. A tablet composition according to claim 1, wherein the disintegrator is a low substituted hydroxypropyl cellulose.

3. A tablet composition according to claim 1 or 2, wherein the N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine is present in an amount of 5 to 50 % by weight, based on the total weight of the composition.

4. A tablet composition according to claim 1, wherein the low substituted hydroxypropyl cellulose contains 5.0 to 16.0 % by weight of hydroxypropyl group.

5. A tablet composition according to claim 1, 2 or 3, wherein the low substituted hydroxypropyl cellulose is present in an amount of 5 to 50 % by weight, based on the total weight of the composition.

6. A tablet composition according to claim 1, further including at least one filler.

7. A tablet composition according to claim 5, wherein the filler is lactose.

8. A tablet composition according to claim 1, further including hydroxypropyl cellulose.

9. A tablet composition according to claim 7, wherein the hydroxypropyl cellulose contains 53.4 to 77.5 % by weight of hydroxypropyl group.

10. A tablet composition according to claim 7 or 8, wherein the hydroxypropyl cellulose is present in an amount of 0.1 to 5 % by weight, based on the total weight of the composition.

11. A tablet composition for lowering blood sugar levels of diabetics, comprising 5 to 50 % by weight of N-(traps-4-isopropylcyclohexanecarbonyl)-D-phenylalanine, 5 to 40 % by weight of low substituted hydroxypropyl cellulose and 10 to 90 % by weight of a filler.

12. A tablet composition according to claim 10, wherein the low substituted hydroxypropyl cellulose contains 5.0 to 16.0 % by weight of hydroxypropyl group.

13. A tablet composition according to claim 10, wherein the filler is lactose.

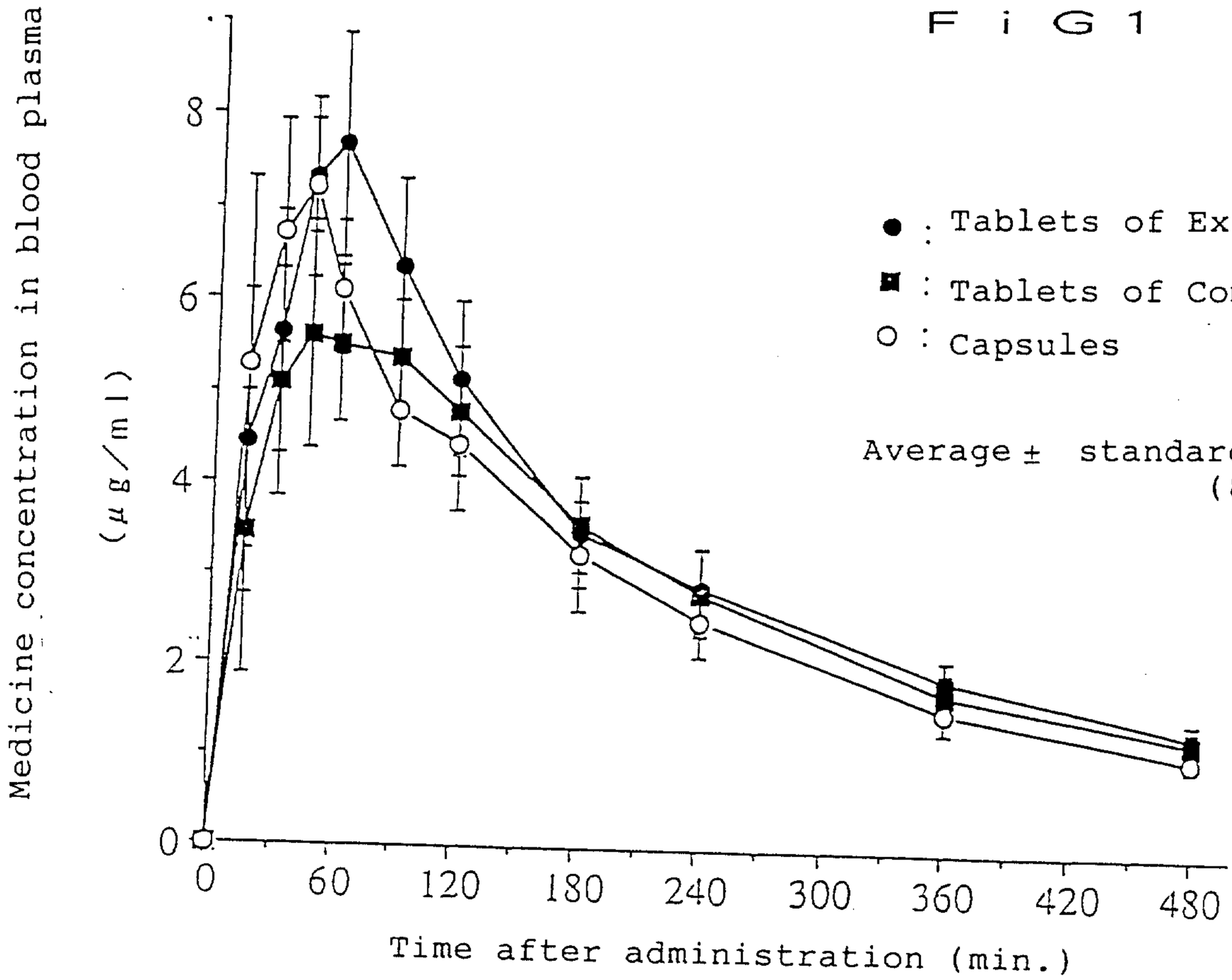
14. A tablet composition according to claim 10, further including hydroxypropyl cellulose.

