(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 May 2018 (11.05.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/084627 A2

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/4178* (2006.01)
A61K 31/4422 (2006.01) *A61K 31/404* (2006.01)

(21) International Application Number:
PCT/KR2017/012396

(22) International Filing Date:
03 November 2017 (03.11.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2016-0145518 03 November 2016 (03.11.2016) KR

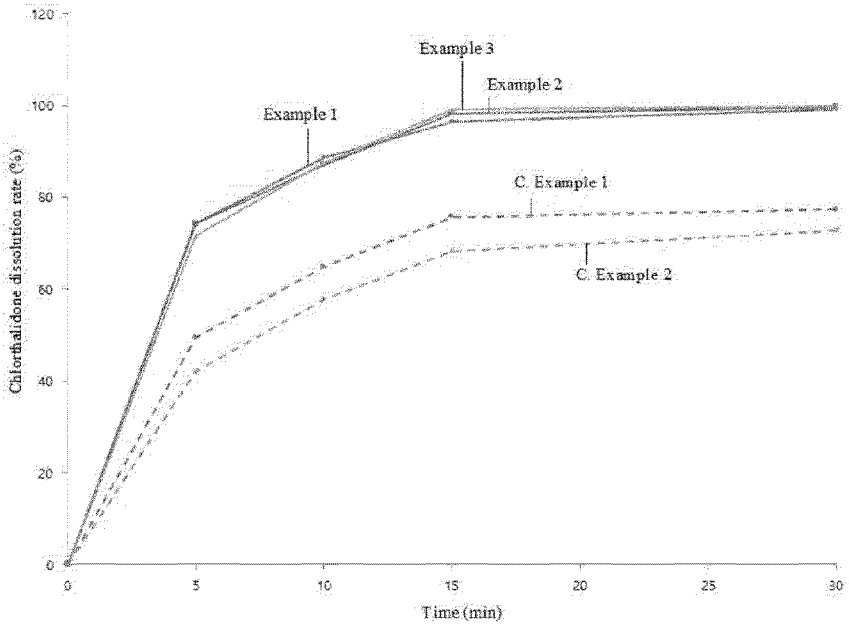
(71) Applicant: **HANMI PHARM. CO., LTD.** [KR/KR]; 214, Muha-ro, Paltan-myeon, Hwaseong-si, Gyeonggi-do 18536 (KR).

(72) Inventors: **CHO, Hyuk Jun**; B-301, 46, Deogyeong-daero 381beon-gil, Jangan-gu, Suwon-si, Gyeonggi-do 16358 (KR). **LIM, Sol Ee**; #905, 17-9, Gwongwang-ro 196beon-gil, Paldal-gu, Suwon-si, Gyeonggi-do 16488 (KR). **IM, Ho Taek**; 117-1204, 27, Yonggu-daero 2394beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do 16909 (KR). **KIM, Yong Il**; 732-504, 52, Jeongja-ro 42beon-gil, Jangan-gu, Suwon-si, Gyeonggi-do 16325 (KR). **PARK, Jae Hyun**; 311-404, 460, Yeongtong-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do 16707 (KR). **WOO, Jong Soo**; 120-2303, 85, Hwasan-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16420 (KR).

(74) Agent: **KIM, Sung Ho** et al.; (WANNABE Patent & Law Firm), (Hongeun Bldg., Yeoksam-dong) 5F, 8, Teheran-ro 8-gil, Gangnam-gu, Seoul 06233 (KR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,

(54) Title: PHARMACEUTICAL COMPLEX FORMULATION COMPRISING AMLODIPINE, LOSARTAN AND CHLORTHALIDONE



(57) Abstract: The present invention relates to a pharmaceutical complex formulation including amlodipine, losartan, and chlorthalidone as active ingredients. The pharmaceutical complex formulation of the present invention including amlodipine, losartan and chlorthalidone as the active ingredients exhibits excellent dissolution characteristics of the active ingredients, and has high content uniformity and heat stability. Therefore, the complex formulation of the present invention can be used as a prophylactic or therapeutic agent for cardiovascular diseases, which has excellent quality and heat stability.

WO 2018/084627 A2

[Continued on next page]

PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

Description

Title of Invention: PHARMACEUTICAL COMPLEX FORMULATION COMPRISING AMLODIPINE, LOSARTAN AND CHLORTHALIDONE

Technical Field

[1] The present invention relates to a pharmaceutical complex formulation including amlodipine, losartan and chlorthalidone as active ingredients.

Background Art

[2] Hypertension refers to a condition in which a systolic blood pressure is greater than or equal to 140 mmHg or a diastolic blood pressure is greater than or equal to 90 mmHg in adults over the age of 18 years. Hypertension is a disease that has the highest incidence frequency among chronic circulatory diseases and shows relatively few symptoms, but requires more intensive cares and treatments because it may cause fetal complications such as strokes, heart failure, coronary artery diseases, and the like.

[3] Drugs widely used to treat hypertension are mainly divided into diuretic agents, sympatholytic agents, and vasodilators according to the mechanism of action of the drugs. The vasodilators commonly used so far are also divided into angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and calcium channel blockers according to the mechanism of action of the vasodilators.

[4] Amlodipine is the generic name of 3-ethyl-5-methyl-2-(2-aminoethoxy-methyl)-4-(-2-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridine dicarboxylate, which is a kind of a dihydropyridine-based calcium channel blocker and is used to block calcium channels so as to treat cardiovascular diseases such as angina, hypertension, and congestive heart failure.

[5] Losartan is the generic name of 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol, which is used to block binding of a vasoconstrictor substance such as angiotensin II to a receptor so as to treat hypertension and heart failure, cure an ischemic peripheral circulatory disorder and myocardial ischemia (angina), prevent the progression of post-myocardial infarction heart failure, and treat diabetic neuropathy, glaucoma, and the like.

[6] A complex formulation of amlodipine and losartan having different mechanisms of action has advantages in that the complex formulation has superior effects in preventing or treating hypertension and cardiovascular diseases when compared to conventional single preparations, reduces side effects of drugs when the drugs are used alone, and has high patients' compliance. The complex formulations are disclosed in

Korean Patent Nos. 1160151 and 1232296, and currently sold under the trade name of Amosartan®.

[7] Chlorthalidone is the generic name of benzene sulfonamide-2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl), and currently sold under the trade name of Hygroton®. Chlorthalidone is a thiazide-based diuretic agent that serves to block a Na^+/Cl^- symporter in the renal distal tubules so as to inhibit the reuptake of Na^+ and Cl^- and increase the excretion of K^+ so as to store water in urine.

[8] To effectively treat cardiovascular diseases, research on complex formulations of amlodipine, losartan and chlorthalidone, which have different mechanisms, have been conducted. By way of example, Korean Unexamined Patent Publication No. 2016-0117055 discloses a complex formulation which includes a first mixing portion including amlodipine and chlorthalidone and a second mixing portion including losartan, wherein the first and second mixing portions are present in a separated state. The complex formulation may be realized as a bilayer tablet, and has an effect of improving a dissolution rate of drugs and stability of the active ingredients with respect to rays and heat due to a minimized interaction between the drugs.

