



(51) International Patent Classification:

A61K 31/663 (2006.01) *A61K 9/20* (2006.01)
A61K 9/16 (2006.01) *A61K 9/48* (2006.01)

(21) International Application Number:

PCT/KR2012/005898

(22) International Filing Date:

24 July 2012 (24.07.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10-2011-0075051 28 July 2011 (28.07.2011) KR

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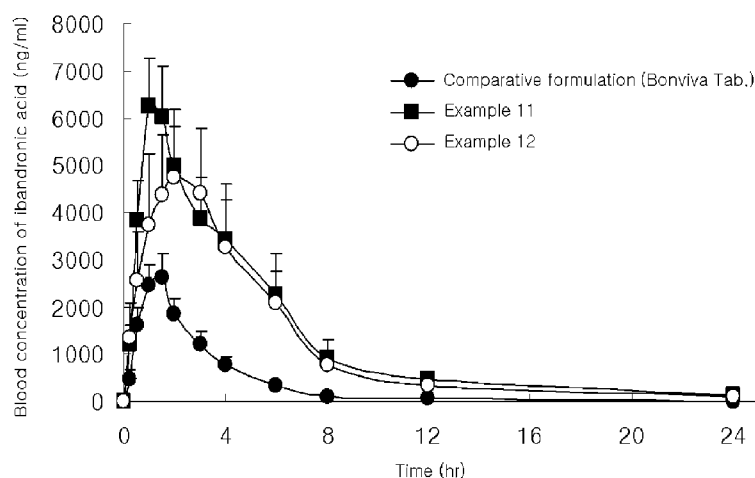
(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, 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, ML, MR, NE, SN, TD, TG).

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(54) **Title:** PHARMACEUTICAL COMPOSITION FOR ORAL ADMINISTRATION COMPRISING BISPHOSPHONIC ACID OR ITS SALT

[Fig. 1]



(57) **Abstract:** The present invention provides a pharmaceutical composition for oral administration, comprising bisphosphonic acid or its pharmaceutically acceptable salt; and gelatin, polyvinylacetate diethylaminoacetate, or a mixture thereof as an absorption enhancer. The pharmaceutical composition according to the present invention remarkably increases gastrointestinal absorption of bisphosphonic acid or its salt, thereby accomplishing high bioavailability thereof. And also, because the pharmaceutical composition according to the present invention shows desired pharmacological effects at a significantly low dose of bisphosphonic acid or its salt, it can minimize any side effects originated from relatively high dose thereof.



Published:

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

Description

Title of Invention: PHARMACEUTICAL COMPOSITION FOR ORAL ADMINISTRATION COMPRISING BISPHOSPHONIC ACID OR ITS SALT

Technical Field

- [1] The present invention relates to a pharmaceutical composition for oral administration comprising bisphosphonic acid or its pharmaceutically acceptable salt. More specifically, the present invention relates to a pharmaceutical composition for oral administration comprising a certain absorption enhancer for increasing a bioavailability of bisphosphonic acid or its pharmaceutically acceptable salt.

Background Art

- [2] Bisphosphonic acid or its pharmaceutically acceptable salt (conventionally referred to as "bisphosphonates") is useful for preventing or treating bone fracture, osteoporosis, Paget's disease, multiple myeloma, and other bone diseases associated with high bone resorption. Bisphosphonates bind to hydroxyapatites and decelerate bone-digesting cells (i.e., osteoclasts), which leads to more effective action by bone-forming cells (i.e., osteoblasts). As bisphosphonates, there are known various drugs such as ibandronic acid or its salt (ibandronate), risedronic acid its salt (risedronate), alendronic acid or its salt (alendronate), pamidronic acid or its salt (pamidronate), zoledronic acid or its salt (zoledronate), etc. In addition, there are known various polymorphs, hydrates, solvates, etc. thereof.
- [3] Meanwhile, bisphosphonates exhibit non-permeability to lipid biomembranes due to excessively high polarity thereof. In addition, it has been reported that such bisphosphonates have high affinity for multivalent metal ions such as calcium, and therefore suffer from difficulty of absorption via cell membranes in digestive tracts due to formation of insoluble complexes upon binding between the drugs and metal ions in vivo (Br. J. Cancer, 71, Suppl. 24, 67, 1995). Further, it is known that bisphosphonates cannot be absorbed through free diffusion and permeation which are absorption mechanisms for most of lipid-soluble drugs and that they can be absorbed via intercellular space. However, since the intercellular spaces occupy only less than 0.1% of the total surface area of the intestinal epithelium; and bisphosphonates also show difficulty even in such absorption via intercellular space, bisphosphonates have very low bioavailability. And also, bisphosphonates have poor permeability of the mucous layer present on the digestive tract mucous membrane and form an insoluble complex by interaction with a substance present in the mucous layer, which results in very low absorption rate. As a result, most of bisphosphonates have low absorption rate of less

than 10%. For example, it has been reported that an absorption rate of sodium ibandronate is less than 1%.

