Description

Title of Invention: PHARMACEUTICAL COMPOSITION COMPRISING METFORMIN AND LOBEGLITAZONE

Technical Field

[1] The present invention relates to a pharmaceutical composition containing metformin and lobeglitazone as active ingredients.

Background Art

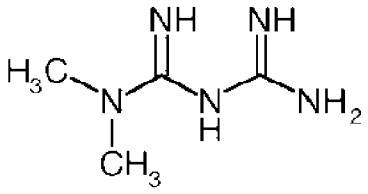
[2] Diabetes is a disease that causes metabolism problems, including hyperglycemia, due to the insufficient action of insulin, and that also has a high likelihood of generating chronic vascular complications, and is largely classified into Type 1 diabetes and Type 2 diabetes. In particular, Type 2 diabetes is a disease associated with insulin secretion disorder due to insulin resistance (i.e. a condition in which the reactivity of cells or tissue to insulin at a given insulin concentration is decreased below normal) and β-cell dysfunction of the pancreas, 85 % or more of diabetes patients correspond to adult-onset Type 2 diabetes, and the number of patients with Type 2 diabetes is continuously increasing owing to the decreasing physical activity habits of modern people and with the increase in obesity.

[3] Type 2 diabetes shows hyperinsulinemia due to glucose intolerance and insulin resistance in the early stages and then progresses to hyperglycemia and hypoinsulinemia. Thus, the selection of a drug that exhibits effectiveness adapted for a given stage of disease is regarded as very important in the treatment of diabetes.

[4] Useful for the treatment of diabetes, oral hypoglycemic agents may be classified into, depending on the action mechanism, 1) insulin secretagogues (sulfonylurea, non-sulfonylurea), 2) biguanide-based drugs, 3) alpha-glycosidase inhibitors, 4) glitazone-based drugs, 5) DPP-IV inhibitors, and 6) SGLT-2 inhibitors.

[5] Metformin, which is one of the biguanide-based drugs, is an oral drug useful as a primary medicament in the treatment of Type 2 diabetes, and is represented by Chemical Formula 1 below.

[6] [Chemical Formula 1]

[7] 

[8] Metformin functions to increase insulin sensitivity in the peripheral tissue of the host, and is associated with the inhibition of glucose uptake from the intestine, the suppression of hepatic gluconeogenesis, and the inhibition of fatty acid oxidation to

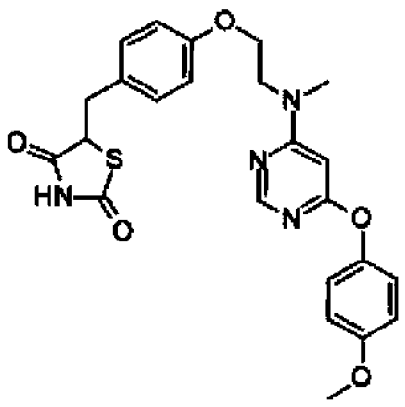
thereby result in glycemic control. The glycemic control mechanism of metformin is independent of insulin secretion, induces a reduction in the body weight of diabetes patients, and exhibits effects of lowering blood triglyceride and low-density lipoproteins and increasing high-density lipoproteins. Hence, metformin may be utilized as a primary medicament for the treatment of Type 2 diabetes patients that show insulin resistance. However, the side effects of metformin, which occur in 20 to 30% of patients to which metformin is administered, are known to include loss of appetite, abdominal distension, nausea, diarrhea and the like. Most such side effects are transient and thus disappear 2 to 3 weeks after the use thereof, but the use thereof has to be stopped in cases where diarrhea or severe abdominal distension fails to disappear. In rare cases, it can cause skin rashes and hives. These side effects may be ameliorated by the use of a sustained-release formulation that is able to decrease the minimum and/or sustainable dose or to lower the frequency of prescription.

[9] On the other hand, a glitazone-based drug is a PPARγ agonist (Peroxisome Proliferator Activated Receptor gamma agonist), and stimulates PPARγ, which is expressed in adipocytes to promote adipogenesis and glucose uptake, thereby increasing insulin sensitivity *in* vivo. The glitazone-based drug has no mechanism for promoting insulin secretion and is thus favorable for protecting β-cells of the pancreas, and may improve insulin resistance and is thus particularly effective in the treatment of diabetes patients showing insulin resistance. Furthermore, this drug is known to maintain the glucose level for a long period of time, slow the progress of Type 2 diabetes, and exhibit higher therapeutic effects on early diabetes. Such a glitazone-based drug is currently exemplified by drugs having a thiazolidinedione (TZD) structure. However, when the glitazone-based drug is used alone, its antidiabetic activity is not high and limited therapeutic effects result. It is known to cause side effects such as edema or weight gain depending on the person.

[10] Among glitazone-based drugs, lobeglitazone is a drug developed by the present applicant, and is represented by Chemical Formula 2 below.

[11] [Chemical Formula 2]

[12]



[13] Lobeglitazone has stable molecular dynamic energy, is structurally adapted for the active site pocket of PPARγ to thus exhibit high drug activity, and is responsible for overcoming the difficulty in lowering the lipid concentration in blood, which is noted as the defect of conventional glitazone-based drugs.

