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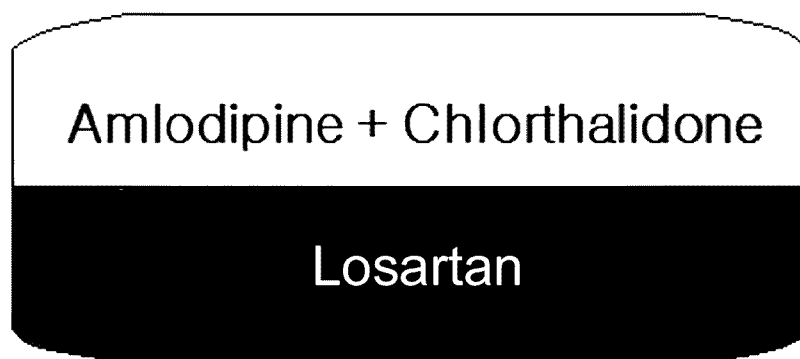
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(54) Title: PHARMACEUTICAL COMPLEX FORMULATION COMPRISING AMLODIPINE, LOSARTAN AND CHLOROTHALIDONE



(57) Abstract: The present invention provides a pharmaceutical complex formulation comprising a first mixture including amlodipine and chlorthalidone and a second mixture including losartan, which has an improved dissolution and stability. The complex formulation according to the present invention may achieve improved preventive or therapeutic effects for cardiovascular diseases by actuating different mechanism of amlodipine, losartan and chlorthalidone, and exhibits high dissolution rates of amlodipine, losartan and chlorthalidone and improved storage stability, due to the minimized drug interactions, and therefore, it is useful in the fields of pharmaceuticals and medicine.



## Description

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

#### **Technical Field**

- [1] The present invention relates to a pharmaceutical complex formulation comprising amlodipine, losartan and chlorthalidone, and more specifically, to a pharmaceutical complex formulation comprising a first mixture containing amlodipine and chlorthalidone and a second mixture containing losartan, which has an improved dissolution and stability.

[2]

#### **Background Art**

- [3] Approximately 90~95% of patients with hypertension have essential (primary) hypertension, of which the cause is not found. Although the underlying cause of essential hypertension is not clear, increase of cardiac output (the volume of blood being pumped by the heart whenever it contracts) or increased peripheral vascular resistance is known to cause it. Risk factors for hypertension are physiological and environmental factors such as drinking, smoking, old age, lack of exercise, obesity, dietary habits eating salty food, stress, etc. Furthermore, since hypertension has a tendency toward family history, when both parents are hypertensive, 80% of their children may be hypertensive later, and when one of parents is hypertensive, 25~50% of their children may be hypertensive.
- [4] The primary goal in the treatment of hypertension is to prevent damage of internal organs resulting from hypertension by maintaining the blood pressure within a normal range. Accordingly, improvement of lifestyle is as important as taking medicine. Patients suffering from hypertension aim to control blood pressure to less than 140/90 mmHg. If the patients have diabetes or renal diseases, the blood pressure goal should be less than 130/80 mmHg.
- [5] Treatment of hypertension may reduce mortality from a stroke or cardiovascular diseases. Controlling blood pressure of the patients with hypertension may reduce the occurrence of a stroke by 35~40%, myocardial infarction by 20~25%, and heart failure by 50% or higher. Reduction of systolic blood pressure by 5 mmHg may decrease the mortality from a stroke by 14%, the mortality from coronary artery diseases by 9%, and total mortality by 7%. Furthermore, since the control of blood pressure relates to dementia, a proper control of blood pressure of hypertensive patients may reduce the occurrence of dementia.

- [6] Thus, it is important for patients with hypertension to prevent cardiovascular complications by consistently controlling blood pressure. Antihypertensive agents are required to administer for a long time, and advanced therapy using a combination of two or more drugs having different pharmacological actions may result in improved preventive or therapeutic effects, while lowering side effects arising from the long term administration of a single drug by reducing the dose.
- [7] Notable antihypertensive drugs are divided into diuretics, sympatholytic agents and vasodilators according to their pharmacological action. Vasodilators are widely prescribed antihypertensive drugs, and they are divided into several groups according to their pharmacological action which include ACE (angiotensin converting enzyme) inhibitors, angiotensin II receptor antagonists and calcium channel blockers.
- [8] Amlodipine is the generic name for 3-ethyl-5-methyl-2-(2-aminoethoxy-methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydro-3,5-pyridine dicarboxylate. Amlodipine besylate is currently marketed as Norvasc® (trade name). Camsylate salt of amlodipine, which has superior physical properties such as solubility or stability compared with besylate salt, has been disclosed in Korean Patent Registration No. 452491, and is currently marketed as Amodipin® (trade name). Amlodipine is a calcium channel blocker which is useful in treating cardiovascular diseases such as angina, hypertension and congestive heart failure.
- [9] Losartan is the generic name for 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-methanol, which has been disclosed in U.S. Patent Nos. 5,608,075; 5,138,069; and 5,153,197. Losartan potassium is commercially available as Cozaar® (trade name). Losartan blocks the interaction of vasoconstrictor angiotensin II and its receptor, and is mainly used for treating hypertension and heart failure. It is also used for treating ischemic peripheral circulatory disorder, myocardial ischemia (angina pectoris), diabetic neuropathy and glaucoma, and also for preventing the progression of post-myocardial infarction heart failure.
- [10] A combined formulation comprising amlodipine and losartan having different pharmacological activities has an advantage that it is more effective on preventing or treating hypertension and cardiovascular diseases than a single drug, and it reduces side effects resulting from a single drug and improves patient compliance. The combined formulation has been disclosed in Korean Patent Registration Nos. 1160151 and 1232296, and is commercially available as Amosartan® (trade name).
- [11] Chlorthalidone is the generic name for benzenesulfonamide-2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl), which is currently marketed as Hygroton® (trade name). Chlorthalidone, a thiazide diuretic, blocks Na<sup>+</sup>/Cl<sup>-</sup> symporter of renal distal tubules, thereby inhibiting the reuptake of Na<sup>+</sup> and Cl<sup>-</sup> and

increasing the excretion of  $K^+$ , which results in water retention in urine. Recently, apart from hydrochlorothiazide which has been a representative thiazide diuretic, chlorthalidone has been newly noted and recommended, instead of hydrochlorothiazide, in a guideline on the treatment of hypertension of National Institute for Health and Care Excellence (NICE).

[12] Chlorthalidone has a half-life of 50 to 60 hours and a reaction time of 48 to 72 hours, and it is more useful for controlling blood pressure at night since it has longer duration of action and reaction time compared with hydrochlorothiazide having a half-life of 9 to 10 hours and a reaction time of 16 to 24 hours.

[13] Although a combined formulation comprising amlodipine, losartan and chlorthalidone having different pharmacological activities is increasingly required for effective treatment of cardiovascular diseases in clinical area, it could have not become commercialized since the interaction of drugs may decrease dissolution rate and stability and the development of combined formulation is highly difficult.

[14] While conducting a study to solve the above problems of the combined formulation, the present inventors have found that the dissolution and stability vary considerably depending on the form and manufacturing method of a complex bilayer tablet and the composition, and have developed a complex formulation comprising amlodipine, losartan and chlorthalidone which has an improved dissolution and stability.

[15]

## **Disclosure of Invention**

### **Technical Problem**

[16] An object of the present invention is to provide a pharmaceutical complex formulation comprising amlodipine, losartan and chlorthalidone, which is very effective on treating cardiovascular diseases by actuating different mechanism, and has high dissolution rates of amlodipine, losartan and chlorthalidone and improved storage stability.

[17]

### **Solution to Problem**

[18] The present invention provides a pharmaceutical complex formulation for preventing or treating cardiovascular diseases, the formulation comprising:

[19] a first mixture including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and

[20] a second mixture including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive,

[21] wherein the first mixture and the second mixture are present in a form separated

physically from each other.

[22]

### **Advantageous Effects of Invention**

[23] The complex formulation according to the present invention comprising amlodipine, losartan and chlorthalidone may achieve improved preventive or therapeutic effects for cardiovascular diseases by actuating different mechanism, and exhibits high dissolution rates of amlodipine, losartan and chlorthalidone and improved storage stability, due to the minimized drug interactions, and therefore, it is useful in the fields of pharmaceuticals and medicine.

[24]

### **Brief Description of Drawings**

[25] Fig. 1 is a schematic diagram of the bilayer tablet according to an embodiment of the present invention.

[26] Fig. 2 is a graph showing the amlodipine dissolution rate observed for the tablets prepared in Example 1 and Comparative Example 1.

[27] Fig. 3 is a graph showing the chlorthalidone dissolution rate observed for the tablets prepared in Example 1 and Comparative Example 1.

[28] Fig. 4 is a graph showing the losartan dissolution rate observed for the tablets prepared in Example 1 and Comparative Example 1.

[29] Fig. 5 is a graph showing the amlodipine dissolution rate observed for the tablets prepared in Examples 1 to 3 and Comparative Examples 3 to 6.

[30] Fig. 6 is a graph showing the chlorthalidone dissolution rate observed for the tablets prepared in Examples 1 to 3 and Comparative Examples 3 to 6.

[31] Fig. 7 is a graph showing the losartan dissolution rate observed for the tablets prepared in Examples 1 to 3 and Comparative Examples 3 to 6.

[32] Fig. 8 is a graph showing the amlodipine dissolution rate observed for the tablets prepared in Example 1 and Comparative Examples 7 and 8.

[33] Fig. 9 is a graph showing the chlorthalidone dissolution rate observed for the tablets prepared in Example 1 and Comparative Examples 7 and 8.

[34] Fig. 10 is a graph showing the losartan dissolution rate observed for the tablets prepared in Example 1 and Comparative Examples 7 and 8.

[35] Fig. 11 is a graph showing the amlodipine dissolution rate observed for the tablets prepared in Examples 4 to 6 and Comparative Examples 9 to 12.

[36] Fig. 12 is a graph showing the chlorthalidone dissolution rate observed for the tablets prepared in Examples 4 to 6 and Comparative Examples 9 to 12.

[37] Fig. 13 is a graph showing the losartan dissolution rate observed for the tablets prepared in Examples 4 to 6 and Comparative Examples 9 to 12.

[38]

### **Best Mode for Carrying out the Invention**

[39] The present invention provides a pharmaceutical complex formulation for preventing or treating cardiovascular diseases, the formulation comprising a first mixture including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and a second mixture including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, wherein the first mixture and the second mixture are present in a form separated physically from each other.

[40] In the complex formulation of the present invention, the first mixture and the second mixture are physically separated from each other. Since the formulation comprises separately amlodipine and losartan, the interaction of amlodipine and losartan may be prevented, which achieves high stability.

