

TITLE OF INVENTION

PHARMACEUTICAL COMPOSITION AND ITS PREPARATION
METHOD

TECHNICAL FIELD

5 Cross-Reference to Related Application(s)

This application claims priority to and the benefit of Korean Patent Application No. 10-2023-0095476, filed on July 21, 2023, the entire contents of which are incorporated herein by reference.

10 The present invention relates to a pharmaceutical composition comprising ezetimibe or a pharmaceutically acceptable salt thereof and fenofibrate or a pharmaceutically acceptable salt thereof, which pharmaceutical composition reduces the decomposition of ezetimibe and the formation of related substances, thereby exhibiting improved stability and excellent efficacy, and a preparation method thereof.

15 **BACKGROUND**

Ezetimibe is a selective cholesterol absorption inhibitor, which is sold under the brand names EZETROL™ or ZETIA™. Ezetimibe has a mechanism that inhibits the reabsorption of cholesterol in a small intestine, and is used as a therapeutic agent or dietary supplement to reduce cholesterol in patients with
20 hyperlipidemia.

On the other hand, fenofibrate exhibits an in vivo mechanism that assists the action of enzymes that break down lipid proteins in the blood to reduce triglycerides and cholesterol, and is used as a therapeutic agent for

hyperlipidemia.

Ezetimibe and fenofibrate are known to be more effective for the treatment of triglycerides or the like when administered together, and accordingly, attempts are being made to develop their combined administration or a
5 combination drug including them.

However, ezetimibe is known to be unstable in a basic environment and thus generate numerous related substances.

Generally, in order for pharmaceutical products to always exert a constant effect, it is necessary to suppress the reduction in the active ingredient content
10 not only immediately after preparation but also during storage, and further it is necessary to minimize the increase in decomposition products of the active ingredient, i.e., impurities or related substances, during the same period. Therefore, preventing the incorporation of impurities and suppressing the increase of related substances in pharmaceutical products is extremely important
15 in pharmaceutical quality control.

As described above, ezetimibe generates numerous related substances in a basic environment, and if ezetimibe and fenofibrate are present together, it has been reported that the decomposition of ezetimibe or the formation of related substances such as ezetimibe ketone further increases. Consequently, the
20 development of combination drugs comprising ezetimibe and fenofibrate that can expect their synergistic effects while enhancing medication convenience for patients with hyperlipidemia is facing limitations.

Therefore, there is an ongoing demand for the development of a

pharmaceutical composition that can reduce the formation of related substances and thus improve the stability in combination drugs comprising ezetimibe and fenofibrate.

5 DETAILED DESCRIPTION OF THE INVENTION

Technical Problem

The present invention provides a pharmaceutical composition comprising ezetimibe or a pharmaceutically acceptable salt thereof and fenofibrate or a pharmaceutically acceptable salt thereof, which pharmaceutical composition
10 reduces the decomposition of ezetimibe and the formation of related substances, thereby exhibiting improved stability and excellent efficacy, and a preparation method thereof.

Technical Solution

According to an aspect of the present invention, provided is a
15 pharmaceutical composition comprising:

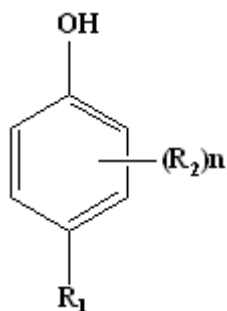
ezetimibe or a pharmaceutically acceptable salt thereof;

fenofibrate or a pharmaceutically acceptable salt thereof;

an antioxidant represented by the following Chemical Formula 1; and

a pharmaceutically acceptable excipient:

20 [Chemical Formula 1]



wherein, in Chemical Formula 1, R₁ is an alkyl group having 1 to 3 carbon atoms or an alkoxy group having 1 to 3 carbon atoms, R₂ is a linear or branched alkyl group having 1 to 5 carbon atoms, and n is an integer of 1 or 2.