[14] Diabetes is a complex group of diseases with a variety of causes and individual diabetes therapeutic agents have distinct advantages and disadvantages, and thus combination therapy using two or more antidiabetic agents having different action mechanisms in order to exhibit simultaneous actions on multiple targets is widely clinically prescribed. Such combination therapy is remarkably improved in glycemic control compared to single therapy, and may decrease the likelihood of causing various side effects due to the administration of a high-dose single active ingredient. However, the co-administration of two or more drugs suffers from poor medication compliance of patients. Accordingly, there is a continuous need to develop a combination formulation in which two or more active ingredients may be administered as a single medicament.

[15] A glitazone-based drug is known to be effective upon co-administration with a drug having a different action mechanism. In particular, in the case where glycemic control is insufficient, the glitazone-based drug may be co-administered with metformin. With regard to the combination formulation of the glitazone-based drug and metformin, European Patent Publication No. 0749751 discloses a combination formulation of pioglitazone and metformin, and International Patent Publication No. WO 98/57634 discloses a combination formulation of rosiglitazone and metformin.

[16] However, when a novel glitazone-based drug, namely lobeglitazone, is co-administered with metformin, the therapeutic effects and side effects have not yet been studied in detail, and furthermore, research into combination formulations thereof that show optimal dissolution patterns and may decrease the frequency of administration has not yet been carried out. Thus, the development of a pharmaceutical composition containing metformin and lobeglitazone and a pharmaceutical formulation thereof is urgent.

Disclosure of Invention

Technical Problem

[17] Accordingly, the present invention has been made keeping in mind the above problems encountered in the related art, and the present invention is intended to provide a pharmaceutical composition containing metformin and lobeglitazone, which may exhibit superior therapeutic activity for Type 2 diabetes and related diseases and is able to reduce the side effects of a single active ingredient.

[18] In addition, the present invention is intended to provide a pharmaceutical for-

mulation, which enables the sustained release of metformin and the immediate release of lobeglitazone, and may exhibit equivalent pharmacokinetic (PK) data and superior physical stability and chemical stability compared to co-administration of single formulations.

Solution to Problem

[19] The present invention provides a pharmaceutical composition containing metformin and lobeglitazone and a pharmaceutical formulation including the same. Below is a detailed description thereof.

[20] **Pharmaceutical composition comprising** metformin and lobeglitazone

[21] The present invention provides a pharmaceutical composition, comprising: (A1) metformin or a pharmaceutically acceptable salt thereof and (A2) lobeglitazone or a pharmaceutically acceptable salt thereof, as active ingredients.

[22] In the pharmaceutical composition according to the present invention, both (A1) metformin or a pharmaceutically acceptable salt thereof and (A2) lobeglitazone or a pharmaceutically acceptable salt thereof, used as active ingredients, are drugs that do not promote insulin secretion and that improve insulin resistance. Thus, the pharmaceutical composition of the present invention is able to exhibit the glycemic control effect while maintaining the functions of β-cells of the pancreas.

[23] The pharmaceutically acceptable salt of metformin is preferably a hydrochloride, and the pharmaceutically acceptable salt of lobeglitazone is preferably a sulfate.

[24] In the pharmaceutical composition according to the present invention, (A1) metformin or the pharmaceutically acceptable salt thereof may be contained in an amount of 250 to 2000 mg, and preferably 500 to 1000 mg. Also, (A2) lobeglitazone or the pharmaceutically acceptable salt thereof may be contained in an amount of 0.1 to 2.0 mg, and preferably 0.2 to 1.0 mg.

[25] The pharmaceutical composition according to the present invention enables the co-administration of, as agents for improving insulin resistance having different action mechanisms, (A1) metformin or a pharmaceutically acceptable salt thereof and (A2) lobeglitazone or a pharmaceutically acceptable salt thereof, and may exhibit a synergistic effect on glycemic control compared to administration of a single active ingredient. Furthermore, the pharmaceutical composition of the present invention manifests a synergistic effect by the co-administration, and thus individual active ingredients may be contained in lower amounts, and the potential to generate side effects upon high-dosage administration may be excluded.

[26] Thus, the pharmaceutical composition according to the present invention may be effective in the prevention or treatment of diabetes, especially Type 2 diabetes.

[27] **Pharmaceutical formulation comprising** metformin and lobeglitazone

[28] In addition, the present invention provides a pharmaceutical formulation containing (A1) metformin or a pharmaceutically acceptable salt thereof and (A2) lobeglitazone or a pharmaceutically acceptable salt thereof.

[29] In the case where metformin or the pharmaceutically acceptable salt thereof, which is well dissolved in water, is provided in the dosage form of a typical tablet, excessive glucose lowering may be caused due to the sudden release, and gastrointestinal disorders may occur. Furthermore, since metformin or the pharmaceutically acceptable salt thereof is administered in a large amount, side effects of metformin and resistance thereto may become increased on account of drastic changes in blood concentration due to rapid release. Also, since the serum half-life of metformin is as short as 2 to 6 hr, the sustained release of metformin or the pharmaceutically acceptable salt thereof is required.

[30] On the other hand, in the case where lobeglitazone or the pharmaceutically acceptable salt thereof, which is difficult to dissolve, is provided in dosage form through typical methods, the dissolution rate thereof may be slowed. Hence, the immediate release of lobeglitazone or the pharmaceutically acceptable salt thereof is required.