[41] In one embodiment of the present invention, the complex formulation may be a bilayer tablet comprising a first layer including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and a second layer including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive (see Fig. 1). In addition to the bilayer tablet, the formulation according to the present invention may be prepared in various forms (for example, core-shell structure) in which the first mixture may be physically separated from the second mixture.

[42] The complex formulation of the present invention includes amlodipine or a pharmaceutically acceptable salt thereof in the first mixture (or the first layer). The pharmaceutically acceptable salts of amlodipine are those prepared from an acid which forms non-toxic acid addition salts comprising pharmaceutically acceptable anions, and include, for example, hydrochloride, hydrobromide, sulfate, phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, besylate and camsylate salts, but are not limited thereto. Among these salts, preferred are the amlodipine besylate and camsylate, and more preferred is the amlodipine camsylate. Also, amlodipine used in the present invention may include an amlodipine racemate and (S)-amlodipine. Although the dose of amlodipine or its pharmaceutically acceptable salts varies depending on age, sex or body weight of patients, severity of the diseases, route of administration, etc., a typical dose for adults (body weight: 60 kg) may be in the range of about 5 to 10 mg per day.

[43] The complex formulation of the present invention includes chlorthalidone or a pharmaceutically acceptable salt thereof in the first mixture. Although the dose of chlorthalidone or its pharmaceutically acceptable salts varies depending on age, sex or

body weight of patients, severity of the diseases, route of administration, etc., a typical dose for adults (body weight: 60 kg) may be in the range of about 12.5 to 25 mg per day.

- [44] The complex formulation of the present invention includes losartan or a pharmaceutically acceptable salt thereof in the second mixture (or the second layer). An example of the pharmaceutically acceptable salt of losartan is losartan potassium, but is not limited thereto. Although the dose of losartan or its pharmaceutically acceptable salts varies depending on age, sex or body weight of patients, severity of the diseases, route of administration, etc., a typical dose for adults (body weight: 60 kg) may be in the range of about 50 to 100 mg per day.
- [45] In the complex formulation of the present invention, amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof and losartan or a pharmaceutically acceptable salt thereof may be used in amounts corresponding to a weight ratio in the range of 1:1.25~5:5~20, preferably 1:2.5~5:10~20.
- [46] In the complex formulation of the present invention, the pharmaceutically acceptable additives, which may be used in the first mixture and the second mixture, may be, for example, pharmaceutically acceptable carriers or excipients. The pharmaceutically acceptable carriers or excipients may include, for example, lactose hydrate, microcrystalline cellulose, mannitol, sodium citrate, calcium phosphate, glycine, starch, disintegrants (e.g., croscopovidone, copovidone, sodium starch glycolate, croscarmellose sodium and a specific composite silicate) and binders (e.g., polyvinylpyrrolidone, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), sucrose, gelatin and acacia gum).
- [47] In one embodiment, the complex formulation of the present invention may comprise an additive selected from the group consisting of lactose hydrate, microcrystalline cellulose, mannitol, starch and combinations thereof in the first mixture. Preferred additive comprises lactose hydrate and/or microcrystalline cellulose. The lactose hydrate may be comprised in an amount of 20 to 60% by weight based on the total amount of the first mixture. In another embodiment of the present invention, the weight ratio of lactose hydrate and microcrystalline cellulose may be 1:0.5 to 1:2 within the above range of amount.
- [48] When lactose hydrate is used in an amount of the above range as a water-soluble excipient, it accelerates dissolution of active substances by forming wetting channel in the formulation, thereby resulting in rapid dissolution. While an amount less than the above range could not accomplish the rapid dissolution, an amount exceeding the above range extends the time for lactose hydrate to be dissolved completely, thereby delaying dissolution of active substances. When microcrystalline cellulose is used in an

amount of the above range, it accomplishes smooth formulation molding in tablet pressing. While an amount less than the above range causes difficulties in tablet pressing, an amount exceeding the above range results in excessively large formulation to be produced.

[49] Accordingly, the dissolution rates of amlodipine, chlorthalidone and losartan may be considerably improved by using lactose hydrate and microcrystalline cellulose in an amount of the above range.

[50] In one embodiment of the present invention, the first mixture and the second mixture of the complex formulation may be granulated by conventional granulation method, for example, compression granulation method, and then tablet pressed. In another embodiment, the first mixture and the second mixture may be granule forms prepared by roller compression process. The results of the Test Examples of the present invention shows that the bilayer tablets comprising the first mixture and the second mixture prepared by compression granulation exhibit enhanced dissolution rates of amlodipine, chlorthalidone and losartan, and excellent dissolution of amlodipine and chlorthalidone.

[51] When a combined formulation of amlodipine, chlorthalidone and losartan is prepared by simple mixture of the drugs, gelation of losartan disadvantageously occurs. Losartan shows very good dissolution pattern in purified water or at a relatively high pH (e.g., pH 4.0 or pH 6.8), but it is very slowly released at a low pH (e.g., pH 1.2 or pH 2.0) because of its gelation. Considering that oral formulations disintegrate and dissolve in stomach first in which digestive fluid of low pH is secreted, gelation of losartan may have a decisive effect on the dissolution rate of the formulation, and also on the uptake of the drugs. Furthermore, in the combined formulation, amlodipine and chlorthalidone mixed with losartan may be locked in the inside of the gel due to the gelation of losartan and their dissolutions decrease. Such decrease of dissolution may be confirmed by Comparative Example 1 of the present specification, in which a single-layer tablet of Comparative Example 1 prepared by dry-type direct compression of simple mixture of the three components shows dissolution rates of amlodipine and chlorthalidone much lower than general dissolution standards (dissolution rate of 80% or higher in artificial gastric juice of pH 1.2 for 30 minutes).

[52] Meanwhile, in the complex formulation of the present invention, the gelation of losartan may be prevented by physically separating the first mixture including amlodipine and chlorthalidone from the second mixture including losartan and reducing the area contacting with losartan, thereby accomplishing improved dissolution and stability of amlodipine, chlorthalidone and losartan.

[53] Furthermore, the present invention provides a fixed-dose combination formulation for preventing or treating cardiovascular diseases, the formulation comprising a first

mixture including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and a second mixture including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive, wherein the first mixture and the second mixture are present in a form separated physically from each other.

- [54] In the fixed-dose combination formulation, amlodipine or a pharmaceutically acceptable salt thereof may be comprised in an amount of 5 to 10 mg in the form of amlodipine free acid, chlorthalidone or a pharmaceutically acceptable salt thereof may be comprised in an amount of 12.5 to 25 mg in the form of chlorthalidone free acid, and losartan or a pharmaceutically acceptable salt thereof may be comprised in an amount of 50 to 100 mg in the form of losartan free acid.
- [55] The present invention also provides a method of preparing a pharmaceutical complex formulation for preventing or treating cardiovascular diseases, the method comprising the steps of 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.
- [56] Furthermore, the present invention provides a method of preparing a bilayer tablet for preventing or treating cardiovascular diseases, the method comprising the steps of a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive to obtain a mixture and granulating the mixture; b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive to obtain a mixture and then granulating the mixture; and c) tablet pressing the resultant granules prepared in steps a) and b) into a bilayer tablet.
- [57] In one embodiment of the present invention, the cardiovascular diseases may be selected from the group consisting of angina pectoris, hypertension, artery vasospasm, cardiac arrhythmia, cardiac hypertrophy, cerebral infarct, congestive heart failure and myocardial infarction, but not limited thereto.

[58]

### **Mode for the Invention**

- [59] Hereinafter, the present invention is explained in detail by Examples. The following Examples are intended to further illustrate the present invention without limiting its scope.

[60]

- [61] **Examples 1 to 3: Preparation of complex bilayer tablet by compression**

**granulation method**

- [62] As shown in Table 1, amlodipine camsylate, chlorthalidone, lactose hydrate, micro-crystalline cellulose and crospovidone were mixed and the mixture was screened through 30 mesh sieve. The screened part was compressed by using a roller compactor (Roller compactor WP200, Alexanderwerk) under a minimum pressure of 20 kN and a roller speed of 2 to 10 rpm to form flake-type granule part. After the obtained granule part was shear-treated by using a mill (Fitz mill; BAS 06, Fitzpatrick, USA) and passed through 20 mesh sieve, magnesium stearate was added thereto and the mixture was finally mixed by a mixer to obtain an amlodipine and chlorthalidone granule part.
- [63] Losartan potassium, microcrystalline cellulose and crospovidone were mixed and the mixture was screened through 30 mesh sieve. The screened part was compressed by using a roller compactor (Roller compactor WP200, Alexanderwerk) under a minimum pressure of 20 kN and a roller speed of 2 to 10 rpm to form flake-type granule part. After the obtained granule part was shear-treated by using a mill (Fitz mill; BAS 06, Fitzpatrick, USA) and passed through 20 mesh sieve, magnesium stearate was added thereto and the mixture was finally mixed by a mixer to obtain a losartan granule part.
- [64] Subsequently, a complex bilayer tablet consisting of amlodipine and chlorthalidone granule part (first layer; upper layer) and losartan granule part (second layer; under layer) was manufactured by using a tablet press (Tablet press; Kilian Synthesis 700, Germany).

[65] [Table 1]

| Layers                                                                        | Ingredients (mg)           | Example 1               | Example 2 | Example 3 |
|-------------------------------------------------------------------------------|----------------------------|-------------------------|-----------|-----------|
| Amlodipine and chlorthalidone layer                                           | Amlodipine camsylate       | 7.8(Amlodipine 5 mg)    | 7.8       | 7.8       |
|                                                                               | Chlorthalidone             | 25.0                    | 25.0      | 25.0      |
|                                                                               | Lactose hydrate            | 58.0                    | 87.0      | 116.0     |
|                                                                               | Microcrystalline cellulose | 116.0                   | 87.0      | 58.0      |
|                                                                               | Crospovidone               | 11.0                    | 11.0      | 11.0      |
|                                                                               | Magnesium stearate         | 2.2                     | 2.2       | 2.2       |
| Weight of first layer                                                         |                            | 220.0                   | 220.0     | 220.0     |
| Proportion of lactose hydrate in first layer                                  |                            | 26.4%                   | 39.5%     | 52.7%     |
| Weight ratio of lactose hydrate and microcrystalline cellulose in first layer |                            | 1:2                     | 1:1       | 2:1       |
| Losartan layer                                                                | Losartan potassium         | 100.0(Losartan 91.6 mg) | 100.0     | 100.0     |
|                                                                               | Microcrystalline cellulose | 216.0                   | 216.0     | 216.0     |
|                                                                               | Crospovidone               | 12.0                    | 12.0      | 12.0      |
|                                                                               | Magnesium stearate         | 2.0                     | 2.0       | 2.0       |

[66]

[67] **Comparative Example 1: Preparation of single-layer tablet by dry-type direct compression method**

[68] As shown in Table 2, amlodipine camsylate, chlorthalidone, losartan potassium, lactose hydrate, microcrystalline cellulose and crospovidone were mixed and the mixture was screened through 30 mesh sieve. Magnesium stearate was added to the screened part and the mixture was finally mixed by a mixer. The mixed part was pressed to obtain a single-layer tablet.