5 According to another aspect of the present invention, provided is a method of preparing the pharmaceutical composition, the method comprising the steps of:

granulating a mixture comprising an active ingredient including ezetimibe, fenofibrate, or a pharmaceutically acceptable salt thereof, the antioxidant of Chemical Formula 1, and a pharmaceutically acceptable excipient including a diluent, a disintegrant and a binder; and

mixing a lubricant with the granulate and tableting the mixture.

Advantageous Effects

The present inventors have continued their studies to improve the stability of pharmaceutical compositions comprising ezetimibe and fenofibrate using various pharmaceutically acceptable stabilizers.

As a result of these studies, the present inventors have confirmed that the antioxidant of Chemical Formula 1 is included as a stabilizer in the pharmaceutical composition, whereby a pharmaceutical composition capable of significantly reducing the decomposition of ezetimibe and the formation of related

substances such as ezetimibe ketone and exhibiting improved stability can be provided.

Therefore, when such a pharmaceutical composition is used, it is possible to maintain excellent synergistic effects due to combined administration of ezetimibe and fenofibrate, while ensuring ease of administration for patients with hyperlipidemia, which can greatly contribute to the effective treatment of hyperlipidemia or the like.

DETAILED DESCRIPTION OF THE EMBODIMENTS

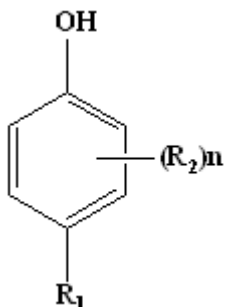
Hereinafter, a pharmaceutical composition and its preparation method according to specific embodiments of the present invention will be described in more detail.

Throughout this specification, the term "related substance" is a substance that may be included in the raw material synthesis process of an active ingredient or in the finished pharmaceutical product prepared from a pharmaceutical composition, and may refer to a kind of impurity of the active ingredient that can be used for evaluating the quality of the finished pharmaceutical product. For example, the category of related substances may include any impurity such as ezetimibe ketone derived from ezetimibe or a salt thereof, or fenofibrate or a salt thereof, which are included as active ingredients in the pharmaceutical composition of one embodiment described below.

According to one embodiment of the invention, there is provided a pharmaceutical composition comprising: ezetimibe or a pharmaceutically acceptable salt thereof; fenofibrate or a pharmaceutically acceptable salt thereof;

an antioxidant represented by the following Chemical Formula 1; and a pharmaceutically acceptable excipient:

[Chemical Formula 1]



5 wherein, in Chemical Formula 1, R₁ is an alkyl group having 1 to 3 carbon atoms or an alkoxy group having 1 to 3 carbon atoms, R₂ is a linear or branched alkyl group having 1 to 5 carbon atoms, and n is an integer of 1 or 2.

 In the initial stage of their studies, the inventors have noticed that ezetimibe generates large amounts of related substances and exhibits poor
10 stability primarily in a basic environment, and attempted to add a stabilizer in the form of organic or inorganic acids such as citric acid or tartaric acid to a pharmaceutical composition comprising ezetimibe and fenofibrate. However, as supported by Comparative Examples or the like below, it was confirmed that the addition of these acidic stabilizers alone cannot sufficiently suppress the
15 formation of related substances resulting from the combined use of ezetimibe and fenofibrate.

 Therefore, the present inventors have continued additional studies and experiments to identify a stabilizer suitable for pharmaceutical compositions comprising ezetimibe and fenofibrate. As a result of these additional studies and
20 experiments, the inventors have found that as the antioxidant of Chemical

Formula 1 is added as a stabilizer, it can significantly suppress the decomposition of ezetimibe and the formation of related substances such as ezetimibe ketone, thereby improving the stability of the pharmaceutical composition and maintaining the excellent synergistic effects of these active ingredients, and completed the present invention.

For reference, the antioxidant of Chemical Formula 1 is a kind of neutral antioxidant component, which is expected to suppress the decomposition of ezetimibe itself without causing a pH change in the pharmaceutical composition.