[9] However, there is a need for research on pharmaceutical complex formulations showing a further improved dissolution rate, content uniformity, and stability to further improve quality and bioavailability of the complex formulations including amlodipine, losartan, and chlorthalidone.

[10] [Prior-art Document]

[11] [Patent Document]

[12] Korean Unexamined Patent Publication No. 2016-0117055 entitled "Pharmaceutical Complex Formulation Comprising Amlodipine, Losartan and Chlorthalidone"

Disclosure of Invention

Technical Problem

[13] The present inventors have conducted research on methods capable of improving a dissolution rate, content uniformity, and stability of a pharmaceutical complex formulation including amlodipine, losartan, and chlorthalidone, thereby having completed the present invention.

[14] Accordingly, it is an aspect of the present invention to provide a pharmaceutical complex formulation including amlodipine, losartan, and chlorthalidone, which exhibits excellent dissolution characteristics, content uniformity, and stability.

[15] It is another aspect of the present invention to provide a method of preparing the pharmaceutical complex formulation.

Solution to Problem

[16] To solve the above problems, according to an aspect of the present invention, there is

provided a pharmaceutical complex formulation which includes:

[17] a first mixing portion including amlodipine or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof; and

[18] a second mixing portion including losartan or a pharmaceutically acceptable salt thereof,

[19] wherein the first and second mixing portions are present in a state in which the first and second mixing portions are physically separated from each other, and

[20] the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 50 ㎛.

[21] Preferably, the chlorthalidone or pharmaceutically acceptable salt thereof may have particle size (D_{90}) of 0.5 to 25 ㎛.

[22] More preferably, the chlorthalidone or pharmaceutically acceptable salt thereof may have a particle size (D_{90}) of 0.5 to 10 ㎛.

[23] In this case, the pharmaceutical complex formulation may be a bilayer tablet including:

[24] a first layer including amlodipine or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof; and

[25] a second layer including losartan or a pharmaceutically acceptable salt thereof.

[26] In this case, the complex formulation may have a chlorthalidone dissolution rate of 85% or more within 30 minutes, more preferably a chlorthalidone dissolution rate of 85% or more within 15 minutes when a dissolution test is performed in purified water according to a paddle method for dissolution test items disclosed in the 'Chlorthalidone Tablet' Section of the United States Pharmacopoeia.

[27] In this case, the first mixing portion may further include a disintegrating agent as an additive.

[28] In this case, the disintegrating agent may include crospovidone, croscarmellose sodium, sodium starch glycolate, starch, pregelatinized starch, or a combination thereof.

[29] In this case, the disintegrating agent may be included at a content of 2 to 7.5% by weight, based on the total weight of the first mixing portion.

[30] In this case, the first mixing portion may further include lactose hydrate and micro-crystalline cellulose as additives.

[31] In this case, the first and second mixing portions may be in the form of granules subjected to a roller compaction process.

[32] According to another aspect of the present invention, there is provided a method of preparing a pharmaceutical complex formulation, which includes:

[33] a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive;

and

[34] b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive,

[35] wherein the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 50 ㎛.

[36] Also, the complex formulation may be prepared using a method of preparing a pharmaceutical complex formulation, which includes:

[37] a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, and granulating the resulting mixture;

[38] b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, and granulating the resulting mixture; and

[39] c) tablet-pressing the granules prepared in steps a) and b) into a bilayer tablet,

[40] wherein the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 50 ㎛.

[41] In this case, the pharmaceutical complex formulation may be a composition or complex formulation for preventing or treating cardiovascular diseases.

Advantageous Effects of Invention

[42] The pharmaceutical complex formulation of the present invention including amlodipine, losartan and chlorthalidone as active ingredients exhibits excellent dissolution characteristics of the active ingredients, and has high content uniformity and heat stability. Therefore, the complex formulation of the present invention can be used as a prophylactic or therapeutic agent for cardiovascular diseases, which has excellent quality and heat stability.

Brief Description of Drawings

[43] FIG. 1 is a graph illustrating chlorthalidone dissolution rates of tablets prepared in Examples 1 to 3 and Comparative Examples 1 and 2.

[44] FIG. 2 is a graph illustrating amlodipine dissolution rates of tablets prepared in Examples 1 to 3 and Comparative Examples 1 and 2.

[45] FIG. 3 is a graph illustrating losartan dissolution rates of tablets prepared in Examples 1 to 3 and Comparative Examples 1 and 2.

[46] FIG. 4 is a graph illustrating chlorthalidone dissolution rates of tablets prepared in Examples 1 and 4 to 7.

Best Mode for Carrying out the Invention

[47] Hereinafter, the present invention will be described in detail so that a person having ordinary skill in the art to which the present invention belongs can easily put the present invention into practice. However, the present invention can be implemented in

various different forms, and is not limited to the embodiments disclosed below.

[48] The present invention provides a pharmaceutical complex formulation, which includes:

[49] a first mixing portion including amlodipine or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof; and

[50] a second mixing portion including losartan or a pharmaceutically acceptable salt thereof,

[51] wherein the first and second mixing portions are present in a state in which the first and second mixing portions are physically separated from each other,

[52] In this case, the chlorthalidone or pharmaceutically acceptable salt thereof may have a particle size (D_{90}) of 0.5 to 50 ㎛.

[53] In the present invention, a particle size of a drug is expressed based on the particle size distribution. D_{90} refers to a particle diameter at a point in which the weight accumulated in decreasing order of the particle sizes reaches 90% when a particle size distribution of the drug obtained by measuring a particle diameter of the drug is drawn on an accumulative curve.

[54] In the present invention, the particle size of chlorthalidone or pharmaceutically acceptable salt thereof (hereinafter referred to as 'chlorthalidone') may be determined using a commercially available apparatus according to a laser diffraction/scattering method based on the Mie theory. For example, the particle size may be measured using a commercially available apparatus such as a HELOS (helium-neon laser for optical spectrometry; Sympatec Ltd.) laser diffraction device, and the like. When particles are irradiated with helium-neon laser beams, such a device is used to calculate a particle diameter distribution by allowing a light scattering pattern to be observed on a detector due to the light scattering and analyzing the light scattering pattern based on the Mie theory. As a method of measurement, any dry and wet methods are possible. However, the following examples describe the results of measurement obtained using the dry method.

[55] In the pharmaceutical complex formulation of the present invention, the chlorthalidone has a particle size of 0.5 to 50 ㎛, preferably a particle size of 0.5 to 25 ㎛, and more preferably a particle size of 0.5 to 10 ㎛.