[31] Hence, the pharmaceutical formulation according to the present invention may be configured to include (L1) a core layer containing metformin or a pharmaceutically acceptable salt thereof as an active ingredient and (L2) an outer layer containing lobeglitazone or a pharmaceutically acceptable salt thereof as an active ingredient.

[32] In the present invention, metformin or the pharmaceutically acceptable salt thereof, which is the active ingredient of the core layer, may be contained in an amount of 250 to 2000 mg, and preferably 500 to 1000 mg, and is also preferably present in an amount of 60 to 80 wt% based on the total weight of the core layer.

[33] Also, the core layer (L1) may include a water-soluble polymer, so as to enable the sustained release of metformin or the pharmaceutically acceptable salt thereof. The water-soluble polymer may be at least one selected from the group consisting of hydroxypropyl methylcellulose (e.g. hypromellose, etc.), hydroxypropylcellulose, ethyl cellulose, methyl cellulose, polyvinyl pyrrolidone, polymethacrylate, and mixtures thereof. Particularly useful is hydroxypropyl methylcellulose. The water-soluble polymer is preferably present in an amount of 15 to 25 wt% based on the total weight of the core layer.

[34] In the present invention, lobeglitazone or the pharmaceutically acceptable salt thereof, which is the active ingredient of the outer layer, may be contained in an amount of 0.1 to 2.0 mg, and preferably 0.2 to 1.0 mg, and is also preferably present in an amount of 0.1 to 2.0 wt% based on the total weight of the outer layer.

[35] In the present invention, lobeglitazone or the pharmaceutically acceptable salt thereof is used in a very small amount, and the outer layer (L2) containing it as the active in-

gredient may be a coating layer.

[36] Also, the outer layer (L2) may include a binder having a viscosity of 6 mPa.s or less so as to increase the coating yield of the outer layer. The binder may be at least one selected from the group consisting of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, lactose, and mixtures thereof. Preferably useful is hydroxypropyl methylcellulose or polyvinyl pyrrolidone, but the present invention is not limited thereto.

[37] According to a preferred embodiment of the present invention, the outer layer may include a plasticizer.

[38] The plasticizer is preferably triethyl citrate. The amount of the plasticizer is about 2.5 to 15 wt%, and preferably about 5 to 10 wt%, based on the total weight of the outer layer.

[39] According to an embodiment of the present invention, the pharmaceutical formulation may further include (L3) an inert intermediate layer between the core layer and the outer layer.

[40] The intermediate layer may include a binder and/or a plasticizer, and the binder and the plasticizer used for the outer layer may be used unchanged, but the present invention is not limited thereto.

[41] The pharmaceutical formulation according to the present invention enables the sustained release of metformin or the pharmaceutically acceptable salt thereof and the immediate release of lobeglitazone or the pharmaceutically acceptable salt thereof, may maintain a constant blood concentration for 24 hr via administration once a day, and may manifest an excellent synergistic effect in the treatment of diabetes. Also, the pharmaceutical formulation of the present invention may show equivalent PK data compared to co-administration of a single formulation containing metformin or a pharmaceutically acceptable salt thereof and a single formulation containing lobeglitazone or a pharmaceutically acceptable salt thereof.

[42] The pharmaceutical formulation according to the present invention may further include a pharmaceutically acceptable additive. The additive may be contained in an amount of 5 to 90 wt% based on the total weight of the pharmaceutical formulation. Examples of the additive may include a binder, a disintegrator, a lubricant, etc., and any additive may be used so long as it is typically useful in each dosage form and is pharmaceutically acceptable.

[43] The binder may be selected from the group consisting of polyvinyl pyrrolidone (povidone), a copolymer of vinyl pyrrolidone and other vinyl derivatives (copovidone), microcrystalline cellulose, hydroxypropyl methylcellulose, methyl cellulose, hydroxypropylcellulose, and pregelatinized starch. Preferably useful is hydroxypropyl methylcellulose or povidone.

[44] The disintegrator may be selected from the group consisting of croscarmellose

sodium (crosslinked carboxymethylcellulose sodium), sodium starch glycolate, crospovidone (crosslinked polyvinyl pyrrolidone), corn starch, pregelatinized starch, low substituted hydroxypropylcellulose, and microcrystalline cellulose. Preferably useful is sodium glycolate or crospovidone.

[45] The lubricant may be colloidal silicon dioxide, sodium stearyl fumarate or magnesium stearate. Preferably useful is magnesium stearate.

[46] The pharmaceutical formulation according to the present invention may be manufactured by techniques widely known to those skilled in the art. Specifically, in order to provide a core layer (L1) containing metformin or a pharmaceutically acceptable salt thereof as an active ingredient, a sustained-release-type metformin composition is produced using a wet granulation process and tableted using an automatic tableting machine, thereby forming a tablet layer. Lobeglitazone or a pharmaceutically acceptable salt thereof is dissolved in an appropriate solvent, stirred together with a binder and a plasticizer, sprayed onto the tablet, and dried. This coating may be performed using a typical process, and aqueous coating using a pan coating process for tablet coating is preferably carried out. Briefly, the coating process is preferably performed while the aqueous suspension of the binder is sprayed. In this case, the coating process is conducted using the aqueous suspension without the use of an organic solvent, and thus problems such as environmental pollution due to the use of organic solvents may not occur.