[69] [Table 2]

| Ingredients (mg)           | Comparative Example 1    |
|----------------------------|--------------------------|
| Amlodipine camsylate       | 7.8 (Amlodipine 5 mg)    |
| Chlorthalidone             | 25.0                     |
| Losartan potassium         | 100.0 (Losartan 91.6 mg) |
| Lactose hydrate            | 250.0                    |
| Microcrystalline cellulose | 137.2                    |
| Crospovidone               | 25.0                     |
| Magnesium stearate         | 5.0                      |

[70]

[71] **Comparative Example 2: Preparation of bilayer tablet by dry-type direct compression method**

[72] As shown in Table 3, amlodipine camsylate, chlorthalidone, lactose hydrate, microcrystalline cellulose and crospovidone were mixed and the mixture was screened through 30 mesh sieve. Magnesium stearate was added thereto and the mixture was finally mixed by a mixer to obtain an amlodipine and chlorthalidone mixture part.

[73] Losartan potassium, microcrystalline cellulose and crospovidone were mixed and the mixture was screened through 30 mesh sieve. Magnesium stearate was added thereto and the mixture was finally mixed by a mixer to obtain a losartan mixture part.

[74] Subsequently, a complex bilayer tablet consisting of amlodipine and chlorthalidone mixture part (first layer; upper layer) and losartan mixture part (second layer; under layer) was manufactured by using a tablet press.

[75] [Table 3]

| Layers                              | Ingredients (mg)           | Comparative Example 2    |
|-------------------------------------|----------------------------|--------------------------|
| Amlodipine and chlorthalidone layer | Amlodipine camsylate       | 7.8 (Amlodipine 5 mg)    |
|                                     | Chlorthalidone             | 25.0                     |
|                                     | Lactose hydrate            | 58.0                     |
|                                     | Microcrystalline cellulose | 116.0                    |
|                                     | Crospovidone               | 11.0                     |
|                                     | Magnesium stearate         | 2.2                      |
| Losartan layer                      | Losartan potassium         | 100.0 (Losartan 91.6 mg) |
|                                     | Microcrystalline cellulose | 216.0                    |
|                                     | Crospovidone               | 12.0                     |
|                                     | Magnesium stearate         | 2.0                      |

[76]

[77] **Comparative Examples 3 to 6: Preparation of complex bilayer tablet by compression granulation method**

[78] As shown in Table 4, a complex bilayer tablet with varied ratio of lactose and cellulose was manufactured according to the same procedures as in Example 1.

[79] [Table 4]

| Layers                                                                        | Ingredients(mg)            | Comp. Ex. 3             | Comp. Ex. 4 | Comp. Ex. 5 | Comp. Ex. 6 |
|-------------------------------------------------------------------------------|----------------------------|-------------------------|-------------|-------------|-------------|
| Amlodipine and chlorthalidone layer                                           | Amlodipine camsylate       | 7.8(Amlodipine 5 mg)    | 7.8         | 7.8         | 7.8         |
|                                                                               | Chlorthalidone             | 25.0                    | 25.0        | 25.0        | 25.0        |
|                                                                               | Lactose hydrate            | -                       | 29.0        | 145.0       | 174         |
|                                                                               | Microcrystalline cellulose | 174                     | 145.0       | 29.0        | -           |
|                                                                               | Crospovidone               | 11.0                    | 10.0        | 10.0        | 11.0        |
|                                                                               | Magnesium stearate         | 2.2                     | 2.2         | 2.2         | 2.2         |
| Weight of first layer                                                         |                            | 220.0                   | 220.0       | 220.0       | 220.0       |
| Proportion of lactose hydrate in first layer                                  |                            | 0%                      | 13.2%       | 65.9%       | 79.1%       |
| Weight ratio of lactose hydrate and microcrystalline cellulose in first layer |                            | -                       | 1:5         | 1:0.2       | -           |
| Losartan layer                                                                | Losartan potassium         | 100.0(Losartan 91.6 mg) | 100.0       | 100.0       | 100.0       |
|                                                                               | Microcrystalline cellulose | 216.0                   | 216.0       | 216.0       | 216.0       |
|                                                                               | Crospovidone               | 12.0                    | 12.0        | 12.0        | 12.0        |
|                                                                               | Magnesium stearate         | 2.0                     | 2.0         | 2.0         | 2.0         |

[80]

[81] **Comparative Example 7: Preparation of complex bilayer tablet with various ingredients in layers**

[82] As shown in Table 5, a complex bilayer tablet having a first layer of amlodipine and losartan granule part and a second layer of chlorthalidone granule part was manufactured according to the same procedures as in Example 1.

[83] [Table 5]

| Layers                        | Ingredients (mg)           | Comparative Example 7    |
|-------------------------------|----------------------------|--------------------------|
| Amlodipine and losartan layer | Amlodipine camsylate       | 7.8 (Amlodipine 5 mg)    |
|                               | Losartan potassium         | 100.0 (Losartan 91.6 mg) |
|                               | Lactose hydrate            | 58.0                     |
|                               | Microcrystalline cellulose | 116.0                    |
|                               | Crospovidone               | 11.0                     |
|                               | Magnesium stearate         | 2.2                      |
| Chlorthalidone layer          | Chlorthalidone             | 25.0                     |
|                               | Microcrystalline cellulose | 216.0                    |
|                               | Crospovidone               | 12.0                     |
|                               | Magnesium stearate         | 2.0                      |

[84]

[85] **Comparative Example 8: Preparation of complex bilayer tablet with various ingredients in layers**

[86] As shown in Table 6, a complex bilayer tablet having a first layer of amlodipine granule part and a second layer of losartan and chlorthalidone granule part was manufactured according to the same procedures as in Example 1.

[87] [Table 6]

| Layers                            | Ingredients (mg)           | Comparative Example 8    |
|-----------------------------------|----------------------------|--------------------------|
| Amlodipine layer                  | Amlodipine camsylate       | 7.8 (Amlodipine 5 mg)    |
|                                   | Lactose hydrate            | 58.0                     |
|                                   | Microcrystalline cellulose | 116.0                    |
|                                   | Crospovidone               | 11.0                     |
|                                   | Magnesium stearate         | 2.2                      |
| Losartan and chlorthalidone layer | Losartan potassium         | 100.0 (Losartan 91.6 mg) |
|                                   | Chlorthalidone             | 25.0                     |
|                                   | Microcrystalline cellulose | 216.0                    |
|                                   | Crospovidone               | 12.0                     |
|                                   | Magnesium stearate         | 2.0                      |

[88]

[89] **Examples 4 to 6: Preparation of complex bilayer tablet with varied amounts of active components**

[90] As shown in Table 7, complex bilayer tablets having changed amounts of active components in Examples 1 to 3 were manufactured.

[91] [Table 7]

| Layers                                                                        | Ingredients (mg)           | Example 4              | Example 5 | Example 6 |
|-------------------------------------------------------------------------------|----------------------------|------------------------|-----------|-----------|
| Amlodipine and chlorthalidone layer                                           | Amlodipine camsylate       | 7.8(Amlodipine 5 mg)   | 7.8       | 7.8       |
|                                                                               | Chlorthalidone             | 12.5                   | 12.5      | 12.5      |
|                                                                               | Lactose hydrate            | 52.8                   | 79.2      | 105.5     |
|                                                                               | Microcrystalline cellulose | 105.5                  | 79.2      | 52.8      |
|                                                                               | Crospovidone               | 9.5                    | 9.5       | 9.5       |
|                                                                               | Magnesium stearate         | 1.9                    | 1.9       | 1.9       |
| Weight of first layer                                                         |                            | 190.0                  | 190.0     | 190.0     |
| Proportion of lactose hydrate in first layer                                  |                            | 27.8%                  | 41.7%     | 55.5%     |
| Weight ratio of lactose hydrate and microcrystalline cellulose in first layer |                            | 1:2                    | 1:1       | 2:1       |
| Losartan layer                                                                | Losartan potassium         | 50.0(Losartan 45.8 mg) | 50.0      | 50.0      |
|                                                                               | Microcrystalline cellulose | 108.0                  | 108.0     | 108.0     |
|                                                                               | Crospovidone               | 6.0                    | 6.0       | 6.0       |
|                                                                               | Magnesium stearate         | 1.0                    | 1.0       | 1.0       |

[92]

[93] **Comparative Examples 9 to 12: Preparation of complex bilayer tablet with varied amounts of active components**

[94] As shown in Table 8, complex bilayer tablets were manufactured according to the same procedures as in Example 1.

[95] [Table 8]

| Layers                                                                        | Ingredients(mg)            | Comp. Ex. 9            | Comp. Ex. 10 | Comp. Ex. 11 | Comp. Ex. 12 |
|-------------------------------------------------------------------------------|----------------------------|------------------------|--------------|--------------|--------------|
| Amlodipine and chlorthalidone layer                                           | Amlodipine camsylate       | 7.8(Amlodipine 5 mg)   | 7.8          | 7.8          | 7.8          |
|                                                                               | Chlorthalidone             | 12.5                   | 12.5         | 12.5         | 12.5         |
|                                                                               | Lactose hydrate            | -                      | 26.4         | 131.9        | 158.3        |
|                                                                               | Microcrystalline cellulose | 158.3                  | 131.9        | 26.4         | -            |
|                                                                               | Crospovidone               | 9.5                    | 9.5          | 9.5          | 9.5          |
|                                                                               | Magnesium stearate         | 1.9                    | 1.9          | 1.9          | 1.9          |
| Weight of first layer                                                         |                            | 190.0                  | 190.0        | 190.0        | 190.0        |
| Proportion of lactose hydrate in first layer                                  |                            | 0%                     | 14%          | 69%          | 83%          |
| Weight ratio of lactose hydrate and microcrystalline cellulose in first layer |                            | -                      | 1:5          | 1:0.2        | -            |
| Losartan layer                                                                | Losartan potassium         | 50.0(Losartan 45.8 mg) | 50.0         | 50.0         | 50.0         |
|                                                                               | Microcrystalline cellulose | 108.0                  | 108.0        | 108.0        | 108.0        |
|                                                                               | Crospovidone               | 6.0                    | 6.0          | 6.0          | 6.0          |
|                                                                               | Magnesium stearate         | 1.0                    | 1.0          | 1.0          | 1.0          |

[96]

[97] **Test Example 1: Dissolution test of bilayer tablet and single-layer tablet**

[98] The tablet prepared in Example 1 and the tablet prepared in Comparative Example 1 were subjected to a drug dissolution test under the following condition to measure dissolution rates of amlodipine, chlorthalidone and losartan over time.