[56] From the results of research by the present inventors, it has been found that, when chlorthalidone is pulverized into fine particles in the pharmaceutical complex formulation including amlodipine, losartan and chlorthalidone as the active ingredients, the dissolution rates, content uniformity and heat stability of the active ingredients may be improved.

[57] The smaller the particle size of chlorthalidone is, the superior such an effect is. However, when the particles of chlorthalidone are very fine with a particle size (D_{90}) of

less than 0.5 ㎛, the particles of chlorthalidone may not be easily recovered during a pulverization process and a process of preparing a complex formulation, resulting in loss of the active ingredients and degraded processability. Therefore, it is desirable that the particle size of chlorthalidone satisfies this range in the present invention.

[58] In the present invention, a method of controlling the particle size of chlorthalidone is not particularly limited. In this case, methods known in the related art may be properly chosen. Specifically, the chlorthalidone may be pulverized using conventional mills configured to pulverizing particles, such as a jet mill, a hammer mill, a ball mill, a fluid energy mill, and the like. Also, the particles of the drug may be further pulverized by a screening method performed using a sieve, or by a size classification method such as air current classification, and the like. In one exemplary embodiment of the present invention, the particle size of chlorthalidone is adjusted using an air jet mill.

[59] The complex formulation of the present invention may be prepared in various forms in which first and second mixing portions may be physically separated like a core-shell structure, and maybe formulated into preparations such as tablets or capsules. According to one preferred embodiment of the present invention, the complex formulation may be a bilayer tablet which includes a first layer including amlodipine or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof; and a second layer including losartan or a pharmaceutically acceptable salt thereof.

[60] Because amlodipine, chlorthalidone and losartan are included in the complex formulation in a state in which amlodipine and chlorthalidone are separated from losartan, the complex formulation may prevent an interaction between the active ingredients, thereby exhibiting high stability and excellent dissolution characteristics.

[61] The complex formulation of the present invention includes amlodipine or a pharmaceutically acceptable salt thereof in a first mixing portion (or a first layer) thereof.

[62] The pharmaceutically acceptable salt of amlodipine is formed from acids which form a non-toxic acid addition salt containing pharmaceutically acceptable anions, and may, for example, include hydrochloride, hydrobromide, sulfate, phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, besylate, and camsylate, but the present invention is not limited thereto. Among these, amlodipine besylate and camsylate are preferred, and camsylate is more preferred. Also, the amlodipine of the present invention includes an amlodipine racemate and (S)-amlodipine. The dose of the amlodipine or pharmaceutically acceptable salt thereof may vary depending on the age, sex and body weight of a patient, the severity of the diseases, a route of administration, and the like. Generally, the dose of amlodipine for adults (body weight: 60 kg) may be in the range of 5 to 10 mg per day.

[63] The complex formulation of the present invention includes chlorthalidone or a phar-

maceutically acceptable salt thereof in a first mixing portion thereof. The dose of the chlorthalidone or pharmaceutically acceptable salt thereof may vary depending on the age, sex and body weight of a patient, the severity of the diseases, a route of administration, and the like. Generally, the dose of chlorthalidone for adults (body weight: 60 kg) may be in the range of 12.5 to 25 mg per day.

[64] The complex formulation of the present invention includes losartan or a pharmaceutically acceptable salt thereof in a second mixing portion (or a second layer) thereof. Examples of the pharmaceutically acceptable salt of losartan may include losartan potassium salt, but the present invention is not limited thereto. The dose of the losartan or pharmaceutically acceptable salt thereof may vary depending on the age, sex and body weight of a patient, the severity of the diseases, a route of administration, and the like. Generally, the dose of losartan for adults (body weight: 60 kg) may be in the range of 40 to 100 mg per day.

[65] The weight ratio of the amlodipine or pharmaceutically acceptable salt thereof, the chlorthalidone or pharmaceutically acceptable salt thereof, and the losartan or pharmaceutically acceptable salt thereof included in the complex formulation according to the present invention may be a range of 1:1.25 to 5:5 to 20, preferably in a range of 1:2.5 to 5:10 to 20 for amlodipine, chlorthalidone, and losartan.

[66] The complex formulation of the present invention includes chlorthalidone satisfying a range of the particle size (D_{90}). In this case, the improved dissolution characteristics and content uniformity of the complex formulation are secured by physically separating a first mixing portion (or a first layer) including amlodipine and chlorthalidone and a second mixing portion (or a second layer) including losartan.

[67] When the complex formulation is prepared by simply mixing amlodipine, chlorthalidone and losartan, gelation of losartan may be problematic. Losartan shows a very good dissolution pattern when losartan is dissolved in purified water at a relatively high pH value such as pH 4.0, pH 6.8, and the like. However, losartan is very slowly dissolved because losartan is gelled at a low pH value (for example, pH 1.2, pH 2.0, etc.). Such a phenomenon may have a huge effect on the dissolution rates of the formulations in consideration that a site in which oral formulations first disintegrate and dissolve when taking the oral formulations is in stomach from which a digestive fluid with low pH is secreted. In addition, the gelation of losartan may have an influence on *in vivo* absorption of the drug. Further, as losartan is gelled as described above, amlodipine and chlorthalidone mixed with losartan may also be buried inside the gel, resulting in decreased dissolution rates.

[68] On the other hand, in the complex formulation of the present invention, a phenomenon in which dissolution of amlodipine and chlorthalidone is delayed due to the gelation of losartan may be prevented even under the low pH condition by

physically separating the first mixing portion including amlodipine and chlorthalidone and the second mixing portion including losartan to reduce an area of contact of amlodipine and chlorthalidone with losartan. Therefore, excellent dissolution rates and stability of amlodipine, chlorthalidone and losartan may be achieved. Also, content uniformity in the complex formulation and dissolution characteristics of chlorthalidone may further improved through the use of chlorthalidone whose particle size is adjusted.

[69] Specifically, the complex formulation of the present invention has a chlorthalidone dissolution rate of 85% or more within 30 minutes, more preferably a chlorthalidone dissolution rate of 85% or more within 15 minutes when a dissolution test is performed in purified water according to a paddle method for dissolution test items disclosed in the 'Chlorthalidone Tablet' Section of the United States Pharmacopoeia.

[70] Meanwhile, the pharmaceutical complex formulation of the present invention may further include pharmaceutically acceptable additives, for example, an excipient, a disintegrating agent, a binder, a lubricant, and the like.

[71] Lactose (i.e., lactose hydrate), microcrystalline cellulose, mannitol, sodium citrate, calcium phosphate, glycine, starch, or a combination thereof may, for example, be used as the excipient.

[72] Crospovidone, croscarmellose sodium, sodium starch glycolate, starch, pregelatinized starch, or a combination thereof may, for example, be used as the disintegrating agent.

[73] Polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sucrose, gelatin, acacia gum, or a combination thereof may, for example, be used as the binder.

[74] Palmitic acid, talc, magnesium stearate, zinc stearate, calcium stearate, or a combination thereof may, for example, be used as the lubricant.