Advantageous Effects of Invention

[47] According to the present invention, a pharmaceutical composition can exhibit synergistic effects on the therapeutic activity of diabetes and can reduce the side effects of a single active ingredient.

[48] Also according to the present invention, a pharmaceutical formulation enables the sustained release of metformin and the immediate release of lobeglitazone, and can manifest equivalent PK data compared to co-administration of single formulations, and high physical stability and chemical stability thereof can result.

Brief Description of Drawings

[49] FIG. 1 is a graph showing the results of dissolution testing of Examples 1, 5, 6, and 9 using a paddle process (50 rpm and 37°C) in a pH 1.2 dissolution medium;

[50] FIG. 2 is a graph showing the blood concentration of metformin upon administration of a combination composition according to the present invention and upon co-administration of single formulations of Comparative Examples 7 and 8; and

[51] FIG. 3 is a graph showing the blood concentration of lobeglitazone upon administration of the combination composition according to the present invention and upon co-administration of the single formulations of Comparative Examples 7 and 8.

Mode for the Invention

[52] A better understanding of the present invention may be obtained through the following examples and test examples, which are merely set forth to illustrate, but are not to be construed as limiting the scope of the present invention. The examples and test examples of the present invention are provided to more fully convey the scope of the present invention to those skilled in the art.

[53] **Example 1: Preparation of pharmaceutical formulation according to the present invention**

[54] Step 1: Preparation of a core layer containing metformin or pharmaceutically acceptable salt thereof

[55] A granular mixture of metformin or a pharmaceutically acceptable salt thereof was prepared through the following method using components in the amounts shown in Table 1 below.

[56] [Table 1]

[57]

Classification		Amounts (unit: mg)
Core layer	Metformin hydrochloride	1000.00
	Hypromellose 2208	290.00
	Croscarmellose sodium	86.00
	Colloidal silicon dioxide	14.00
	Magnesium stearate	14.00
Total		1404.00

[58] 1) Granulation

[59] Metformin hydrochloride, hypromellose 2208, and croscarmellose sodium were mixed, and kneaded with purified water, thus forming granules, which were then dried and sieved.

[60] 2) Final mixing

[61] The sieved granules of 1) above were placed in a mixer, and mixed with colloidal silicon dioxide and magnesium stearate, which were sieved, thus obtaining a final mixture.

[62] 3) Tableting

[63] The final mixture of 2) above was tableted using an automatic tableting machine (XP1, Korsch, Germany), thus obtaining a tablet (a core layer) having a total weight of 1404 mg.

[64] Step 2: Coating with an intermediate layer

[65] An intermediate layer was formed on the surface of the tablet (core layer) obtained in Step 1 through the following method using components in the amounts shown in Table 2 below.

[66] [Table 2]

[67]

Classification		Amounts (unit: mg)
Intermediate layer	Hypromellose 2910	23.00
	Triethyl citrate	5.00
Total		28.00

[68] 1) Preparation of a spray solution

[69] Purified water, hypromellose 2910, and triethyl citrate were placed in a stirrer and completely dissolved, thus obtaining a spray solution.

[70] 2) Coating with the intermediate layer

[71] The tablet (core layer) obtained in Step 1 was placed in a coating machine (HC-LABO, FREUND, Germany), onto which the spray solution of 1) above was then sprayed and dried, thus obtaining a coating having a total weight of 1432 mg.

[72] Step 3: Coating with an outer layer containing lobeglitazone or pharmaceutically acceptable salt thereof

[73] An outer layer containing lobeglitazone or a pharmaceutically acceptable salt thereof was formed through the following method using components in the amounts shown in Table 3 below.

[74] [Table 3]

[75]

Classification		Amounts (unit: mg)
Outer layer	Lobeglitazone sulfate	0.25
	Hypromellose 2910 (3 mPa.s)	89.75
	Triethyl citrate	10.00
Total		100.00

[76] 1) Preparation of a spray solution

[77] Purified water, lobeglitazone sulfate, hypromellose 2910, and triethyl citrate were placed in a stirrer and completely dissolved, thus obtaining a spray solution.

[78] 2) Coating with the outer layer

[79] The tablet obtained in Step 2 was placed in a coating machine (HC-LABO, FREUND, Germany), onto which the spray solution of 1) above was then sprayed and dried, thus obtaining a tablet having a total weight of 1532 mg.

[80] **Examples 2 to 4 and Comparative Example 1: Preparation of pharmaceutical formulation with binders having different** viscosities contained in the outer layer

[81] In order to evaluate the yield loss or appearance depending on changes in the viscosity of the binder of the outer layer, pharmaceutical formulations were produced by changing the viscosity of the binder used in Step 3 of Example 1, as shown in Table 4 below.

[82] [Table 4]

[83]

Classification (unit: mg)	Examples				Comp. Example
	1	2	3	4	1
Lobeglitazone sulfate	0.25	0.25	0.25	0.25	0.25
Hypromellose 2910 (3 mPa.s)	89.75	-	-	-	-
Hypromellose 2208 (3 mPa.s)	-	89.75	-	-	-
Hypromellose 2910 (5 mPa.s)	-	-	89.75	-	-
Hypromellose 2910 (6 mPa.s)	-	-	-	89.75	-
Hypromellose 2910 (15 mPa.s)	-	-	-	-	89.75
Triethyl citrate	10.00	10.00	10.00	10.00	10.00

[84] **Examples 5 to 7: Preparation of pharmaceutical formulation using different kinds of binder contained in the outer layer**

[85] In order to determine the kind and amount of the binder for preferred drug dissolution, pharmaceutical formulations were produced by changing the kind of binder used in Step 3 of Example 1, as shown in Table 5 below.