In the pharmaceutical composition of one embodiment, the antioxidant may be a compound wherein in Chemical Formula 1, R_1 is a methyl group, an ethyl group, or a methoxy group, R_2 is a t-butyl group, and n is 1 or 2. In a more specific example, the antioxidant may be a compound wherein R_1 is a methyl group, R_2 is a t-butyl group, and n is 2. In a most specific example, the antioxidant of Chemical Formula 1 may have a structure in which the t-butyl group of the R_2 is bonded to the 2,6-position adjacent to the hydroxyl group.

As the antioxidant has such a structure, it may more effectively inhibit the decomposition of ezetimibe and the formation of related substances, and also may reduce adverse effects such as the antioxidant affecting the efficacy of the pharmaceutical composition or causing toxicity in the human body.

Additionally, the antioxidant may be contained in an amount of about 0.07 to about 0.60 wt.%, or about 0.08 to about 0.55 wt.%, or about 0.1 to about 0.5 wt.%, based on the total weight of the pharmaceutical composition, for example, the total weight of a unit dosage form such as a tablet of the pharmaceutical

composition.

If the content of the antioxidant is excessively low, it was confirmed that the formation of related substances including ezetimibe ketone cannot be sufficiently suppressed, and it is difficult to excellently maintain the stability and efficacy of the pharmaceutical composition. Furthermore, in a preparation process of the pharmaceutical composition, the antioxidant may not be uniformly mixed, which may locally reduce the stability of the pharmaceutical composition. Conversely, if the content of the antioxidant is excessively high, not only it is difficult to suppress the formation of related substances any more, but also the antioxidant may exhibit toxicity in the human body.

Unlike the same, as the content of the antioxidant is optimized, the formation of related substances may be minimized, and the stability of the pharmaceutical composition of one embodiment may be maximized. For example, according to the results of experiments by the inventors, the pharmaceutical composition of one embodiment including the antioxidant in an optimized content can exhibit excellent stability even after being stored in an opened system for at least 3 months under accelerated conditions of about 40°C and about 75% relative humidity, with the total amount of formation of related substances including ezetimibe ketone being less than 0.4 wt.%, or about 0 wt.% or more and less than about 0.4 wt.%, or about 0 wt.% or more and less than about 0.35 wt.%, or about 0 wt.% or more and less than about 0.30 wt.%, and the amount of formation of ezetimibe ketone as the related substance being less than about 0.2 wt.%, or 0 wt.% or more and less than about 0.2 wt.%, or about 0 wt.%

or more and less than about 0.19 wt.%, based on the total weight of the pharmaceutical composition.

Meanwhile, in the pharmaceutical composition of the above-described embodiments, the ezetimibe may be included in the form of ezetimibe or a salt thereof, and specific examples of the ezetimibe salt include calcium salt, hydrochloride salt, hydrobromide salt, sulfate salt, phosphate salt, acetate salt, malate salt, fumarate salt, lactate salt, tartrate salt, citrate salt, gluconate salt, besylate salt, camsylate salt, or the like.

Such ezetimibe or a salt thereof may be contained in an amount of about 1 to about 5 wt.%, or about 1.5 to about 4 wt.%, based on the total weight of the pharmaceutical composition. In a specific example, the ezetimibe or a salt thereof may be contained in an amount of about 5 to about 25 mg, or about 7.5 to about 20 mg, in a unit dosage form (e.g., one tablet) of the pharmaceutical composition.

Further, in the pharmaceutical composition of one embodiment, the fenofibrate may be included in the form of fenofibrate, fenofibrate choline salt or the like.

The fenofibrate or a salt thereof may be contained in an amount of about 15 to about 40 wt.%, or about 20 to about 35 wt.%, based on the total weight of the pharmaceutical composition. In a specific example, the fenofibrate or a salt thereof may be contained in an amount of about 75 to about 200 mg, or about 100 to about 180 mg in a unit dosage form (e.g., one tablet) of the pharmaceutical composition. In this way, by optimizing the content of each active ingredient, it is

possible to exhibit excellent synergistic effects due to the combined use of ezetimibe and fenofibrate.