[99] - Dissolution test condition -

[100] Effluent: artificial gastric juice 900 mL (pH 1.2)

[101] Dissolution test system: USP paddle method, 50 rpm

[102] Temperature: 37°C

- [103] Dissolution time: After dissolution rates were measured at 5, 10, 15, 30, 45, 60, 90 and 120 minutes, the paddle speed was changed from 50 rpm to 150 rpm, and then final dissolution rate was measured at 150 minutes.
- [104] - Analytical condition -
- [105] Column: stainless steel column (inner diameter: 4.6 mm, length: 15 cm) filled with octadecylsilylated silica gel for 3  $\mu$ m liquid chromatography
- [106] Mobile phase: \*6 mM sodium 1-hexanesulfonate/0.05% (v/v) phosphoric acid:acetonitrile (60:40, v/v)
- [107] (\*6 mM sodium 1-hexanesulfonate/0.05% (v/v) phosphoric acid: After 1.24 g of sodium 1-hexanesulfonate monohydrate was put into an 1 L flask, 0.5 mL of phosphoric acid was cautiously added thereto, and then the mixture was dissolved and diluted by adding purified water)
- [108] Detector: ultraviolet spectrophotometer (254 nm)
- [109] Flow rate: 1.3 mL/minute
- [110] Injection volume: 10  $\mu$ L
- [111] Column temperature: 45°C
- [112] - Criteria of dissolution rate -
- [113] 80% or higher at 30 minutes (For amlodipine and chlorthalidone)
- [114] The measured results of dissolution rates are shown in Figs. 2 to 4. As shown in Figs. 2 and 3, the bilayer tablet having amlodipine and chlorthalidone layer separated from losartan layer according to Example 1 exhibited higher dissolution rates compared with the single-layer tablet prepared by dry-type direct compression method in Comparative Example 1. Unlike the single-layer tablet prepared in Comparative Example 1, the bilayer tablet of Example 1 showed good dissolution characteristics and the dissolution rates of amlodipine and chlorthalidone satisfied the criteria.
- [115] Furthermore, as shown in Fig. 4, the dissolution rate of losartan was 20% or lower at 60 minutes in the single-layer tablet of Comparative Example 1 while the bilayer tablet of Example 1 exhibited remarkably high dissolution rate of losartan.
- [116] The above results show that the dissolution of amlodipine or chlorthalidone slows down due to the gelation of losartan when losartan is in the same layer with amlodipine or chlorthalidone.
- [117]
- [118] **Test Example 2: Uniformity of dosage units in bilayer tablet prepared by compression granulation method and bilayer tablet prepared by dry-type direct compression method**
- [119] For the bilayer tablet prepared by compression granulation method in Example 1 and the bilayer tablet prepared by dry-type direct compression of simple mixture in Comparative Example 2, mass variation and content uniformity of amlodipine,

chlorthalidone and losartan were tested. The results are shown in Tables 9 and 10.

[120] [Table 9]

| Tablets               | Weight (mg) | Standard deviation | Acceptance value |
|-----------------------|-------------|--------------------|------------------|
| Example 1             | 549.3       | 1.4                | 3.4              |
| Comparative Example 2 | 548.7       | 3.5                | 8.4              |

[121]

[122] [Table 10]

| Tablets               | Ingredients    | Content (%) | Standard deviation | Acceptance value |
|-----------------------|----------------|-------------|--------------------|------------------|
| Example 1             | Amlodipine     | 100.0       | 1.7                | 4.1              |
|                       | Chlorthalidone | 100.0       | 1.3                | 3.1              |
|                       | Losartan       | 100.0       | 0.6                | 1.4              |
| Comparative Example 2 | Amlodipine     | 99.9        | 6.4                | 15.4             |
|                       | Chlorthalidone | 99.8        | 6.8                | 16.3             |
|                       | Losartan       | 99.7        | 0.7                | 1.7              |

[123]

[124] As shown in Table 9, the bilayer tablet prepared by dry-type direct compression of simple mixture, without using roller compactor, in Comparative Example 2 exhibited relatively degraded mass variation compared with the bilayer tablet prepared in Example 1. As shown in Table 10, the bilayer tablet of Comparative Example 2 did not satisfy the criteria of content uniformity (acceptance value of 15 or lower) in amlodipine and chlorthalidone. Moreover, the bilayer tablet prepared in Comparative Example 2, without being processed by compression and screening, showed low productivity by the occurrence of capping in tablet pressing. On the other hand, the bilayer tablet prepared by using roller compactor in Example 1 exhibited excellent content uniformity of amlodipine and chlorthalidone, and satisfied the criteria of uniformity of dosage units

[125] The above results confirm that the roller compacting process of amlodipine-chlorthalidone granule and losartan granule affects the uniformity of dosage units of the three active components as well as the productivity of tablet pressing process.

[126]

[127] **Test Example 3: Change in dissolution depending on ratio of excipients in amlodipine-chlorthalidone layer**

[128] For the bilayer tablets prepared in Examples 1 to 3 and the bilayer tablets prepared in

Comparative Examples 3 to 6, dissolution rates of amlodipine, chlorthalidone and losartan were measured according to the same method as in Test Example 1. The results are shown in Figs. 5 to 7.

[129] As shown in Fig. 7, the dissolution rate of losartan in the bilayer tablets of Examples 1 to 3 was little different from that of Comparative Examples 3 to 6.

[130] As shown in Figs. 5 and 6, however, for the dissolution rates of amlodipine and chlorthalidone, the bilayer tablets of Examples 1 to 3 exhibited rapid and good dissolution satisfying the criteria, while the bilayer tablets of Comparative Examples 3 to 6 did not satisfy the criteria of dissolution test (80% or higher at 30 minutes in artificial gastric juice, pH 1.2).

[131] The above results show that lactose hydrate of 20 to 60% by weight and the weight ratio of lactose hydrate and microcrystalline cellulose of 1:0.5 to 1:2 in amlodipine-chlorthalidone layer result in preferable dissolution rates.

[132]

[133] **Test Example 4: Dissolution test of tablet prepared in Comparative Example 7 (consisting of amlodipine-losartan layer and chlorthalidone layer) and tablet prepared in Comparative Example 8 (consisting of amlodipine layer and losartan-chlorthalidone layer)**

[134] For the bilayer tablet prepared in Example 1 and the bilayer tablets prepared in Comparative Examples 7 and 8, dissolution rates of amlodipine, chlorthalidone and losartan were measured according to the same method as in Test Example 1. The results are shown in Figs. 8 to 10.

[135] As shown in Figs. 8 to 10, the bilayer tablet of Example 1 consisting of amlodipine-chlorthalidone layer and losartan layer exhibited rapid and good dissolution satisfying the criteria of dissolution rates for amlodipine and chlorthalidone. On the other hand, the bilayer tablet of Comparative Example 7 consisting of amlodipine-losartan layer and chlorthalidone layer did not satisfy the criteria of dissolution rate for amlodipine, and the bilayer tablet of Comparative Example 8 consisting of amlodipine layer and losartan-chlorthalidone layer did not satisfy the criteria of dissolution rate for chlorthalidone.

[136] The above results show that since gelation of losartan reduces dissolution of the tablet consisting of amlodipine-losartan layer and chlorthalidone layer or the tablet consisting of amlodipine layer and losartan-chlorthalidone layer, the bilayer tablet consisting of amlodipine-chlorthalidone layer and losartan layer is preferred, and also show that separation of the three drugs is most important for good dissolution.

[137]

[138] **Test Example 5: Change in contents according to stability test under accelerated storage condition**

- [139] For the tablets prepared in Examples 1 to 3, changes in contents of amlodipine, chlorthalidone and losartan were measured under the following accelerated storage condition to assess the stability of tablets. The results are shown in Table 11.
- [140] - Accelerated storage condition -
- [141] Storage condition: packaged in HDPE (High Density Polyethylene) bottle at 40°C, 75% relative humidity
- [142] Test time: 0(initial), 1, 2, 4 and 6 months
- [143] Subject of test: amlodipine, chlorthalidone and losartan
- [144] - Analytical condition -
- [145] Column: stainless steel column (inner diameter: 4.6 mm, length: 15 cm) filled with octadecylsilylated silica gel for 3 µm liquid chromatography
- [146] Mobile phase: 6 mM sodium 1-hexanesulfonate/0.05% (v/v) phosphoric acid:acetonitrile (6:4, v/v)
- [147] Detector: ultraviolet spectrophotometer (254 nm)
- [148] Flow rate: 1.3 mL/minute
- [149] Injection volume: 10 µL
- [150] Column temperature: 45°C
- [151] [Table 11]

| Ingredients    | Formulation | Initial | 1 month | 2 months | 4 months | 6 months |
|----------------|-------------|---------|---------|----------|----------|----------|
| Amlodipine     | Example 1   | 100.0%  | 99.7%   | 99.5%    | 99.2%    | 99.1%    |
|                | Example 2   | 100.0%  | 99.8%   | 99.7%    | 99.5%    | 99.3%    |
|                | Example 3   | 100.0%  | 99.8%   | 99.5%    | 99.4%    | 99.3%    |
| Chlorthalidone | Example 1   | 100.0%  | 99.6%   | 99.5%    | 99.3%    | 99.2%    |
|                | Example 2   | 100.0%  | 99.5%   | 99.4%    | 99.3%    | 99.1%    |
|                | Example 3   | 100.0%  | 99.6%   | 99.5%    | 99.4%    | 99.3%    |
| Losartan       | Example 1   | 100.0%  | 99.8%   | 99.7%    | 99.3%    | 99.1%    |
|                | Example 2   | 100.0%  | 99.8%   | 99.6%    | 99.4%    | 99.2%    |
|                | Example 3   | 100.0%  | 99.8%   | 99.6%    | 99.4%    | 99.3%    |

- [152]
- [153] As shown in Table 11, it is confirmed that the bilayer tablets prepared in Examples 1 to 3 have superior stability since the contents of amlodipine, chlorthalidone and losartan have rarely decreased after 6 months of accelerated storage condition.
- [154]
- [155] **Test Example 6: Storage test under light and heat stress conditions**