[86] [Table 5]

[87]

Classification (unit: mg)	Ex.1	Ex.5	Ex.6	Ex.7
Lobeglitazone sulfate	0.25	0.25	0.25	0.25
Hypromellose 2910 (3 mPa.s)	89.75	49.75	49.75	49.75
Lactose hydrate	-	40.00	-	20.00
Povidone	-	-	40.00	20.00
Starch	-	-	-	-
Hydroxypropylcellulose	-	-	-	-
Triethyl citrate	10.00	10.00	10.00	10.00

[88] **Comparative Examples 2 and 3: Preparation of pharmaceutical formulation using different kinds of** plasticizer contained in the outer layer

[89] In order to evaluate the drug stability depending on the kind of plasticizer of the outer layer, pharmaceutical formulations were produced by changing the kind of plasticizer used in Step 3 of Example 1, as shown in Table 6 below.

[90] [Table 6]

[91]

Classification (unit: mg)	Example	Comp. Examples	
	1	2	3
Lobeglitazone Sulfate	0.25	0.25	0.25
Hypromellose 2910	89.75	89.75	89.75
Triethyl citrate	10.00	-	-
Polyethyleneglycol	-	10.00	-
Propyleneglycol	-	-	10.00

[92] **Examples 8 and 9 and Comparative Examples 4 to 6: Preparation of pharmaceutical formulation using different amounts of** plasticizer contained in the outer layer

[93] In order to evaluate the effects depending on the amount of the plasticizer of the outer layer, pharmaceutical formulations were produced by changing the amount of the plasticizer used in Step 3 of Example 1, as shown in Table 7 below.

[94] [Table 7]

[95]

Classification (unit: mg)	Examples			Comp. Examples		
	1	8	9	4	5	6
Lobeglitazone sulfate	0.25	0.25	0.25	0.25	0.25	0.25
Hypromellose 2910	89.75	94.75	92.25	97.25	87.25	84.75
Triethyl citrate	10.00	5.00	7.50	2.50	12.50	15.00

[96] **Comparative Examples 7 and 8: Single composition containing** metformin or lobeglitazone as an active ingredient

[97] As a composition containing metformin hydrochloride, 1000 mg Glucophage XR tablets (extended release), made by and purchased from Merck, were used (Comparative Example 7). Also, as a composition containing lobeglitazone sulfate, 0.5 mg Duvie tablets, made by and purchased from the present applicant (Chong Kun Dang Pharmaceutical Corp.), were used (Comparative Example 8).

[98] **Test Example 1: Measurement of amount of combination composition according to the present invention**

[99] 1) Test method

[100] In the pharmaceutical formulation according to the present invention, the amounts of metformin and lobeglitazone of Example 1 were measured. The measurement method was as follows.

[101] A. Metformin amount testing

[102] - Detector: UV spectrophotometer (measurement wavelength: 255 nm)

[103] - Column: C18 (4.6 mm × 250 mm, 5 μm)

[104] - Mobile phase: A solution at pH 3.0 resulting from adding phosphoric acid to a mixture of 10 mM ammonium phosphate solution and acetonitrile (700:300)

[105] - Flow rate: 1.0 ml/min

[106] - Column temperature: 30 ℃

[107] - Sample temperature: 25 ℃

[108] B. Lobeglitazone amount testing

[109] - Detector: UV spectrophotometer (measurement wavelength: 250 nm)

[110] - Column: C18 (4.6 mm × 250 mm, 5 μm)

[111] - Mobile phase: 50 mM ammonium acetate (pH 5.0) buffer/acetonitrile = 50/40

[112] - Flow rate: 1.5 ml/min

[113] - Column temperature: 40 ℃

[114] - Sample temperature: 25 ℃

[115] 2) Test results

[116] The amounts of metformin and lobeglitazone of Example 1 were measured to be about 98 % and about 99 %, respectively, as shown in Table 8 below. These values fell in the amount range of 90 to 110 %, corresponding to the amount standard of the combination composition, from which tableting and coating processes can be confirmed to be appropriately performed.

[117] [Table 8]

[118]

Material	Number of tests	Example 1
Metformin	1	98.56
	2	99.36
	3	97.56
	Mean	98.49
Lobeglitazone	1	100.43
	2	98.26
	3	100.06
	Mean	99.58

[119] **Test Example 2: Evaluation of pharmacological effects of combination composition of the present invention**

[120] 1) Test method

[121] In order to evaluate the pharmacological effects of the combination composition of the present invention, clinical testing was performed using a lobeglitazone composition as a test drug, a pioglitazone composition as a control drug, a metformin composition as a combination drug, and a lobeglitazone composition placebo and a pioglitazone composition placebo. This clinical testing was carried out through active-controlled

stratified randomized double-blind double-dummy parallel group multicenter design, and the effectiveness and safety were evaluated when lobeglitazone or pioglitazone and metformin were co-administered to 253 subjects for about 2 years.