Meanwhile, the pharmaceutical composition of one embodiment may further include a pharmaceutically acceptable excipient, in addition to the above-mentioned active ingredients and antioxidant. Examples of such excipients include at least one selected from the group consisting of a diluent, a disintegrant, a binder, and a lubricant.

Among these, the diluent may include at least one selected from the group consisting of lactose, starch, mannitol, microcrystalline cellulose, carboxymethyl cellulose and hydrates thereof, sodium lauryl sulfate, polysorbate (e.g., polysorbate 80), polyethylene oxide, polypropylene oxide, and combinations thereof. Further, the binder may include at least one selected from the group consisting of povidone, hypromellose, hydroxypropyl cellulose, copovidone, and derivatives thereof.

Further, the disintegrant may include at least one selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, and derivatives thereof.

In addition, the lubricant may include at least one selected from the group consisting of magnesium stearate, talc, colloidal silicon dioxide, light anhydrous silicic acid, and sodium stearyl fumarate.

However, the excipient used in the pharmaceutical composition of one embodiment are not limited to the examples described above, and needless to say, various other pharmaceutically acceptable excipients may be further used.

Further, the content of each excipient may be included in a typical amount according to its function, and therefore, further description thereof will be omitted.

Meanwhile, the pharmaceutical composition may be prepared and provided, for example, in the form of tablets that are orally administered, for example, once or twice a day, and more specifically, may be provided in the form of film-coated tablets that are administered once a day. In accordance with the provision of such a dosage form, the synergistic effect of ezetimibe and fenofibrate can be exhibited with once-daily administration, thereby improving the convenience of administration for patients with hyperlipidemia or the like.

When the pharmaceutical composition is provided in the form of such a film-coated tablet, the above-described pharmaceutical composition is prepared in tablet form, and then a coating agent such as an Opadry-based coating agent for coating the composition may be further included.

The above-described pharmaceutical composition may be used as a therapeutic agent or dietary supplement for patients with hyperlipidemia, and may also be used as a therapeutic agent or supplement for various diseases requiring reduction in cholesterol and/or triglyceride.

Meanwhile, according to another embodiment of the invention, a method of preparing the above-mentioned pharmaceutical composition is provided. Such a preparation method includes, for example, a step of granulating a mixture comprising an active ingredient including ezetimibe, fenofibrate, or a pharmaceutically acceptable salt thereof, the antioxidant of Chemical Formula 1, and a pharmaceutically acceptable excipient including a diluent, a disintegrant

and a binder; and a step of mixing a lubricant with the granulate and tableting the mixture.

In a more specific example, a diluent, a disintegrant, and an antioxidant may be primarily mixed with the fenofibrate or a salt thereof, the ezetimibe or a salt thereof under stirring, and then the binder may be further mixed with a solvent, such as purified water, and granulated by a wet granulation process or the like.

Subsequently, the wet granulate is dried and sieved by a fluidized bed drying method, and a lubricant is mixed with the granulate and tableted, thereby preparing an oral tablet comprising the pharmaceutical composition of one embodiment.

In addition, if necessary, a pharmaceutical composition in the form of a film-coated tablet can be prepared by coating the oral tablet with a coating agent.

By adjusting the mixing order of the active ingredient, antioxidant and the like, and preparing the pharmaceutical composition in tablet form through granulation or the like, a pharmaceutical composition of one embodiment with improved stability can be prepared.

Hereinafter, preferred examples are provided to facilitate understanding of the present invention. However, the following examples are merely provided for a better understanding of the present invention, and the scope of the present invention is not limited thereto.

Comparative Examples 1 to 5 and Examples 1 to 6

Pharmaceutical compositions (tablets) of Examples and Comparative Examples, including the compositions shown in Table 1 or 2 below, were prepared by the following method.