- [156] For the tablets prepared in Examples 1 to 3 and Comparative Examples 1 to 8, changes in content of related compounds derived from amlodipine, chlorthalidone and losartan were measured under light and heat stress condition to access the stability. The results are shown in Table 12.
- [157] - Condition of photostability test chamber (light stress condition) -
- [158] (1) Instrument: Xe-3-HC (Q-Lab)
- [159] (2) Temperature and humidity:  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$  /  $60\% \pm 5\%$  RH
- [160] (3) Illumination:  $0.80 \text{ W/m}^2/\text{nm}$ , 18.44 hours
- [161] (1,200,000 lux, photostability test condition suggested by ICH guideline)
- [162] (4) Sample: stored in petri dish
- [163] (5) Test time: beginning of test and after light exposure (after exposure at 1,200,000 lux)
- [164] - Condition of heat stability test chamber (heat stress condition) -
- [165] (1) Temperature and humidity:  $50^{\circ}\text{C} \pm 2^{\circ}\text{C}$
- [166] (2) Sample: packaged in HDPE bottle
- [167] (3) Test time: beginning of test and after 28-day storage
- [168] - Analytical condition -
- [169] Column: stainless steel column (inner diameter: 4.6 mm, length: 25 cm) filled with octadecylsilylated silica gel for  $5 \mu\text{m}$  liquid chromatography
- [170] Mobile phase: 6 mM sodium 1-hexanesulfonate/0.05% (v/v) phosphoric acid:acetonitrile (6:4, v/v)
- [171] Detector: ultraviolet spectrophotometer (239 nm)
- [172] Flow rate: 1.0 mL/minute
- [173] Injection volume: 10  $\mu\text{L}$
- [174] Column temperature:  $45^{\circ}\text{C}$

[175] [Table 12]

| Sample<br>s    | Initial                                                  |                                                              |                                                     | Light exposure,<br>1,200,000 lux                         |                                                              |                                                     | 50°C, packaged in HDPE<br>bottle 28-day storage          |                                                              |                                                     |
|----------------|----------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------|
|                | Related<br>compo<br>und<br>from<br>amlodi<br>pine<br>(%) | Related<br>compo<br>und<br>from<br>chlorth<br>alidone<br>(%) | Related<br>compo<br>und<br>from<br>losarta<br>n (%) | Related<br>compo<br>und<br>from<br>amlodi<br>pine<br>(%) | Related<br>compo<br>und<br>from<br>chlorth<br>alidone<br>(%) | Related<br>compo<br>und<br>from<br>losarta<br>n (%) | Related<br>compo<br>und<br>from<br>amlodi<br>pine<br>(%) | Related<br>compo<br>und<br>from<br>chlorth<br>alidone<br>(%) | Related<br>compo<br>und<br>from<br>losarta<br>n (%) |
| Ex. 1          | 0.02                                                     | 0.01                                                         | 0.01                                                | 0.13                                                     | 0.10                                                         | 0.04                                                | 0.08                                                     | 0.10                                                         | 0.04                                                |
| Ex. 2          | 0.01                                                     | 0.02                                                         | 0.02                                                | 0.14                                                     | 0.15                                                         | 0.05                                                | 0.06                                                     | 0.13                                                         | 0.04                                                |
| Ex. 3          | 0.03                                                     | 0.01                                                         | 0.01                                                | 0.11                                                     | 0.11                                                         | 0.05                                                | 0.09                                                     | 0.11                                                         | 0.05                                                |
| Comp.<br>Ex. 1 | 0.10                                                     | 0.05                                                         | 0.03                                                | 1.25                                                     | 0.33                                                         | 0.10                                                | 1.01                                                     | 0.45                                                         | 0.57                                                |
| Comp.<br>Ex. 2 | 0.03                                                     | 0.02                                                         | 0.02                                                | 0.17                                                     | 0.15                                                         | 0.06                                                | 0.10                                                     | 0.13                                                         | 0.05                                                |
| Comp.<br>Ex. 3 | 0.02                                                     | 0.01                                                         | 0.01                                                | 0.14                                                     | 0.16                                                         | 0.04                                                | 0.09                                                     | 0.14                                                         | 0.04                                                |
| Comp.<br>Ex. 4 | 0.02                                                     | 0.02                                                         | 0.01                                                | 0.12                                                     | 0.17                                                         | 0.05                                                | 0.08                                                     | 0.12                                                         | 0.04                                                |
| Comp.<br>Ex. 5 | 0.01                                                     | 0.02                                                         | 0.01                                                | 0.10                                                     | 0.17                                                         | 0.04                                                | 0.11                                                     | 0.14                                                         | 0.05                                                |
| Comp.<br>Ex. 6 | 0.01                                                     | 0.02                                                         | 0.01                                                | 0.11                                                     | 0.16                                                         | 0.05                                                | 0.10                                                     | 0.13                                                         | 0.06                                                |
| Comp.<br>Ex. 7 | 0.09                                                     | 0.02                                                         | 0.04                                                | 1.14                                                     | 0.19                                                         | 0.10                                                | 0.97                                                     | 0.13                                                         | 0.34                                                |
| Comp.<br>Ex. 8 | 0.01                                                     | 0.06                                                         | 0.04                                                | 0.15                                                     | 0.30                                                         | 0.08                                                | 0.10                                                     | 0.42                                                         | 0.20                                                |

[176]

[177]

As shown in Table 12, it is confirmed that the tablets prepared in Examples 1 to 3 have little related compounds derived from amlodipine, chlorthalidone and losartan produced under light or heat stress condition and are highly stable. However, it may be confirmed that the tablet prepared by simple mixture of the three components in Com-

parative Example 1 has increased related compounds by 3 to 10 times compared with those of Examples 1 to 3. The results show that the tablet prepared by simple mixture is difficult to ensure sufficient stability due to changes over time under light or heat stress condition.

[178] Furthermore, the related compounds produced in the tablets of Comparative Examples 7 and 8 were as high as that of Comparative Example 1. The result of Comparative Example 7 shows that the bilayer tablet consisting of amlodipine-losartan layer and chlorthalidone layer is difficult to ensure sufficient stability due to changes over time under light or heat stress condition. The result of Comparative Example 8 shows that the bilayer tablet consisting of amlodipine layer and losartan-chlorthalidone layer is also difficult to ensure sufficient stability due to changes over time under light or heat stress condition.

[179] The above results confirm that the bilayer tablets consisting of amlodipine-chlorthalidone layer and losartan layer prepared in Examples 1 to 3 are stable.

[180]

[181] **Test Example 7: Change in dissolution depending on ratio of excipients** in amlodipine-chlorthalidone layer in bilayer tablet with varied amounts of active components

[182] For the tablets with varied amounts of active components prepared in Examples 4 to 6 and Comparative Examples 9 to 12, dissolution rates of amlodipine, chlorthalidone and losartan were measured according to the same method as in Test Example 1. The results are shown in Figs. 11 to 13.

[183] As shown in Figs. 11 to 13, the tablets of Examples 4 to 6 exhibited dissolution patterns similar to those of Examples 1 to 3, satisfying the criteria, although the amounts of losartan and chlorthalidone are changed to 50 mg and 12.5 mg, respectively.

[184] On the other hand, the tablets of Comparative Examples 9 to 12 did not satisfy the criteria for the dissolution rates of amlodipine and chlorthalidone.

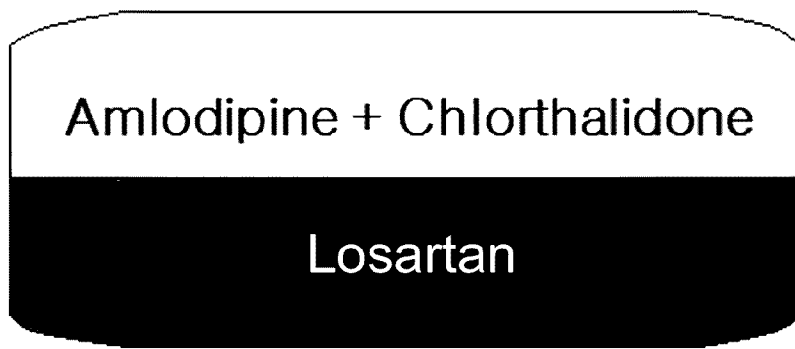
[185] The above results show that the tablets in which the content of lactose hydrate is 20 to 60% by weight and the ratio of lactose and microcrystalline cellulose is 1:0.5 to 1:2 in amlodipine-chlorthalidone layer are preferable for good dissolution rate, irrelevant to the contents of active components.

## Claims

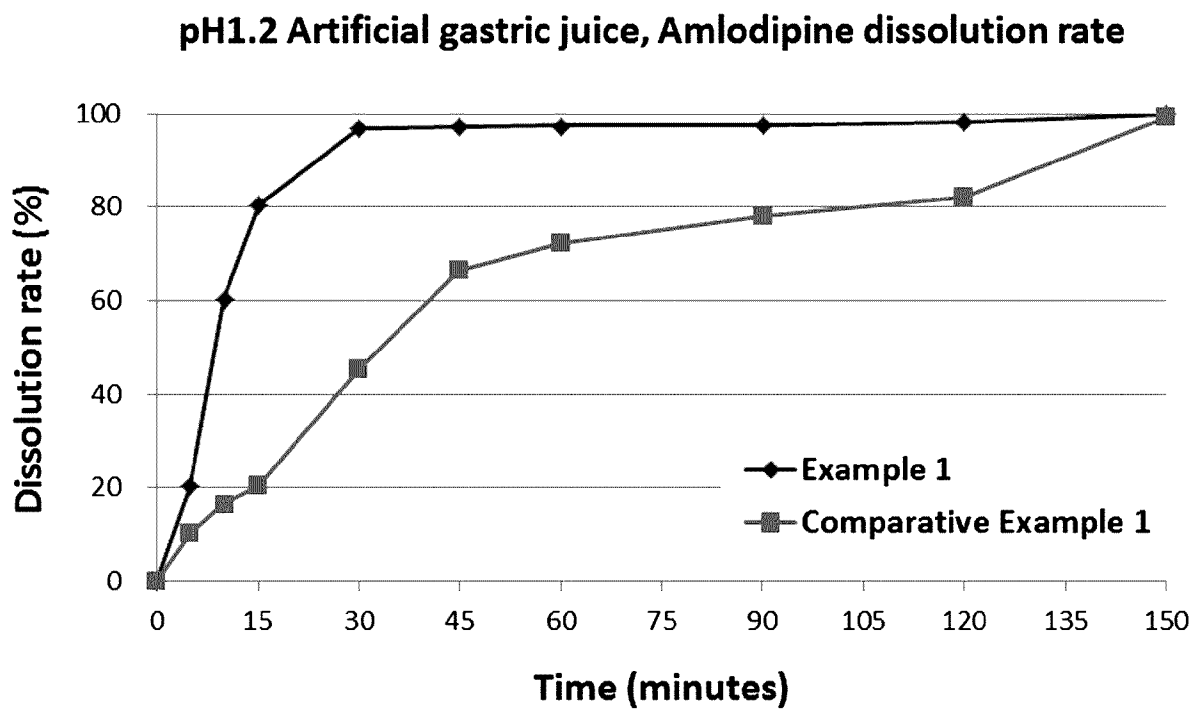
- [Claim 1] A pharmaceutical complex formulation for preventing or treating cardiovascular diseases, the formulation comprising:  
a first mixture including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and  
a second mixture including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive,  
wherein the first mixture and the second mixture are present in a form separated physically from each other.
- [Claim 2] The formulation of claim 1, wherein the complex formulation is a bilayer tablet comprising:  
a first layer including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and  
a second layer including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive.
- [Claim 3] The formulation of claim 1, wherein the additive of the first mixture is selected from the group consisting of lactose hydrate, microcrystalline cellulose, mannitol, starch and combinations thereof.
- [Claim 4] The formulation of claim 3, wherein the lactose hydrate is comprised in an amount of 20 to 60% by weight based on the total amount of the first mixture.
- [Claim 5] The formulation of claim 3, wherein the additive is lactose hydrate and microcrystalline cellulose, and the weight ratio therebetween is 1:0.5 to 1:2.
- [Claim 6] The formulation of claim 1, wherein the first mixture and the second mixture are granule forms prepared by roller compression process.
- [Claim 7] A fixed-dose combination formulation for preventing or treating cardiovascular diseases, the formulation comprising:  
a first mixture including amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive; and  
a second mixture including losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive,  
wherein the first mixture and the second mixture are present in a form separated physically from each other.