[122] 2) Test results

[123] - Results for effectiveness

[124] The primary purpose of this clinical test is to prove that when comparing changes after 24 weeks from baseline for HbA1c in each administered group, the group administered with the combination composition containing lobeglitazone and metformin shows non-inferiority in terms of an HbA1c reduction effect, compared to the group administered with the combination composition containing pioglitazone and metformin.

[125] As a result, based on a difference in changes of the two administered groups, the lower limit of the confidence interval was measured to be -0.16, which is greater than -0.4, corresponding to an allowable non-inferiority tolerance, from which non-inferiority could be confirmed. Secondary effectiveness evaluation was performed using glycemic parameters and lipid parameters. Based on the comprehensive results of tests on glycemic parameters, administration of the lobeglitazone composition was found to realize the effective glycemic control and improve the insulin functions, and such results are similar to the change pattern of the group administered with the pioglitazone composition. In the lipid parameters, total cholesterol and LDL-C were significantly increased in both the lobeglitazone composition-administered group and the pioglitazone composition-administered group. Triglyceride was significantly decreased in both of the administered groups, and HDL-C, small dense LDL-C, and FFA were statistically significantly improved.

[126] - Results for safety

[127] Total adverse reactions occurred in 51.38 % of all subjects, adverse drug reactions occurred in 5.53 % thereof, and serious adverse reactions occurred in 5.14 % thereof. Most such adverse reactions also occurred in the conventional drug of the same type, and other specific adverse reactions were not reported. The serious adverse reactions were revealed to have no relation with clinical drugs. As for the total adverse reactions, adverse drug reactions and serious adverse reactions, when comparing each of the detailed adverse reaction, adverse reaction series, and total expression rate between the two administered groups, there was no statistically significantly different item. In particular, risk factors reviewed for the risk of liver failure, fat accumulation, hemodilution and congestive heart failure, known to be caused by thiazolidinedione-based drugs, did not show any significant difference compared to the baseline and between the administered groups.

[128] **Test Example 3: Evaluation of effect depending on viscosity of binder contained**

in the outer layer

[129] The viscosity of a coating solution varies depending on the viscosity of the binder used upon coating with the outer layer, which may have an influence on the coating yield and appearance of a coating. In order to evaluate the effects depending on the viscosity of the binder, testing was performed at different viscosities of the binder.

[130] 1) Test method

[131] The formulations of Examples 1 to 4 and Comparative Example 1 were obtained under the condition that the viscosity of the binder contained in the coating solution of the outer layer was changed from 3 mPa.s to 15 mPa.s. After the coating process, the coating yield and appearance were measured. The appearance was observed using a digital microscope (KH-7700, HIROX, Japan).

[132] 2) Test results

[133] The formulations of Examples 1 to 4 were uniformly coated. The formulation of Comparative Example 1 was observed to be partially coagulated or sticky, and thus the yield of Comparative Example 1 was very low, about 88%, as shown in Table 9 below. On the other hand, Examples 1 to 4 exhibited remarkably high yields compared to Comparative Example 1. The lower the viscosity of hypromellose, the higher the yield.

[134] [Table 9]

[135]

Yield (%)	Ex.1	Ex.2	Ex.3	Ex.4	C.Ex.1
1 times	100.1	100.7	99.7	98.4	94.1
2 times	99.6	101.1	98.9	97.8	88.0
3 times	99.8	99.7	100.2	99.4	96.2
Mean	99.8	100.5	99.6	98.5	92.8

[136] **Test Example 4: Evaluation of effect depending on kind of binder contained in the outer layer**

[137] 1) Test method

[138] In order to evaluate the dissolution rate depending on the kind of binder contained in the outer layer of the pharmaceutical formulation according to the present invention, the dissolution rate of lobeglitazone of the formulations of Examples 1, 5, 6 and 7 in the dissolution medium at pH 1.2 was measured. The dissolution test method was as follows.

[139] - Dissolution medium: pH 1.2

[140] - Dissolution method: paddle process (50 rpm)

[141] - Dissolution temperature: 37 ℃

[142] The test solution in the above method was measured as follows.

[143] - Detector: UV spectrophotometer (measurement wavelength: 250 nm)

[144] - Column: C18 (4.6 mm × 250 mm, 5 μm)

[145] - Mobile phase: 50 mM ammonium acetate (pH 5.0) buffer/acetonitrile = 50/40

[146] - Flow rate: 1.5 ml/min

[147] - Column temperature: 40 ℃

[148] - Sample temperature: 25 ℃

[149] 2) Test results

[150] The dissolution rates of Examples 1, 5, 6 and 7 in the dissolution medium at pH 1.2 are shown in Table 10 below and FIG. 1. In Example 1, using only hypromellose as the binder, 5-min dissolution seldom occurred. In Examples 5 and 6, where the amount of hypromellose was decreased and lactose hydrate or povidone was used, the early dissolution rate was improved. In Example 7, containing all of hypromellose, lactose hydrate and povidone, the early dissolution rate was greatly increased.