[75] Preferably, the complex formulation of the present invention includes a disintegrating agent as the additive in the first mixing portion thereof.

[76] The disintegrating agent is a compound that is added to promote disintegration of the formulation in a digestive fluid, and may serve to improve the dissolution characteristics of the active ingredient, thereby making it possible to more effectively release a drug to be absorbed.

[77] Types of the disintegrating agent that may be used in the present invention are not particularly limited. For example, the aforementioned disintegrating agents may be used. Preferably, crospovidone may be used.

[78] In this case, the disintegrating agent is preferably included at a content of 2 to 7.5% by weight, more preferably 5 to 7.5% by weight, based on the total weight of the first mixing portion. When the content of the disintegrating agent in the first mixing portion is less than 2% by weight, the initial dissolution of the active ingredient may be

delayed. On the other hand, when the content of the disintegrating agent is greater than 7.5% by weight, stability of the formulation may be degraded due to an increase in generation of related compounds derived from the active ingredients during storage. Therefore, the content of the disintegrating agent is properly adjusted within this content range.

[79] Also, the complex formulation of the present invention may preferably include a disintegrating agent as the additive in the first mixing portion thereof. Specifically, the disintegrating agent may include lactose hydrate and microcrystalline cellulose.

[80] The lactose hydrate may be included at a content of 20 to 60% by weight, based on the total weight of the first mixing portion. According to another exemplary embodiment of the present invention, the weight ratio of the lactose hydrate and the microcrystalline cellulose, which are present in this content range, may be in a range of 1:0.5 to 1:2.

[81] When lactose hydrate is used in this content range as a water-soluble excipient, the lactose hydrate may serve to form wet channels in the formulation to promote dissolution of the active ingredients, resulting in a rapid dissolution pattern. However, when the content of lactose hydrate is less than this content range, it is impossible to achieve the rapid dissolution pattern. On the other hand, when the content of lactose hydrate is greater than this content range, a time required to completely dissolve lactose hydrate may be extended, and thereby a time to dissolve the active ingredients is rather extended. Also, when microcrystalline cellulose is used in this content range, preparations may be smoothly molded during a tablet-pressing process. However, when the content of microcrystalline cellulose is less than this content range, a difficulty in tablet pressing may be caused. On the other hand, when the content of microcrystalline cellulose is greater than this content range, excessively large formulations may be produced.

[82] In addition, the pharmaceutical complex formulation of the present invention may further include a pH control agent, a suspending agent, a preservative, a flavoring agent, a coloring agent, a sweetening agent, an absorbent, a solubilizing agent, and the like, when necessary. The contents of the additives may be properly adjusted when necessary, but the present invention is not particularly limited thereto.

[83] In the complex formulation of the present invention, the first and second mixing portions may be granulated by a conventional granulation method, for example, a compacting granulation method, and the resulting granules may be then pressed into tablets. According to another exemplary embodiment, the first and second mixing portions may be in the form of granules subjected to a roller compaction process. As described above, when the compacted/granulated first and second mixing portions are pressed into bilayer tablets, the amlodipine, chlorthalidone and losartan exhibit

excellent dissolution patterns.

[84] The aforementioned pharmaceutical complex formulation of the present invention may be prepared by the method of preparing which includes a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive.

[85] Also, the pharmaceutical complex formulation of the present invention may be prepared into bilayer tablets by the method of preparing which includes a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, and granulating the resulting mixture; b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, and granulating the resulting mixture; and c) tablet-pressing the granules prepared in steps a) and b) into a bilayer tablet.

[86] When the pharmaceutical complex formulation of the present invention and the bilayer tablet are prepared according to the method, the method may further include adjusting a particle size of each of the active ingredients prior to step a). In this case, the adjusting of the particle size may be performed using the aforementioned method of adjusting the particle size.

[87] The aforementioned pharmaceutical complex formulation of the present invention may be used to prevent or treat cardiovascular diseases such as angina, hypertension, arteriospasm, cardiac arrhythmia, cardiomegaly, cerebral infarction, congestive heart failure, and myocardial infarction.

Mode for the Invention

[88] Hereinafter, preferred exemplary embodiments of the present invention will be described in order to aid in understanding the present invention. However, it will be apparent to those skilled in the art that the following examples are given herein for the purpose of illustrations only, and various changes and modifications can be made to the embodiments of the present invention without departing from the scope of the present invention. Thus, it should be understood that the present invention covers all such changes and modifications provided they are within the scope of the appended claims and their equivalents.

[89]

[90] **[EXAMPLES]**

[91] **Example 1: Preparation of bilayer tablets containing pulverized chlorthalidone**

[92] Powder of chlorthalidone was ground (at a grinding pressure of 1.5 bar) using an air

jet mill (AS50, Hosokawa Micron) to prepare a source material having a particle size (D_{90}) of 10.4 m. Thereafter, amlodipine camsylate, pulverized chlorthalidone, lactose hydrate, microcrystalline cellulose, and crospovidone were mixed according to the compositions listed in the following Table 1, and the resulting mixture was compressed at a hydraulic pressure of approximately 6.5 MPa, a hopper speed of 5 rpm and a roller speed of 1 rpm using a roller compactor (TF-1-A60, Freund vector) to form flake-shaped granules. The flake-shaped granules were screened through a sieve having a mess size of 1.0 mm. Magnesium stearate screened through a 24 mesh sieve was added to the granules, and finally mixed in a mixer to prepare an amlodipine/chlorthalidone granule part.

[93] Also, losartan potassium, microcrystalline cellulose, and crospovidone were mixed, and the resulting mixture was compressed at a hydraulic pressure of approximately 6.0 MPa, a hopper speed of 5 rpm and a roller speed of 1 rpm using a roller compactor (TF-1-A60, Freund vector) to form flake-shaped granules. The flake-shaped granules were screened through a sieve having a mess size of 0.8 mm. Magnesium stearate screened through a 24 mesh sieve was added to the resulting granules, and finally mixed in a mixer to prepare a losartan granule part.

[94] Next, a complex bilayer tablet, which included the amlodipine/chlorthalidone granule part (a first layer; an upper layer) and the losartan granule part (a second layer; an under layer), was prepared using a tablet press (Autotab-200TR, Ichihashi Seiki Co.).

[95] [Table 1]

Items	Components	Content (mg)
Amlodipine/chlorthalidone-containing layer (upper layer)	Amlodipine camsylate	7.84
	Chlorthalidone	25.0
	Lactose hydrate	100.96
	Microcrystalline cellulose	54.0
	Crospovidone	10
	Magnesium stearate	2.2
Total weight of upper layer		200.0
Losartan-containing layer (lower layer)	Losartan potassium	100.0
	Microcrystalline cellulose	206.0
	Crospovidone	12.0
	Magnesium stearate	2.0
Total weight of lower layer		320.0
Total weight of tablet		520.0

[96]

[97] **Examples 2 to 3 and Comparative Examples 1 to 2: Preparation of bilayer tablets having different particle sizes of chlorthalidone**

[98] Complex bilayer tablets were prepared in the same manner as in Example 1 according to the compositions listed in the following Table 2, except that chlorthalidone having different particle sizes were used.