- [Claim 8] The formulation of claim 7, wherein the amlodipine or the pharmaceutically acceptable salt thereof is comprised in an amount of 5 to 10 mg in the form of amlodipine free acid.
- [Claim 9] The formulation of claim 7, wherein the chlorthalidone or the pharmaceutically acceptable salt thereof is comprised in an amount of 12.5 to 25 mg in the form of chlorthalidone free acid.
- [Claim 10] The formulation of claim 7, wherein the losartan or the pharmaceutically acceptable salt thereof is comprised in an amount of 50 to 100 mg in the form of losartan free acid.
- [Claim 11] A method of preparing a pharmaceutical complex formulation for preventing or treating cardiovascular diseases, the method comprising the steps of:
- 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.
- [Claim 12] A method of preparing a bilayer tablet for preventing or treating cardiovascular diseases, the method comprising the steps of:
- a) mixing amlodipine or a pharmaceutically acceptable salt thereof, chlorthalidone or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive to obtain a mixture and granulating the mixture;
  - b) mixing losartan or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable additive to obtain a mixture and then granulating the mixture; and
  - c) tablet pressing the resultant granules prepared in steps a) and b) into a bilayer tablet.

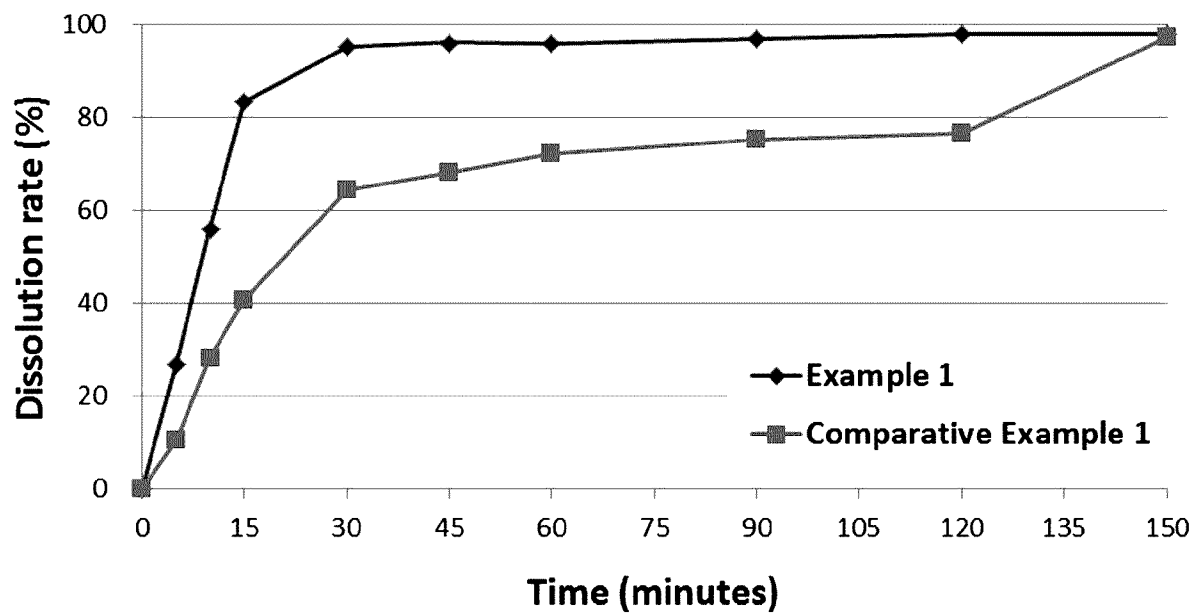
[Fig. 1]



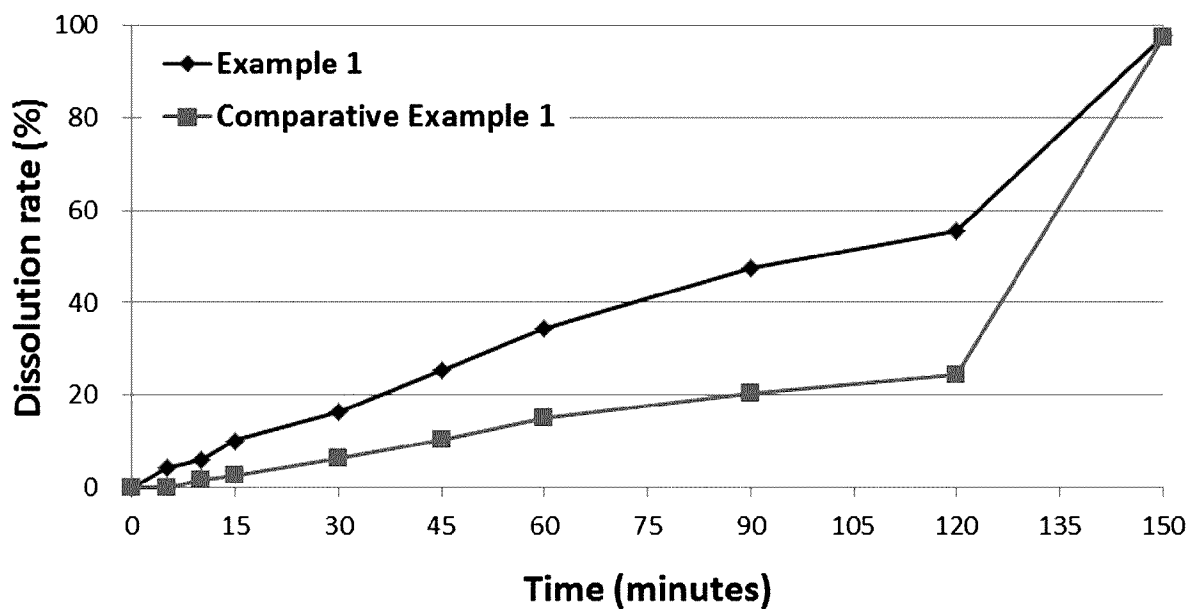
[Fig. 2]



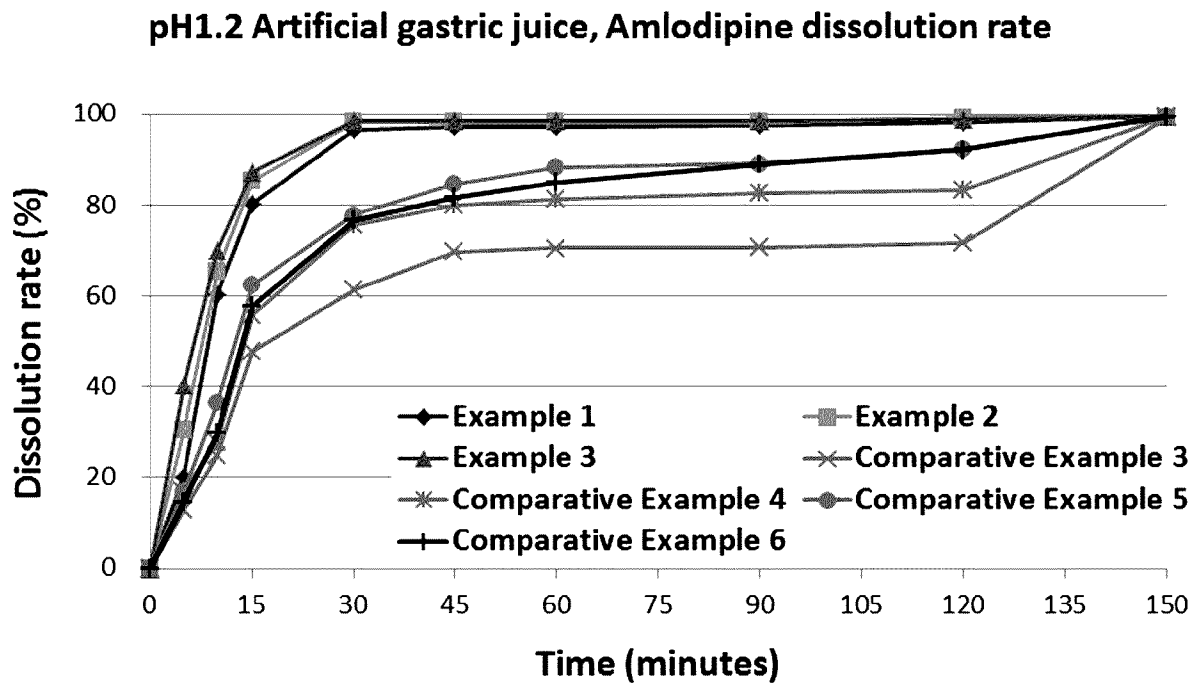
[Fig. 3]