- [4] Various methods have been tried in order to improve bioavailability of drugs. It is necessary to appropriately design the methods according to physicochemical and pharmacological properties of individual drugs. Among the methods, there are uses of absorption enhancer.
- [5] Prior arts disclosing absorption enhancers for improving the bioavailability of bisphosphonates include WO 99/18972, WO 01/76577, WO 06/080780, US4,980,171, WO 00/61111, etc. WO 99/18972 and WO 01/76577 disclose the use of medium chain glycerides and zwitterionic phospholipids as an absorption enhancer, respectively. And also, WO 06/080780 and US4,980,171 disclose the use of chitosan and sodium lauryl sulfate as an absorption enhancer, respectively. In addition, WO 00/61111 discloses the use of various surfactant, a bile acid, fatty acid and saponification salts thereof, medium chain glycerides, oil, enamine, a chelating agent, phenothiazine, fatty acid derivatives of carnitine or peptide, azone, concanavalin A, phosphate and derivatives thereof, diphosphate and derivatives thereof, products from Maillard reactions, polymers including copolymers and biodegradable polymers, chitosan and chitosan derivatives as an absorption enhancer.
- [6] However, although various absorption enhancers are proposed, they did not still attain to satisfactory level. And also, according to physicochemical properties of the absorption enhancers, additional problems could be brought about. For example, fat-derived absorption enhancers (such as fatty acid, medium chain triglycerides, etc), which are in the form of liquid or semi-solid, should be used in very higher amount than the active ingredient, which makes it very difficult to formulate into solid dosage forms. And also, zwitterionic phospholipids have very low stability and perishable problems, thereby being difficult in applying to industrial mass production.

Disclosure of Invention

Technical Problem

- [7] The present inventors performed various researches for addressing the above problems, including very low bioavailability of bisphosphonates. Especially, the present inventors carried out various researches for finding an absorption enhancer for increasing the gastrointestinal absorption rate of bisphosphonates, which does not show gastrointestinal side effects and has biocompatibility. As a result, the present inventors surprisingly found that gelatin and/or polyvinylacetal diethylaminoacetate, which are widely used as a pharmaceutical excipient without safety concerns, can remarkably increase the gastrointestinal absorption rate of bisphosphonates, thereby resulting in high bioavailability.

- [8] Therefore, it is an object of the present invention to provide a bisphosphonate-containing pharmaceutical composition for oral administration comprising gelatin and/or polyvinylacetal diethylaminoacetate as an absorption enhancer.

Solution to Problem

- [9] In accordance with an aspect of the present invention, there is provided a pharmaceutical composition for oral administration, comprising bisphosphonic acid or its pharmaceutically acceptable salt; and gelatin, polyvinylacetal diethylaminoacetate, or a mixture thereof as an absorption enhancer.
- [10] In the pharmaceutical composition of the present invention, the bisphosphonic acid may be selected from the group consisting of ibandronic acid, risedronic acid, alendronic acid, pamidronic acid, and zoledronic acid. In an embodiment, the bisphosphonic acid may be ibandronic acid. In another embodiment, the ibandronic acid or its pharmaceutically acceptable salt may be present in an amount ranging from 50 mg to 120 mg per a unit dosage form; and the unit dosage form may be for once-a-month administration.
- [11] In the pharmaceutical composition of the present invention, a weight ratio of the bisphosphonic acid and the absorption enhancer may be from 10:1 to 1:10
- [12] The pharmaceutical composition of the present invention may further comprise one or more organic or inorganic acid selected from the group consisting of citric acid, succinic acid, fumaric acid, acetic acid, phosphoric acid, sulfuric acid and hydrochloric acid; and the organic or inorganic acid may be present in an amount ranging from 0.05 to 10 parts by weight, based on 1 part by weight of the bisphosphonic acid. And also, the pharmaceutical composition of the present invention may further comprise a surfactant or oil. The surfactant or oil may be one or more selected from the group consisting of caprylocaproyl macrogolglycerides, macrogol 15 hydroxystearate, vitamin E polyethylene glycol succinate, propyleneglycol dicaprylocaprate, propyleneglycol monolaurate, and propyleneglycol monocaprylate; and may be present in an amount ranging from 0.05 to 10 parts by weight, based on 1 part by weight of the bisphosphonic acid.
- [13] The pharmaceutical composition of the present invention may have a dosage form of powders; granules; a tablet; a capsule; a syrup; a solution; or a freeze-drying formulation that is reconstituted into a suspension, an emulsion, or a solution at the time of administration.
- [14] In an embodiment, there is provided a pharmaceutical composition for oral administration, wherein the pharmaceutical composition has a tablet form obtained by formulating powders or granules comprising bisphosphonic acid or its pharmaceutically acceptable salt; the absorption enhancer; an organic or inorganic acid; and a surfactant