[99] [Table 2]

	Chlorthalidone particle size (D_{90}, ㎛)
Example 2	20.5
Example 3	31.6
Comparative Example 1	50.4
Comparative Example 2	72.4

[100]

[101] **Examples 4 to 7: Preparation of bilayer tablets in which upper layer has disintegrating agent in different ratios**

[102] Complex bilayer tablets were prepared in the same manner as in Example 1, except that the disintegrating agent of the upper layer was used in different ratios with respect

to the total weight of the upper layer as listed in the following Table 3. In this case, chlorthalidone having a particle size (D_{90}) of 10.4 ㎛ was used, and the content of lactose hydrate was adjusted with an increasing/decreasing content of the disintegrating agent so that the total weight of the upper layer was identically set to 200 mg.

[103] [Table 3]

Components	Example 4	Example 5	Example 6	Example 7
Crospovidone (mg)(Ratio based on the total weight of upper layer)	0(0.0%)	5(2.5%)	15(7.5%)	20(10%)

[104]

[105] **Test Example 1: Measurement of dissolution rate of oral complex formulation according to particle size (D_{90}) of chlorthalidone**

[106] The tablets prepared in Examples 1 to 3 and the complex bilayer tablets prepared in Comparative Examples 1 and 2 were tested under the following conditions to measure dissolution rates of amlodipine, chlorthalidone and losartan with time.

[107] - Dissolution Conditions -

[108] Equipment: Device used in second method (paddle method) of dissolution test method for dissolution test items disclosed in the 'Chlorthalidone Tablet' Section of the United States Pharmacopoeia.

[109] Test Solution: Purified water, 900 mL

[110] Dissolution Temperature: 37 °C

[111] Number of Revolutions: 75 rpm

[112]

[113] - Analytical Conditions -

[114] Detector: Ultraviolet Absorptiometer (Wavelength for measurement: 254 nm)

[115] Column: Column (150 × 4.6 nm, 3 ㎛) filled with octadecylsilylated silica gel for liquid chromatography

[116] Mobile phase: Buffer:Acetonitrile = 60:40

[117] (Method of preparing a buffer: 6 mM sodium 1-hexanesulfonate/0.05% (v/v) phosphoric acid: 1.24 g of sodium 1-hexanesulfonate monohydrate is put into a 1 L flask, and 0.5 mL of phosphoric acid is carefully added thereto. Thereafter, the resulting mixture is dissolved in purified water, diluted, and then thoroughly mixed.)

[118] Column Temperature: 45 °C

[119] Flow Rate: 1.3 mL/min

[120] Injection Volume: 10 ㎕

[121] Criteria for evaluation: Dissolution rate of 85% or more at a time point of 15 minutes

[122] The results of measurement of the dissolution rates are shown in FIGS. 1 to 3.

[123] As shown in FIGS. 2 and 3, both of the two components (amlodipine and losartan) exhibited the dissolution rates suitable for the criteria for evaluation in the case of Examples 1 to 3 and Comparative Examples 1 and 2.

[124] Meanwhile, as shown in FIG. 1, chlorthalidone had a significant difference in dissolution rate depending on the particle size of chlorthalidone. The tablets of Examples 1 to 3 including pulverized chlorthalidone had a rapid dissolution rate at the beginning, and had a dissolution rate suitable for the criteria for evaluation. However, the tablets Comparative Examples 1 and 2 including chlorthalidone having a particle size of 50 ㎛ or more had a relatively low initial dissolution rate, which was unsuitable for the criteria for evaluation.

[125] From the results of experiments, it can be seen that the dissolution rates of the active ingredients in the complex formulation including amlodipine, losartan and chlorthalidone were improved by adjusting the particle size of chlorthalidone within a certain range.

[126]

[127] **Test Example 2: Measurement of content uniformity of oral complex formulation**

[128] To check the content uniformity of the complex formulation according to the particle size of chlorthalidone, an experiment was performed according to the content uniformity test method specified in the General Test Methods of the Korean Pharmacopoeia.

[129] The tablets prepared in Examples 1 to 3 and Comparative Examples 1 and 2 were tested according to the content uniformity test method specified in the General Test Methods of the Korean Pharmacopoeia. The contents were analyzed by HPLC using the analytical method disclosed in Test Example 1, and the decision value calculated accordingly. The results are listed in the following Table 4.

[130] [Table 4]

	Example 1	Example 2	Example 3	Comparative Example 1	Comparative Example 2
Chlorthalidone	2.9	3.0	6.6	10.6	14.1
Amlodipine	3.4	2.8	3.2	2.5	2.7
Losartan	2.3	2.7	2.4	2.4	2.6

[131]

[132] As seed from the results of Table 4, the decision values for content uniformity were significantly enhanced when the content uniformities of the tablets of Examples 1 to 3 in which the particle size (D_{90}) of chlorthalidone was less than or equal to ap-

proximately 50 ㎛ were compared to those of the complex bilayer tablets of Comparative Examples 1 and 2 in which the particle size of chlorthalidone was greater than approximately 50 ㎛.

[133] From these facts, it can be seen that the mixing uniformity and content uniformity of the complex formulation including amlodipine, losartan and chlorthalidone were improved through the use of chlorthalidone having a certain range of particle size.

[134]

[135] **Test Example 3: Measurement of dissolution rate of oral complex formulation according to ratio of disintegrating agent in upper layer**

[136] The tablets prepared in Examples 1 and 4 to 7 were tested under the same conditions as in Test Example 1 to measure a dissolution rate of chlorthalidone with time. The results of measurement are shown in FIG. 4.

[137] As shown in FIG. 4, the tablet of Example 5 including the disintegrating agent at 2.5% by weight with respect to the weight of the first layer had a relatively slow initial dissolution rate, but the initial dissolution rate of the tablet was suitable for the criteria for evaluation, and the tablet of Example 4 including no disintegrating agent in the first layer thereof exhibited lesser dissolution characteristics.

[138] Meanwhile, it was confirmed that the tablets of Examples 1, 6 and 7 including the disintegrating agent at 5 to 10% by weight with respect to the weight of the first layer had a rapid initial dissolution rate, which was suitable for the criteria for evaluation.

[139]

[140] **Test Example 4: Heat stability test on oral complex formulation according to ratio of disintegrating agent in upper layer**

[141] The tablets of Examples 1 and 4 to 7 were packaged in high-density polyethylene (HDPE) bottles, and then stored for 14 days under a stress condition (60 °C). Thereafter, changes in contents of the related compounds were measured to evaluate the stability of the tablets. The results are listed in the following Table 5.