First, using a high-speed mixer, ezetimibe and diluents passed through a 20-mesh standard sieve, and a disintegrant and antioxidant (or stabilizer) passed through a 50-mesh standard sieve were sequentially added to fenofibrate and mixed under high-speed stirring. Separately, a binder was further mixed with purified water to prepare a binder solution. The binder solution was then added, and the mixture was granulated by a wet granulation process. The wet granulate was then dried in a fluidized bed dryer, and sieved using a 1.2 mm oscillator.

A lubricant passed through a 30-mesh standard sieve was then further mixed with the resulting granulate, and the mixture was tableted under conditions of $500 \pm 3\%$ and 7 ± 3 kp to prepare tablets according to Examples and Comparative Examples

[Table 1]

Category	Ingredient name	Comparative Example 1 (wt.%)	Example 1 (wt.%)	Example 2 (wt.%)	Example 3 (wt.%)	Example 4 (wt.%)	Example 5 (wt.%)	Example 6 (wt.%)
Active ingredient 1	Ezetimibe	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Active ingredient 2	Fenofibrate	32.00	32.00	32.00	32.00	32.00	32.00	32.00
Diluent		43.60	43.5875	43.50	43.40	43.10	42.60	40.60
Disintegrant		15.00	15.00	15.00	15.00	15.00	15.00	15.00
Binder		5.00	5.00	5.00	5.00	5.00	5.00	5.00

Antioxidant (or stabilizer)	Butylhydroxytoluene	0	0.0125	0.10	0.20	0.50	1.00	3.00
Lubricant		2.40	2.40	2.40	2.40	2.40	2.40	2.40
Total (based on 1 tablet; wt.%)		100.0	100.0	100.0	100.0	100.0	100.0	100.0

[Table 2]

Category	Ingredient name	Comparative Example 2 (wt.%)	Comparative Example 3 (wt.%)	Comparative Example 4 (wt.%)	Comparative Example 5 (wt.%)
Active ingredient 1	Ezetimibe	2.00	2.00	2.00	2.00
Active ingredient 2	Fenofibrate	32.00	32.00	32.00	32.00
Diluent		42.60	41.60	42.60	41.60
Disintegrant		15.00	15.00	15.00	15.00
Binder		5.00	5.00	5.00	5.00
Antioxidant (or stabilizer)	Citric acid	1.00	2.00	0	0
	Tartaric acid	0	0	1.00	2.00
Lubricant		2.40	2.40	2.40	2.40
Total (based on 1 tablet; wt.%)		100.0	100.0	100.0	100.0

Test Example 1: Evaluation of the stability of pharmaceutical compositions by type of antioxidant (stabilizer)

5 For the pharmaceutical compositions of Examples 2 and 3 and Comparative Examples 1 to 5, the amount of formation of related substances and the stability of the pharmaceutical compositions by type of antioxidant (stabilizer) were evaluated by the following method. Specifically, each pharmaceutical composition was stored in a high-density plastic (HDPE) bottle, and while being

stored with the lid open under accelerated storage conditions of $40\pm 2^{\circ}\text{C}$, $75\pm 5\%$ RH for about one month, the amount of formation of related substances was analyzed and evaluated every one to two weeks using an HPLC system. The amount of formation of related substances was analyzed and evaluated by dividing it into the content of ezetimibe ketone related substances, the content of other related substances, and the content of total related substances. The evaluation results are summarized in Table 3 below:

[Table 3]

Category	Antioxidant (wt.%)	Evaluation object	Initial stage (wt.%)	After 7 days (wt.%)	After 14 days (wt.%)	After 28 days (wt.%)
Comparative Example 1	None	Ezetimibe ketone	0.02	0.08	0.17	0.21
		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.08	0.17	0.21
Comparative Example 2	Citric acid (1 wt.%)	Ezetimibe ketone	0.02	0.07	0.16	0.18
		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.07	0.16	0.18
Comparative Example 3	Citric acid (2 wt.%)	Ezetimibe ketone	0.02	0.07	0.14	0.17
		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.07	0.14	0.17
Comparative Example 4	Tartaric acid (1 wt.%)	Ezetimibe ketone	0.02	0.08	0.16	0.17