[151] [Table 10]

[152]

Dissolution rate (%)	5 min	10 min	15 min	30 min	45 min	60 min
Ex.1	0.0	13.4	26.0	59.0	84.7	97.0
Ex.5	24.1	41.2	58.7	72.3	81.5	84.3
Ex.6	24.8	40.5	52.7	76.0	82.9	87.9
Ex.7	65.9	82.7	91.9	99.0	98.7	98.4

[153] **Test Example 5:** Pharmacokinetic testing of combination composition of present invention and single formulations of Comparative Examples 7 and 8

[154] 1) Test method

[155] For the combination composition according to the present invention and the single formulations of Comparative Examples 7 and 8, pharmacokinetic testing (PK testing) was performed upon single administration, and the bioequivalence thereof was evaluated and compared to co-administration. Specifically, healthy male volunteers were orally administered with the combination composition or were orally co-administered with single formulations of Comparative Examples 7 and 8. The same time after single administration, blood sampling was carried out, and respective blood concentrations of lobeglitazone and metformin were measured using LC-MS/MS. After the measurement, the AUC and Cmax values of lobeglitazone and metformin in the combination composition and the orally co-administered formulations of Comparative Examples 7 and 8 were converted into log values to determine a geometric mean, and a 90 % confidence interval relative to the ratio of the geometric mean was calculated. When the 90 % confidence interval is in the range of 0.8 to 1.25, two formulations are regarded as having bioequivalence.

[156] - Test drug: Combination composition of lobeglitazone and metformin 0.5/1000 mg (Example 7)

[157] - Control drug ①: Glucophage XR tablet 1000 mg (Comparative Example 7)

[158] - Control drug ②: Duvie tablet 0.5 mg (Comparative Example 8)

[159] 2) Test results

[160] The results of evaluation of bioequivalence are shown in Tables 11 and 12 below. The ratio of the geometric mean of AUC and Cmax values of lobeglitazone and metformin fell in the 90 % confidence interval range of 0.8 to 1.25 and thus PK equivalence was ensured in the combination composition and the orally co-administered formulations of Comparative Examples 7 and 8 (FIGS. 2 and 3).

[161] [Table 11]

[162]

	PK parameter	Lower limit (0.8 or more)	Upper limit (1.25 or less)
Lobeglitazone	AUC_t	0.98	1.09
	C_{max}	0.88	0.98

[163] [Table 12]

[164]

	PK parameter	Lower limit (0.8 or more)	Upper limit (1.25 or less)
Metformin	AUCt	0.93	1.00
	Cmax	0.96	1.08

[165] **Test Example 6: Evaluation of effect depending on kind of** plasticizer contained in the outer layer

[166] 1) Test method

[167] In order to evaluate the stability effect depending on the kind of plasticizer contained in the outer layer of the pharmaceutical formulation according to the present invention, the formulations of Example 1 and Comparative Examples 2 and 3 were hermetically stored in an HDPE bottle for 8 weeks under accelerated conditions (40 ℃, 75 % RH) and in an HDPE bottle for 2 weeks under stress conditions (60 ℃), after which the degradation products of lobeglitazone were measured. The measurement method was as follows.

[168] - Detector: UV spectrophotometer (measurement wavelength: 250 nm)

[169] - Column: C18 (4.6 mm × 250 mm, 5 mm)

[170] - Mobile phase: A-50 mM ammonium acetate (pH 5.0) buffer, B-acetonitrile

[171] The concentration gradient was as follows.

[172]

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	60	40
35	50	50
50	55	45
60	60	40
65	60	40

[173] - Flow rate: 0.8 ml/min

[174] - Column temperature: 40 ℃

[175] - Sample temperature: 25 ℃

[176] 2) Test results

[177] For results of measurement of the amount (%) of the related material of lobeglitazone after storage under accelerated conditions and stress conditions, the results under accelerated conditions are shown in Tables 13, 14 and 15 below and the results under stress conditions are shown in Table 16 below.

[178] As shown in Table 15 below, the amount of the related material in Example 1 was not greatly increased up to 8 weeks under accelerated conditions, and satisfactory results appeared. In contrast, as shown in Tables 14 and 15 for Comparative Examples 2 and 3, the individual unknown related material was high from the initial case and the extent of increase thereof was very significant up to 8 weeks under accelerated conditions, and unsatisfactory results appeared from 4 weeks under accelerated conditions. Based on the results of storage under stress conditions for 1 week as shown in Table 16 below, Example 1 exhibited a very low related material value compared to Comparative Examples 2 and 3. Hence, the use of triethyl citrate as the plasticizer is confirmed to be preferable in order to attain the drug stability of the outer layer.

[179] [Table 13]

[180]

Example 1	Standard	Initial	Accelerated 1 week	Accelerated 4 weeks	Accelerated 8 weeks
Related material A	1.0% or less	Not detected	Not detected	Not detected	0.0
Related material B	1.0% or less	Not detected	Not detected	Not detected	Not detected
Max. individual unknown related material	0.5% or less	0.0	0.0	0.0	0.1
Total related material	2.0% or less	0.0	0.0	0.0	0.1

[181] [Table 14]

[182]

Comparative Example 2	Standard	Initial	Accelerated 1 week	Accelerated 4 weeks	Accelerated 8 weeks
Related material A	1.0% or less	0.1	0.3	0.7	0.7
Related material B	1.0% or less	0.0	0.0	0.1	0.2
Max. individual unknown related material	0.5% or less	0.5	0.5	0.6	1.6
Total related material	2.0% or less	1.6	1.8	3.5	4.8

[183] [Table 15]

[184]