15. A tablet composition according to claim 13, wherein the hydroxypropyl cellulose contains 53.4 to 77.5 % by weight of hydroxypropyl group.

16. A tablet composition according to claim 13 or 14, wherein the hydroxypropyl cellulose is present in an amount of 0.1 to 5 % by weight, based on the total weight of the composition.

17. A tablet composition for lowering blood sugar levels of diabetics, comprising 5 to 50 % by weight of N-(trans-4--isopropylcyclohexanecarbonyl)-D-phenylalanine, 5 to 40 % by weight of low substituted hydroxypropyl cellulose having a hydroxypropyl group content of 5.0 to 16.0 % by weight, 10 to 90 % by weight of a filler and 0. 1 to 5 % by weight of hydroxypropyl cellulose having a hydroxypropyl group content of 53.4 to 77.5 % by weight.

18. A tablet composition according to claim 16, wherein the filler is lactose.



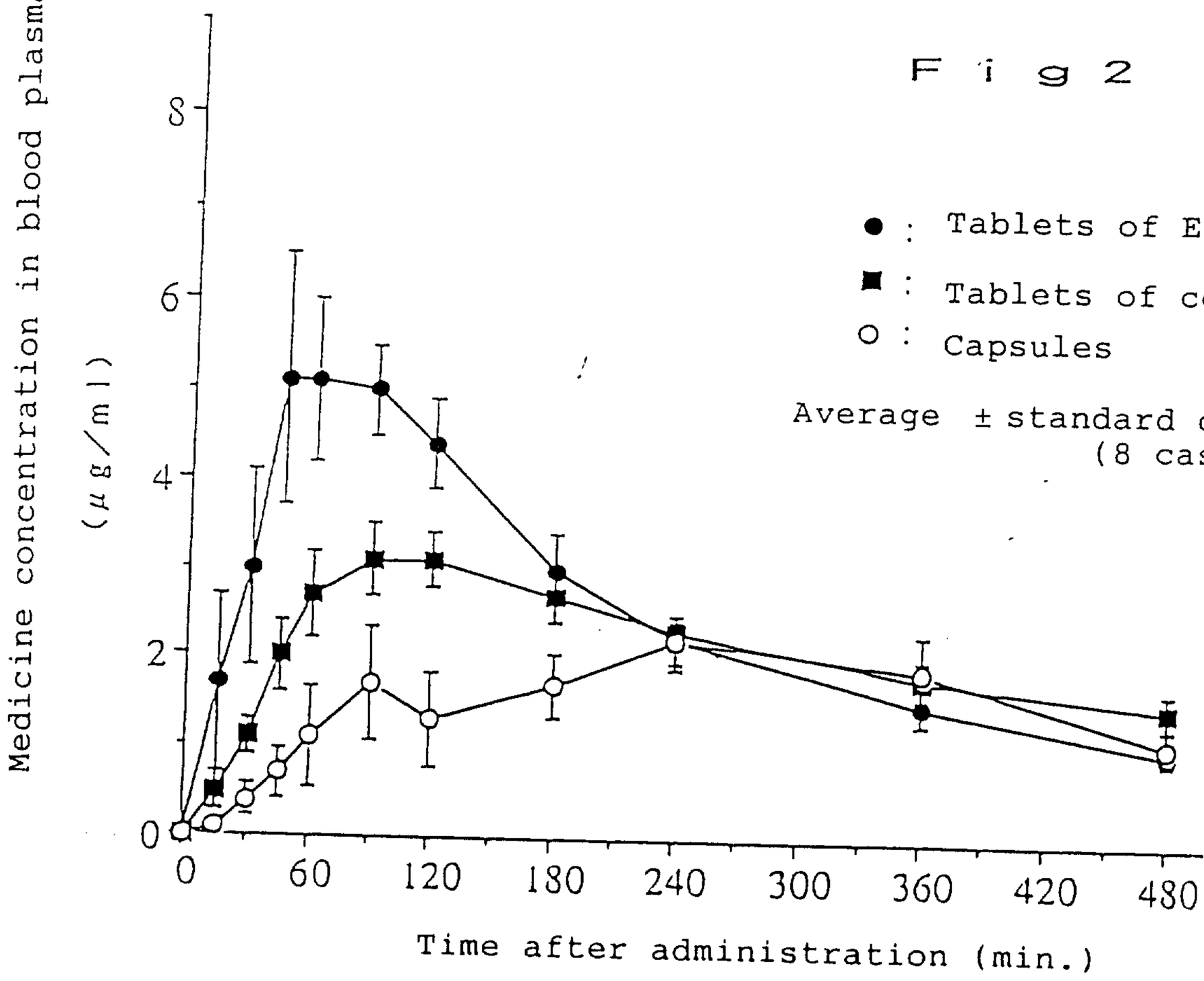
F i G 1

● : Tablets of Ex. 2

■ : Tablets of Comp. Ex.1

○ : Capsules

Average ± standard deviations
(8 cases)



F i g 2

● : Tablets of Ex. 2

■ : Tablets of comp. Ex. 1

○ : Capsules

Average ± standard deviation
(8 cases)