		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.08	0.16	0.17
Comparative Example 5	Tartaric acid (2 wt.%)	Ezetimibe ketone	0.02	0.08	0.13	0.18
		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.08	0.13	0.18
Example 2	Butylhydroxytoluene (0.1 wt.%)	Ezetimibe ketone	0.02	0.02	0.02	0.02
		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.02	0.02	0.02
Example 3	Butylhydroxytoluene (0.2 wt.%)	Ezetimibe ketone	0.02	0.02	0.02	0.02
		Other related substance	0.00	0.00	0.00	0.00
		Total related substance	0.02	0.02	0.02	0.02

Referring to Table 3, it was confirmed that as compared to Comparative Example 1, which did not contain a separate antioxidant or stabilizer, and Comparative Examples 2 to 5, which included an organic acid-based stabilizer, the pharmaceutical compositions of Examples 2 and 3 showed significantly reduced amount of formation of related substances, thereby exhibiting excellent stability.

Test Example 2: Evaluation of the stability of pharmaceutical compositions under open, accelerated conditions (40°C and 75% relative

humidity)

The pharmaceutical compositions of Comparative Example 1 and Examples 1 to 4 were stored in a high-density plastic bottle (HDPE), and while being stored in the state the lid was opened under accelerated storage conditions of $40\pm 2^{\circ}\text{C}$, $75\pm 5\%$ RH, for approximately 3 months, the amount of formation of related substances was analyzed and evaluated by a HPLC system. The amount of formation of related substances was analyzed and evaluated by dividing it into the content of ezetimibe ketone related substance and the content of other related substances. The evaluation results are summarized in Table 4 below.

[Table 4]

Category	Antioxidant (wt.%)	Evaluation object	Initial stage (wt.%)	After 3 months (wt.%)
Comparative Example 1	None	Ezetimibe ketone	N/D	0.21
		Other related substance	N/D	0.47
Example 1	Butylhydroxytoluene (0.0125 wt.%)	Ezetimibe ketone	N/D	0.21
		Other related substance	N/D	0.03
Example 2	Butylhydroxytoluene (0.1 wt.%)	Ezetimibe ketone	N/D	0.19
		Other related substance	N/D	0.03
Example 3	Butylhydroxytoluene (0.2 wt.%)	Ezetimibe ketone	N/D	0.12
		Other related substance	N/D	0.03
Example 4	Butylhydroxytoluene (0.5 wt.%)	Ezetimibe ketone	N/D	0.11
		Other related substance	N/D	0.03

Referring to Table 4, it was confirmed that the pharmaceutical compositions of Examples 1 to 4 showed a lower amount of formation of

related substances than in Comparative Example 1 even under accelerated conditions, thereby exhibiting excellent stability. However, it was confirmed that in Example 1, the amount of formation of ezetimibe ketone related substances was close to the reference value, and thus the stability of the pharmaceutical compositions was not sufficient compared to Examples 2 to 4.

Test Example 3: Evaluation of the stability of pharmaceutical compositions under open severe conditions (75°C)

The pharmaceutical compositions of Comparative Example 1 and Examples 4 to 6 were stored in a high-density plastic bottle (HDPE), and while being stored in the state the lid was opened in an oven under a severe condition of 75°C for about four days, and the amount of formation of related substance was analyzed and evaluated by a HPLC system. The amount of formation of related substances was analyzed and evaluated by dividing it into the content of ezetimibe ketone related substance, the content of other related substances and the content of the total related substance. The evaluation results are summarized in Table 5 below.