[142] [Table 5]

Samples	Initial			When packaged in HDPE bottle and stored at 60 °C for 14 days		
	Amlodipine-derived related compound (%)	Chlorthalidone-derived related compound (%)	Losartan-derived related compound (%)	Amlodipine-derived related compound (%)	Chlorthalidone-derived related compound (%)	Losartan-derived related compound (%)
Example 1	0.00	0.76	0.02	0.04	0.92	0.02
Example 4	0.00	0.79	0.01	0.04	0.94	0.04
Example 5	0.01	0.78	0.04	0.05	0.92	0.03
Example 6	0.00	0.79	0.01	0.07	0.97	0.04
Example 7	0.01	0.76	0.02	0.21	1.63	0.03

[143]

[144] As seen from Table 5, it was confirmed that the tablets of Examples 1 and 4 to 6 were stable to heat because the related compounds of amlodipine, chlorthalidone and losartan were less generated under the heat stress condition. However, the generation of the amlodipine- and chlorthalidone-derived related compounds increased two-fold in the tablet of Example 7, compared to the tablet of Example 1.

[145] From these facts, it can be seen that the complex formulation, in which the content of the disintegrating agent was greater than 10% by weight based on the total weight of the first mixing portion, had no sufficiently secured stability according to a change with time under the heat stress condition.

[146] From the results of Test Examples 1 and 2, it can be seen that the complex formulations of the present invention exhibited further improved dissolution characteristics and content uniformity of the active ingredients when chlorthalidone with controlled particle size was used in the complex formulation.

[147] From the results of Test Examples 3 and 4, it can also be seen that the complex formulations of the present invention exhibited superior dissolution characteristics when the complex formulations included the disintegrating agent in the first mixing portion thereof. Also, it can be seen that the content of the disintegrating agent was preferably in a range of 2 to 7.5% by weight, based on the total weight of the first mixing portion of the complex formulation in order to secure the heat stability as well as the dissolution characteristics.

Claims

[Claim 1] A pharmaceutical complex formulation comprising:
a first mixing portion comprising amlodipine or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof; and
a second mixing portion comprising losartan or a pharmaceutically acceptable salt thereof,
wherein the first and second mixing portions are present in a state in which the first and second mixing portions are physically separated from each other, and
the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 50 ㎛.

[Claim 2] The pharmaceutical complex formulation of claim 1, wherein the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 25 ㎛.

[Claim 3] The pharmaceutical complex formulation of claim 2, wherein the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 10 ㎛.

[Claim 4] The pharmaceutical complex formulation of claim 1, wherein the pharmaceutical complex formulation is a bilayer tablet comprising:
a first layer comprising amlodipine or a pharmaceutically acceptable salt thereof, and chlorthalidone or a pharmaceutically acceptable salt thereof; and
a second layer comprising losartan or a pharmaceutically acceptable salt thereof.

[Claim 5] The pharmaceutical complex formulation of claim 4, wherein the complex formulation has a chlorthalidone dissolution rate of 85% or more within 30 minutes when a dissolution test is performed in purified water according to a paddle method for dissolution test items disclosed in the 'Chlorthalidone Tablet' Section of the United States Pharmacopoeia.

[Claim 6] The pharmaceutical complex formulation of claim 4, wherein the complex formulation has a chlorthalidone dissolution rate of 85% or more within 15 minutes when a dissolution test is performed in purified water according to a paddle method for dissolution test items disclosed in the 'Chlorthalidone Tablet' Section of the United States Pharmacopoeia.

[Claim 7] The pharmaceutical complex formulation of claim 1, wherein the first mixing portion further comprises a disintegrating agent as an additive.

[Claim 8] The pharmaceutical complex formulation of claim 7, wherein the disintegrating agent comprises crospovidone, croscarmellose sodium, sodium starch glycolate, starch, pregelatinized starch, or a combination thereof.

[Claim 9] The pharmaceutical complex formulation of claim 7, wherein the disintegrating agent is included at a content of 2 to 7.5% by weight, based on the total weight of the first mixing portion.

[Claim 10] The pharmaceutical complex formulation of claim 1, wherein the first mixing portion comprises lactose hydrate and microcrystalline cellulose as additives.

[Claim 11] The pharmaceutical complex formulation of claim 1, wherein the first and second mixing portions are in the form of granules subjected to a roller compaction process.

[Claim 12] A method of preparing a pharmaceutical complex formulation, comprising:

a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and

b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive,

wherein the chlorthalidone or pharmaceutically acceptable salt thereof has a particle size (D_{90}) of 0.5 to 50 ㎛.

[Claim 13] The method of claim 12, which comprises:

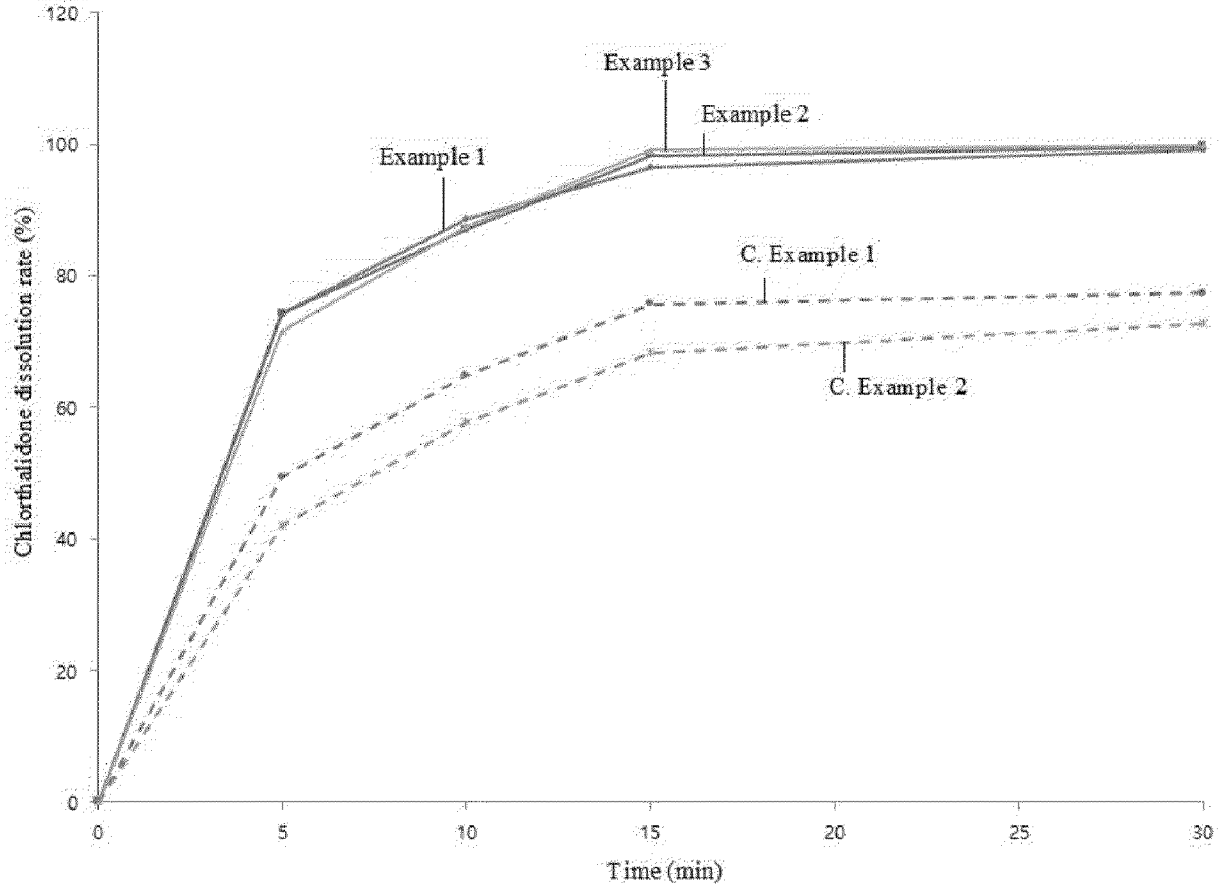
a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, and granulating the resulting mixture;