**pH1.2 Artificial gastric juice, Chlorthalidone dissolution rate**

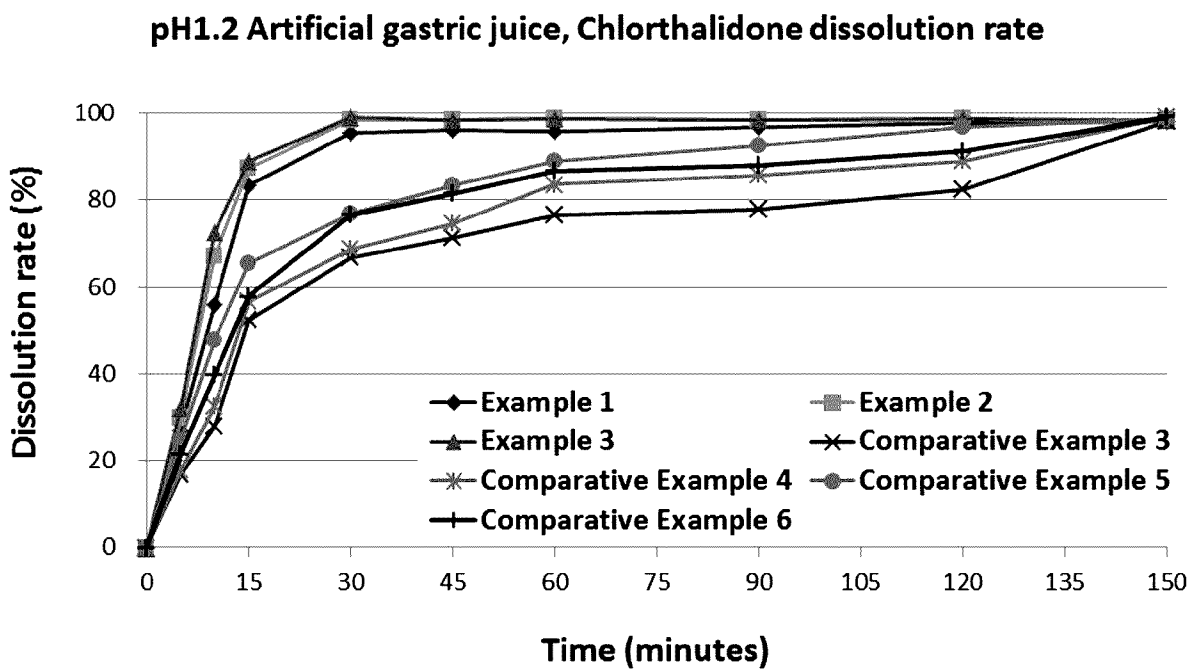
[Fig. 4]

**pH1.2 Artificial gastric juice, Losartan dissolution rate**

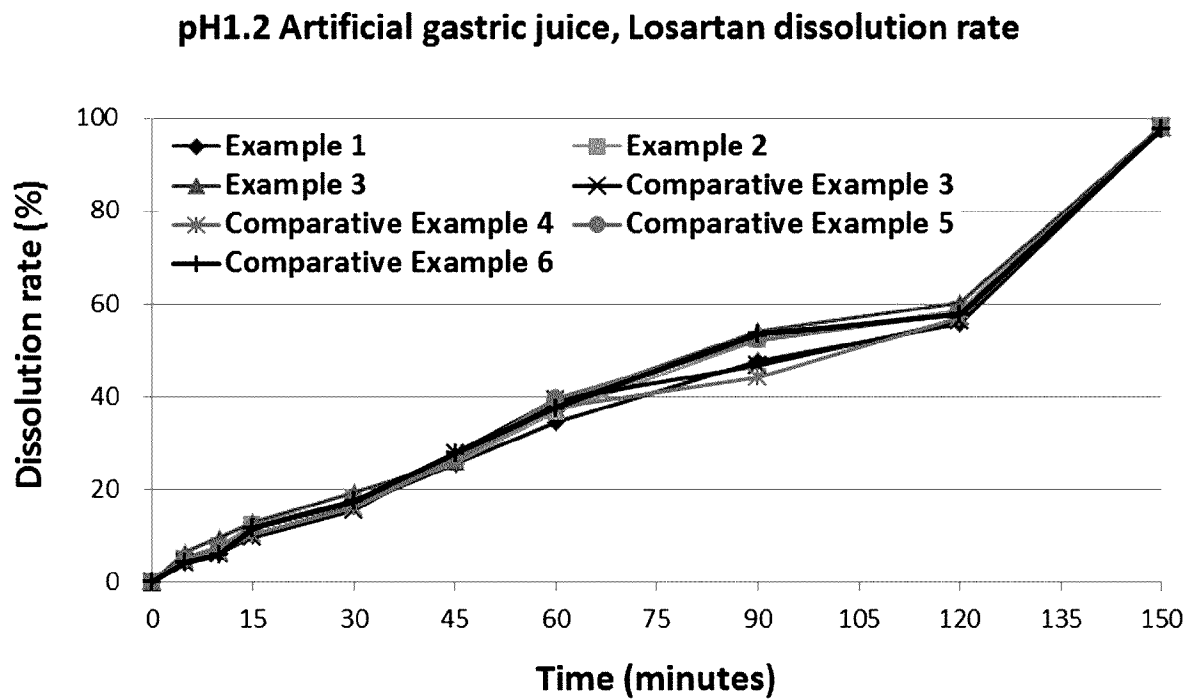
[Fig. 5]



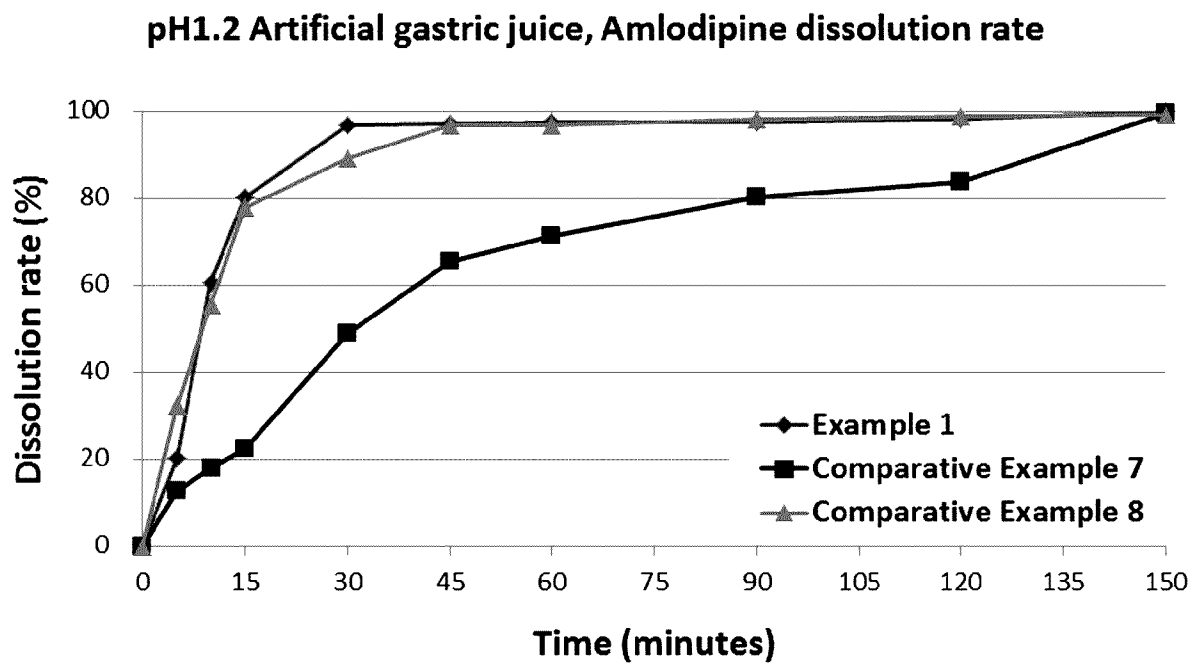
[Fig. 6]



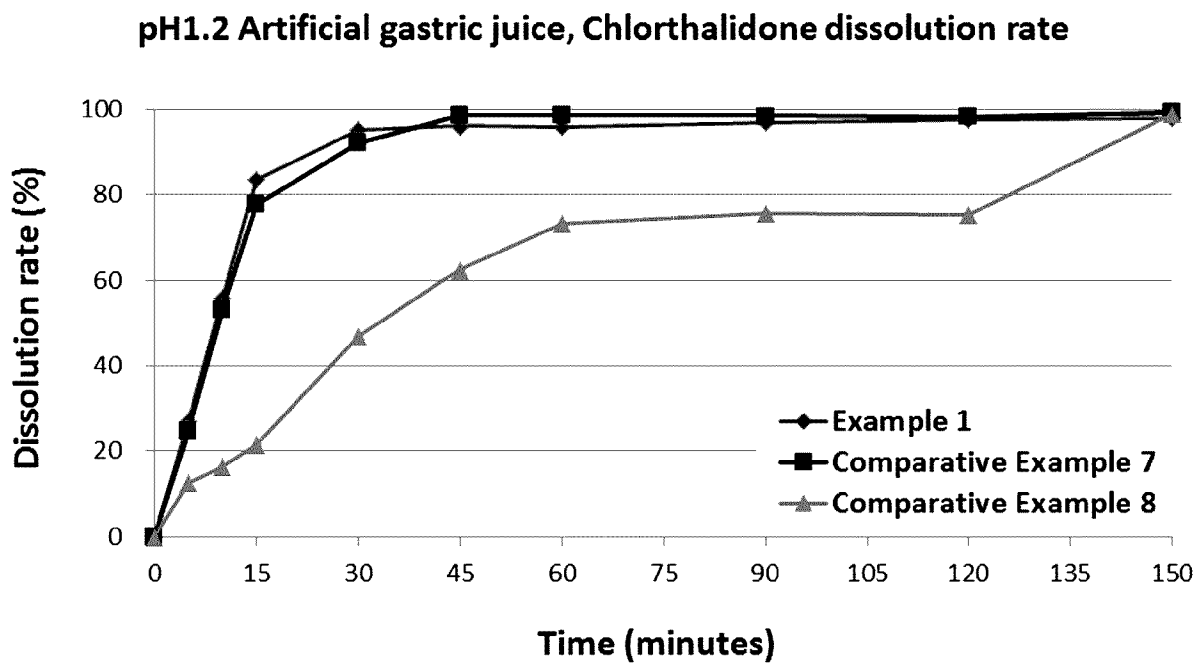
[Fig. 7]



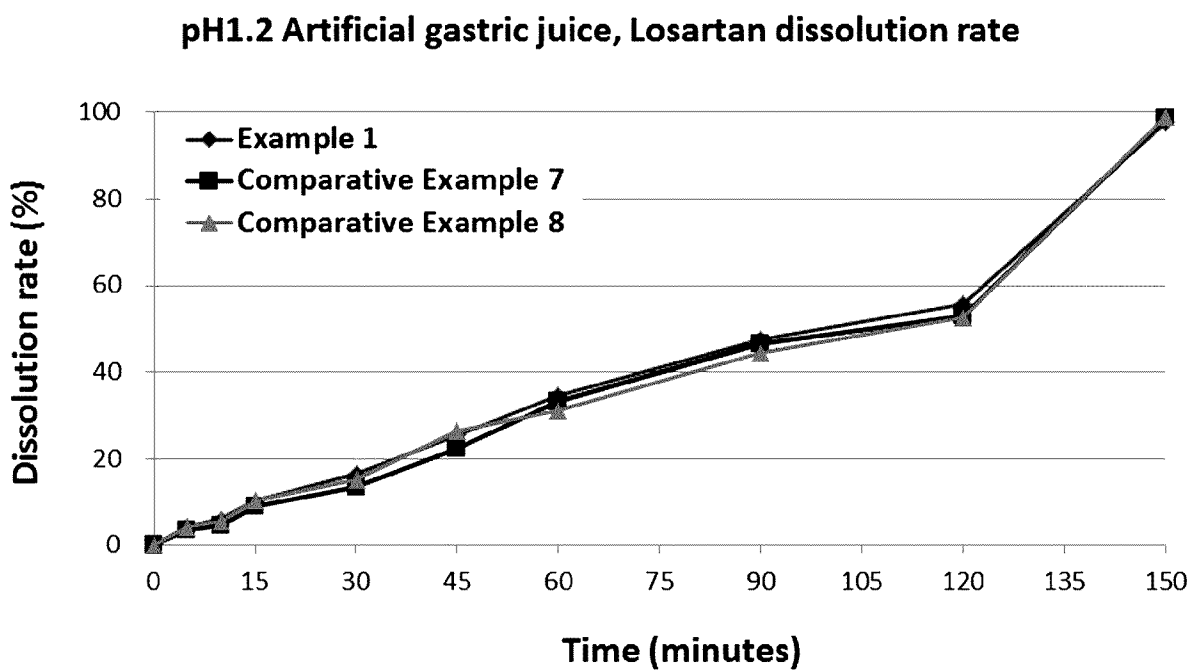
[Fig. 8]