[Table 5]

Category	Antioxidant (wt.%)	Evaluation object	Initial stage (wt.%)	After 1 day (wt.%)	After 3 days (wt.%)	After 4 days (wt.%)
Comparative Example 1	None	Ezetimibe ketone	N/D	N/D	N/D	N/D
		Other related substance	0.02	0.18	0.44	0.61

		Total related substance	0.02	0.43	1.18	1.45
Example 4	Butylhydroxytoluene (0.5 wt.%)	Ezetimibe ketone	N/D	N/D	N/D	N/D
		Other related substance	0.02	0.18	0.23	0.16
		Total related substance	0.02	0.21	0.52	0.62
Example 5	Butylhydroxytoluene (1.0 wt.%)	Ezetimibe ketone	N/D	N/D	N/D	N/D
		Other related substance	0.02	0.18	0.22	0.24
		Total related substance	0.02	0.31	0.64	0.85
Example 6	Butylhydroxytoluene (3.0 wt.%)	Ezetimibe ketone	N/D	N/D	N/D	N/D
		Other related substance	0.02	0.16	0.25	0.38
		Total related substance	0.02	0.30	0.63	1.04

Referring to Table 5, the pharmaceutical composition of Example 4 showed a lower amount of formation of related substances than Comparative Example 1, even under a severe condition. It was confirmed that the amount of formation of total related substances in Examples 5 and 6, which increased the pharmaceutical composition in Example 4, rather increased, and therefore, the stability of the pharmaceutical composition was not sufficient compared to Example 4.

WHAT IS CLAIMED IS:

[Claim 1]

A pharmaceutical composition comprising:

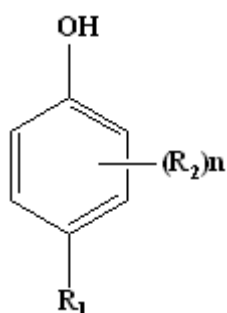
ezetimibe or a pharmaceutically acceptable salt thereof;

5 fenofibrate or a pharmaceutically acceptable salt thereof;

an antioxidant represented by the following Chemical Formula 1; and

a pharmaceutically acceptable excipient:

[Chemical Formula 1]



10 wherein, in Chemical Formula 1, R₁ is an alkyl group having 1 to 3 carbon atoms or an alkoxy group having 1 to 3 carbon atoms, R₂ is a linear or branched alkyl group having 1 to 5 carbon atoms, and n is an integer of 1 or 2.

[Claim 2]

15 The pharmaceutical composition according to claim 1, wherein the antioxidant comprises a compound wherein in Chemical Formula 1, R₁ is a methyl group, an ethyl group, or a methoxy group, and R₂ is a t-butyl group.

[Claim 3]

20 The pharmaceutical composition according to claim 1, wherein the

antioxidant is contained in an amount of 0.07 to 0.60 wt.% based on the total weight of the pharmaceutical composition.

[Claim 4]

- 5 The pharmaceutical composition according to claim 1, wherein the ezetimibe or a pharmaceutically acceptable salt thereof is contained in an amount of 1 to 5 wt.% based on the total weight of the pharmaceutical composition.

[Claim 5]

- 10 The pharmaceutical composition according to claim 1, wherein the fenofibrate or a pharmaceutically acceptable salt thereof is contained in an amount of 15 to 40 wt.% based on the total weight of the pharmaceutical composition.

15 [Claim 6]

 The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable excipient comprises at least one selected from the group consisting of a diluent, a disintegrant, a binder, and a lubricant.

20 [Claim 7]

 The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition has a form of an oral tablet.

[Claim 8]

The pharmaceutical composition according to claim 1, wherein after being stored in an opened system for at least three months under conditions of 40°C and 75% relative humidity, the total content of related substances including
5 ezetimibe ketone is less than 0.4 wt.%.

[Claim 9]

A method of preparing the pharmaceutical composition set forth in claim 1, the method comprising the steps of:

10 granulating a mixture comprising an active ingredient including ezetimibe, fenofibrate, or a pharmaceutically acceptable salt thereof, the antioxidant of Chemical Formula 1, and a pharmaceutically acceptable excipient including a diluent, a disintegrant and a binder; and
mixing a lubricant with the granulate and tableting the mixture.

15

[Claim 10]

The method of preparing the pharmaceutical composition according to claim 9, wherein the granulating step comprises:

wet granulating the mixture; and
20 subjecting the wet granulate to a fluidized bed drying.