b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, and granulating the resulting mixture; and

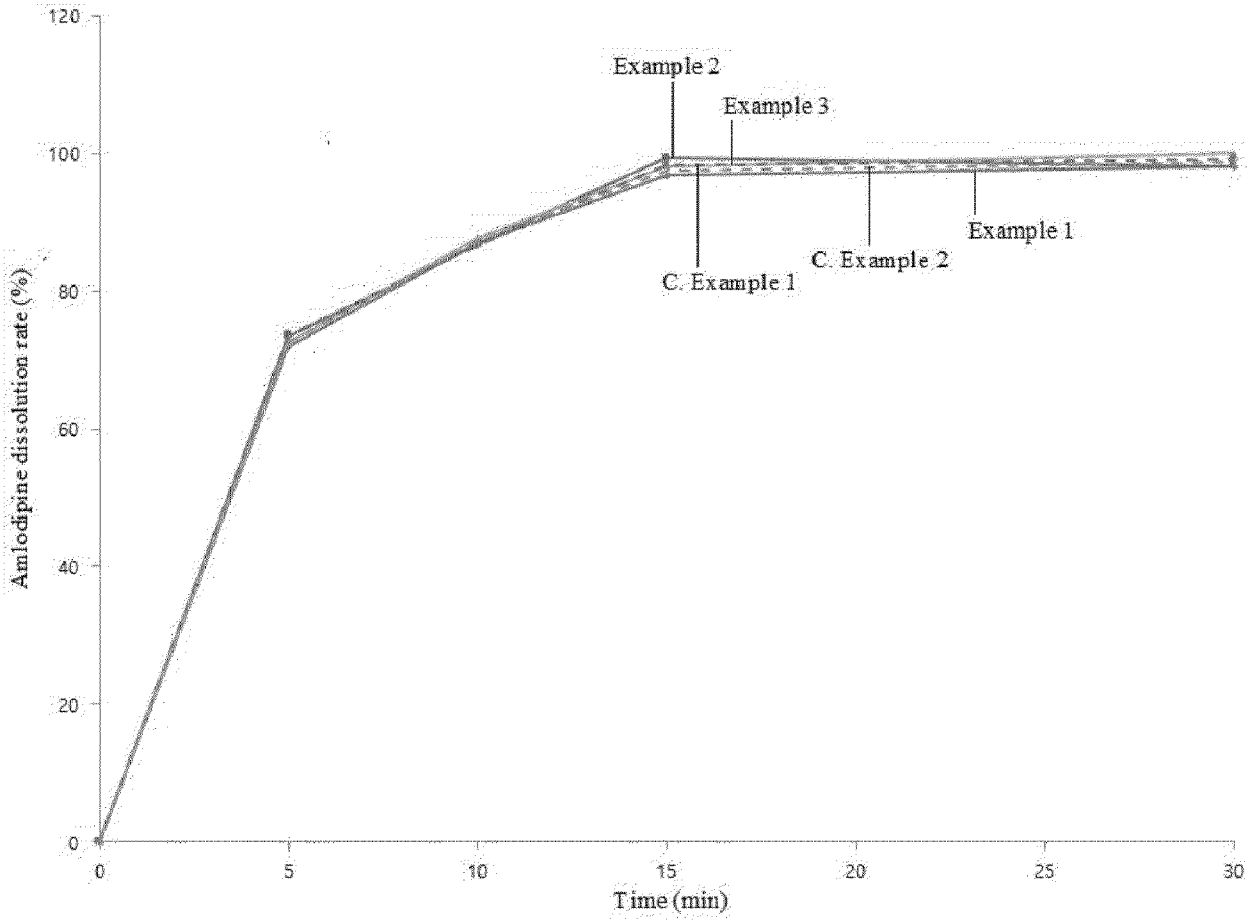
c) tablet-pressing the granules prepared in steps a) and b) into a bilayer tablet.

[Claim 14] The pharmaceutical complex formulation of claim 1, wherein the pharmaceutical complex formulation is used to prevent or treat cardiovascular diseases.