Comparative Example 3	Standard	Initial	Accelerated 1 week	Accelerated 4 weeks	Accelerated 8 weeks
Related material A	1.0% or less	Not detected	0.1	0.3	0.6
Related material B	1.0% or less	Not detected	0.0	0.0	0.1
Max. individual unknown related material	0.5% or less	0.3	0.7	0.8	0.9
Total related material	2.0% or less	0.6	1.2	2.4	4.0

[185] [Table 16]

[186]

Stress 1 week	Standard	Ex.1	C.Ex.2	C.Ex.3
Related material A	1.0% or less	Not detected	14.9	8.9
Related material B	1.0% or less	Not detected	1.8	2.5
Max. individual unknown related material	0.5% or less	0.1	6.9	6.0
Total related material	2.0% or less	0.2	35.5	29.1

[187] **Test Example 7: Evaluation of effect depending on amount of** plasticizer contained in the outer layer

[188] Testing for evaluating the effect depending on the amount of the plasticizer used upon coating with the outer layer was performed.

[189] 1) Test method

[190] The formulations of Example 1 (10.00 wt%), Example 8 (5.00 wt%), Example 9 (7.501 wt%), Comparative Example 4 (2.50 wt%), Comparative Example 5 (12.50 wt%), and Comparative Example 6 (15.00 wt%) were obtained by adjusting the amount of triethyl citrate as the plasticizer contained in the coating solution of the outer layer. After the coating process, the coating yield, appearance, hardness and stability were measured. The appearance was observed using a digital microscope (KH-7700, HIROX, Japan), and the hardness of 10 tablets in each of the Examples and Comparative Examples was determined using a hardness meter (PTP-411, Pharma-Test, Germany).

[191] The stability was tested in a manner in which the corresponding formulation was hermetically stored in an HDPE bottle for 8 weeks under accelerated conditions (40 °C, 75 % RH) and in an HDPE bottle for 2 weeks under stress conditions (60 °C) and then the degradation products of lobeglitazone were measured. The measurement method

was performed in the same manner as Test Example 4.

[192] 2) Test results

[193] The results of testing of stability showed no significant difference, as shown in Tables 17 and 18 below.

[194] However, when the appearance of the final tablet of Comparative Example 4 was observed using a microscope, cracking appeared on the surface of the tablet, and the surfaces of the final tablets of Comparative Examples 5 and 6 were not smooth. Also, based on the results of measurement of average hardness as shown in Table 19 below, there was a significant difference in hardness. Therefore, taking into consideration appearance and hardness, it is preferred that triethyl citrate is contained in an amount of 5 to 10 wt% based on the total weight of the outer layer.

[195] [Table 17]

[196]

Accelerated 8 weeks	Standard	Examples			Comp. Examples		
		1	8	9	4	5	6
Related material A	1.0% or less	0.0	0.0	0.0	Not detected	0.0	0.0
Related material B	1.0% or less	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
Max. individual unknown related material	0.5% or less	0.1	0.1	0.1	0.0	0.1	0.1
Total related material	2.0% or less	0.1	0.1	0.1	0.1	0.2	0.2

[197] [Table 18]

[198]

Stress 2 weeks	Standard	Example			Comp. Example		
		1	8	9	4	5	6
Related material A	1.0% or less	Not detected	Not detected	Not detected	Not detected	0.0	0.0
Related material B	1.0% or less	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
Max. individual unknown related material	0.5% or less	0.1	0.1	0.1	0.1	0.1	0.1
Total related material	2.0% or less	0.3	0.3	0.3	0.2	0.3	0.3

[199] [Table 19]

[200]

Hardness (Kp)	Examples			Comp. Examples		
	1	8	9	4	5	6
	28	25	25	27	Not measured	Not measured

CLAIMS

1. A pharmaceutical formulation, comprising:

a core layer containing metformin or a pharmaceutically acceptable salt thereof as an active ingredient; and

an outer layer containing lobeglitazone or a pharmaceutically acceptable salt thereof as an active ingredient;

wherein the outer layer comprises a binder having a viscosity of 6 mPa.s or less and triethyl citrate as a plasticizer.

2. The pharmaceutical formulation of claim 1, wherein the metformin or the pharmaceutically acceptable salt thereof is present in an amount of 60 to 80 wt% based on a total weight of the core layer.

3. The pharmaceutical formulation of claim 1, wherein the core layer comprises a water-soluble polymer.

4. The pharmaceutical formulation of claim 3, wherein the water-soluble polymer is selected from the group consisting of hydroxypropyl methylcellulose, ethyl cellulose, methyl cellulose, hydroxypropylcellulose, polyvinyl pyrrolidone, polymethacrylate, and mixtures thereof.

5. The pharmaceutical formulation of claim 3, wherein the water-soluble polymer is present in an amount of 15 to 25 wt% based on a total weight of the core layer.

6. The pharmaceutical formulation of claim 1, wherein the lobeglitazone or the pharmaceutically acceptable salt thereof is present in an amount of 0.1 to 2.0 wt% based on a total weight of the outer layer.

7. The pharmaceutical formulation of claim 1, wherein the binder is selected from the group consisting of hydroxypropyl methylcellulose, polyvinyl pyrrolidone, lactose, and mixtures thereof.

8. The pharmaceutical formulation of claim 1, wherein the triethyl citrate is present in an amount of 5 to 10 wt% based on a total weight of the outer layer.

9. The pharmaceutical formulation of claim 1, further comprising an inert intermediate layer between the core layer and the outer layer.