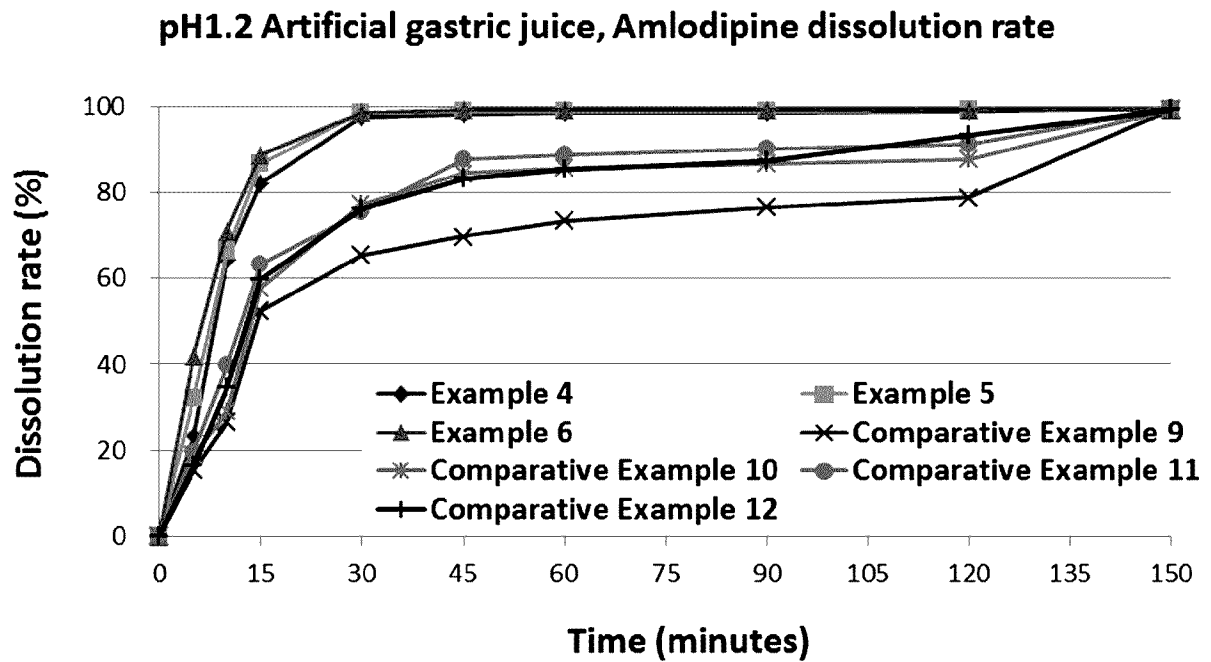
[Fig. 9]



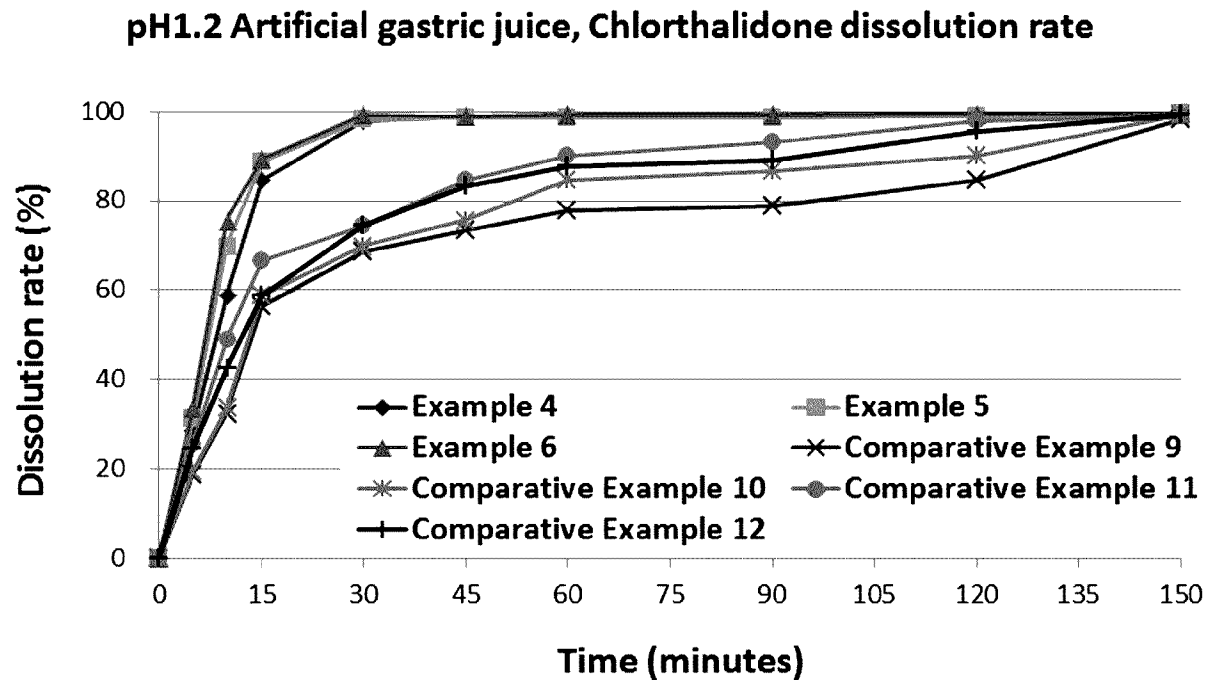
[Fig. 10]



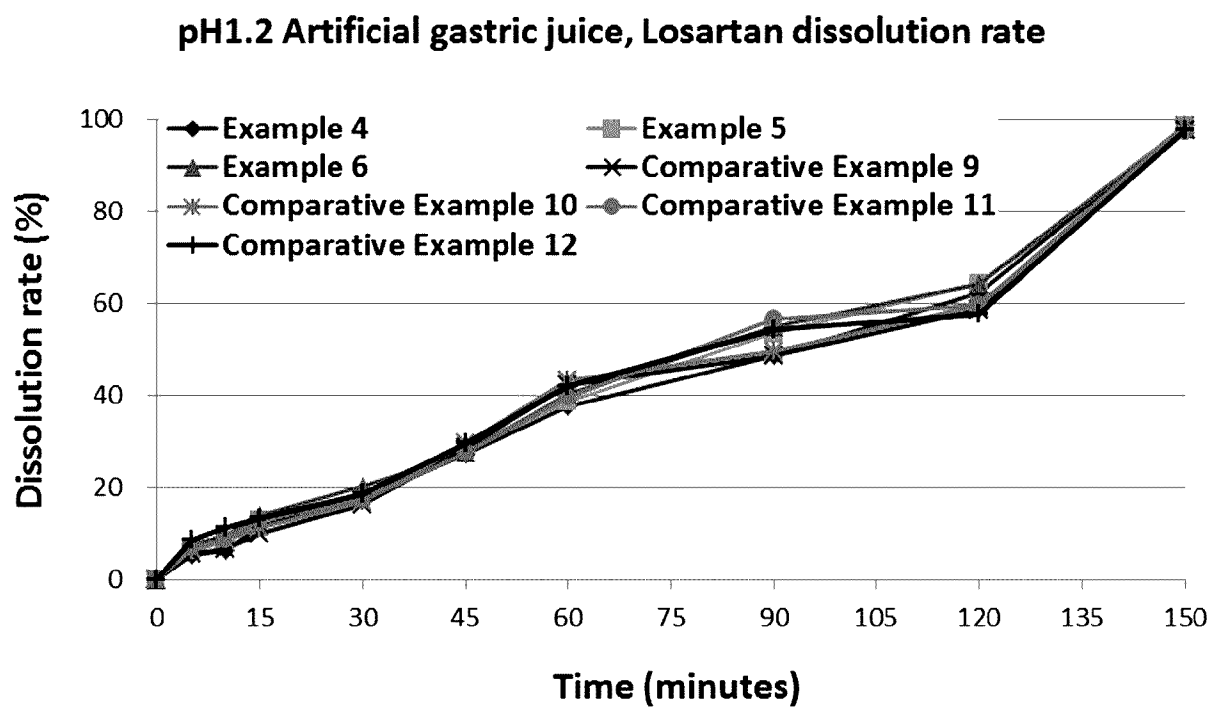
[Fig. 11]



[Fig. 12]



[Fig. 13]



**A. CLASSIFICATION OF SUBJECT MATTER****A61K 9/24(2006.01)i, A61K 9/20(2006.01)i, A61K 31/4422(2006.01)i, A61K 31/4178(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/24; A61K 31/417; A61K 9/14; A61K 9/22; A61K 31/4422; A61K 9/20; A61K 9/44; A61K 31/41; A61K 9/48; A61K 31/4178

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) &amp; Keywords: amlodipine, chlorthalidone, losartan, bilayer tablet, fixed-dose, granulation, compression

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                    | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | US 2012-0115854 A1 (SHETTY, S. S. et al.) 10 May 2012<br>See abstract; paragraphs [0042]-[0047]; and claims 1, 2, 16. | 1-12                  |
| A         | US 2007-0237815 A1 (SOLOMON, L. et al.) 11 October 2007<br>See the whole document.                                    | 1-12                  |
| A         | WO 2013-100630 A1 (HANMI PHARM. CO., LTD.) 04 July 2013<br>See the whole document.                                    | 1-12                  |
| A         | WO 2009-084040 A1 (RUBICON RESEARCH PRIVATE LIMITED) 09 July 2009<br>See the whole document.                          | 1-12                  |
| A         | US 2003-0152622 A1 (LOUIE-HELM, J. et al.) 14 August 2003<br>See the whole document.                                  | 1-12                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

07 September 2016 (07.09.2016)

Date of mailing of the international search report

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Name and mailing address of the ISA/KR

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/KR2016/002437**

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