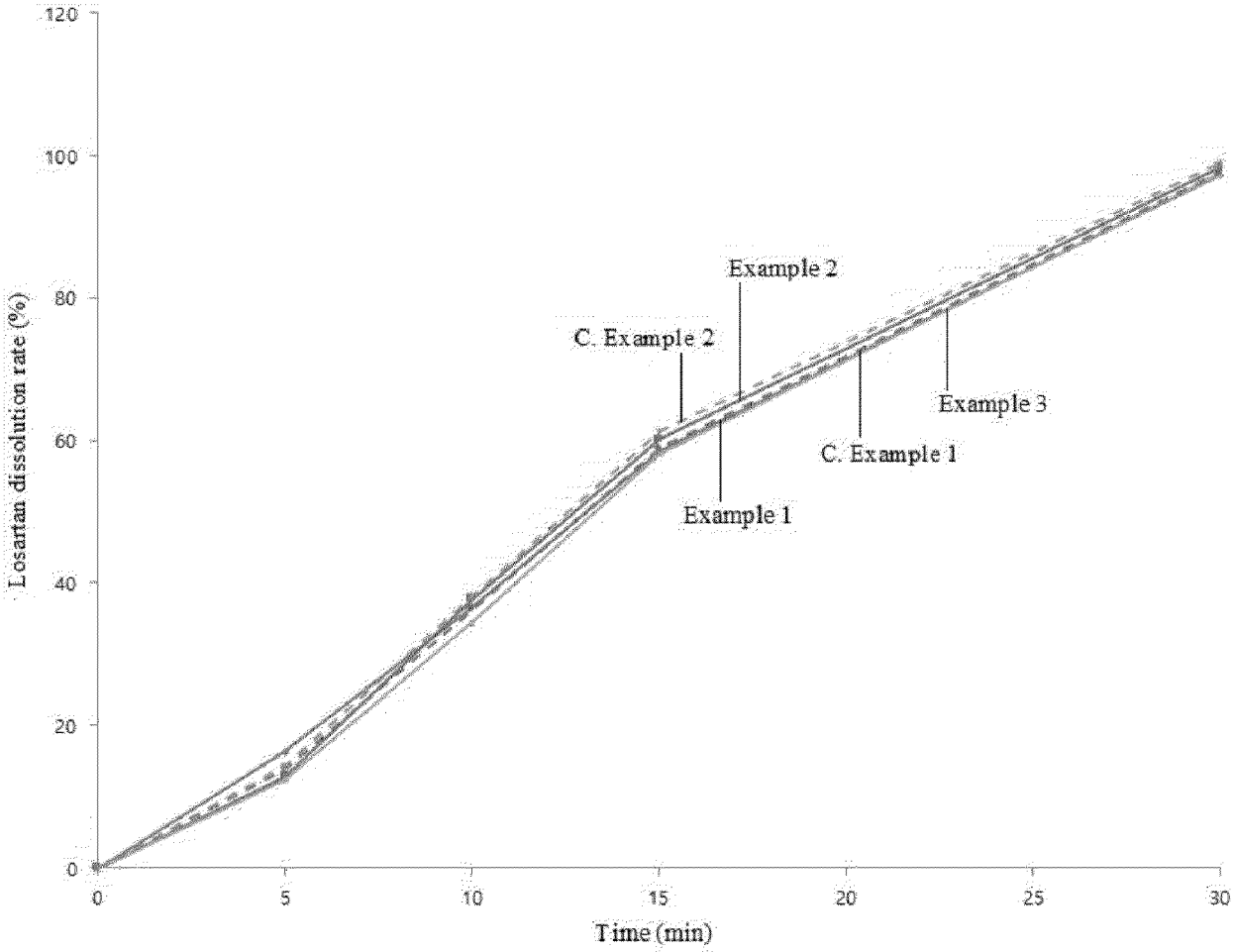
[Fig. 1]


Example 3
Example 2
Example 1
C. Example 1
C. Example 2
Chlorthalidone dissolution rate (%)
Time (min)
0
20
40
60
80
100
120
0
5
10
15
20
25
30

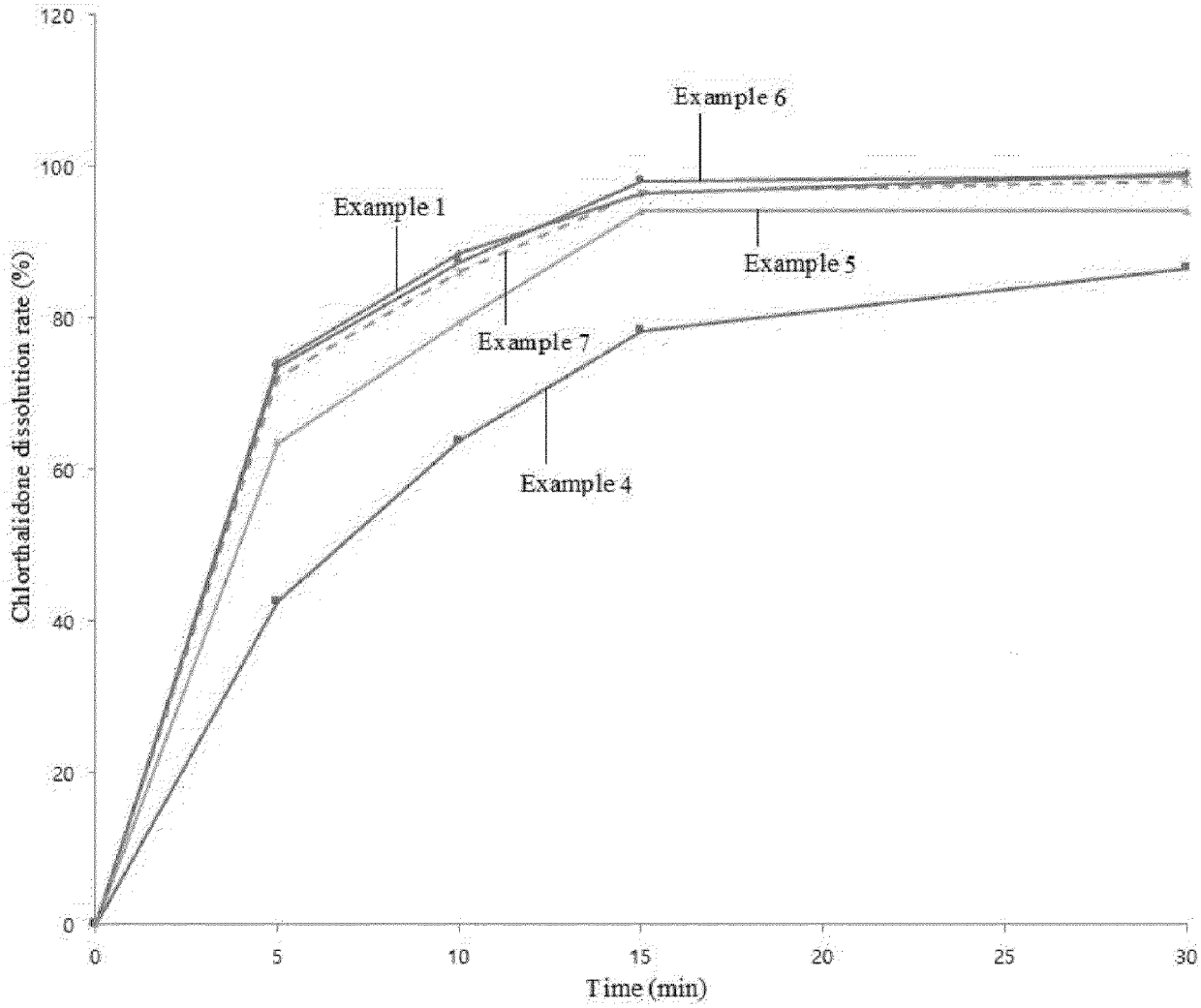
[Fig. 2]


Example 2
Example 3
Example 1
C. Example 2
C. Example 1
Amlodipine dissolution rate (%)
Time (min)
0
20
40
60
80
100
120
0
5
10
15
20
25
30

[Fig. 3]


120
100
80
60
40
20
0
Losartan dissolution rate (%)
0
5
10
15
20
25
30
Time (min)
Example 2
C. Example 2
Example 3
C. Example 1
Example 1

[Fig. 4]


120
100
80
60
40
20
0
Chlorthalidone dissolution rate (%)
0
5
10
15
20
25
30
Time (min)
Example 6
Example 1
Example 5
Example 7
Example 4