or oil. The formulating may be carried out by compressing a mixture of the powders or granules and a pharmaceutically acceptable excipient to form a tablet. And also, the pharmaceutical composition for oral administration in the tablet form may further comprise an enteric coating layer on the tablet.

- [15] In another embodiment, the pharmaceutical composition of the present invention may further comprise vitamin D3 as an active ingredient. The vitamin D3 may be present in an amount ranging from 12,000 IU to 24,000 IU in a unit dosage form.

Advantageous Effects of Invention

- [16] The pharmaceutical composition of the present invention comprises gelatin and/or polyvinylacetal diethylaminoacetate as an absorption enhancer, which remarkably increases gastrointestinal absorption of bisphosphonic acid or its salt, thereby accomplishing high bioavailability thereof. And also, because the pharmaceutical composition according to the present invention shows desired pharmacological effects at a significantly low dose of bisphosphonic acid or its salt, it can minimize any side effects originated from relatively high dose thereof.

Brief Description of Drawings

- [17] FIG. 1 shows blood concentration profiles obtained after oral administrations of the tablets according to the present invention (Examples 11 and 12) and the comparative formulation (Bonviva™ Tab) to beagle dogs, respectively.
- [18] FIG. 2 shows the results of dissolution tests of the tablets according to the present invention (Examples 26 and 27).

Best Mode for Carrying out the Invention

- [19] The present invention provides a pharmaceutical composition for oral administration, comprising bisphosphonic acid or its pharmaceutically acceptable salt; and gelatin, polyvinylacetal diethylaminoacetate, or a mixture thereof as an absorption enhancer.
- [20] By using gelatin and/or polyvinylacetal diethylaminoacetate as an absorption enhancer according to the present invention, gastrointestinal absorption of bisphosphonic acid or its salt can be remarkably increased, thereby accomplishing high bioavailability thereof. Although the mechanism thereof is not still established clearly, we assume the mechanism as one of the followings: (i) the gelatin and/or polyvinylacetal diethylaminoacetate could mask the anionic site of bisphosphonic acid or its salt to expose the cationic site of the drugs, which results in improving the penetration via intercellular space; or (ii) the gelatin and/or polyvinylacetal diethylaminoacetate could inhibit the interaction(s) with the mucous layer and/or a substance present in the mucous layer, which results in improving the gastrointestinal absorption of drug; or (iii) the gelatin and/or polyvinylacetal diethylaminoacetate could increase a relative concentration of the drug in the mucous layer; or (iv) the gelatin and/or

polyvinylacetal diethylaminoacetate could both decrease polarity of the drug and increase affinity to lipid biomembranes, which induces favorable conditions for free diffusion and distribution through the lipid membrane.

- [21] In the pharmaceutical composition of the present invention, the bisphosphonic acid or its pharmaceutically acceptable salt include all known bisphosphonate derivatives useful in preventing and/or treating osteoporosis. For example, the bisphosphonic acid or its pharmaceutically acceptable salt includes, but not limited to, ibandronic acid or its salt, risedronic acid or its salt, alendronic acid or its salt, pamidronic acid or its salt, zoledronic acid or its salt. In an embodiment, the bisphosphonic acid or its pharmaceutically acceptable salt may be selected from the group consisting of ibandronic acid, an alkali metal salt of ibandronic acid (e.g., sodium ibandronate), risedronic acid, an alkali metal salt of risedronic acid (e.g., sodium risedronate), alendronic acid, an alkali metal salt of alendronic acid (e.g., sodium alendronate), pamidronic acid, an alkali metal salt of pamidronic acid (e.g., sodium pamidronate), zoledronic acid, and an alkali metal salt of zoledronic acid (e.g., sodium zoledronate); preferably ibandronic acid or an alkali metal salt of ibandronic acid. And also, the bisphosphonic acid or its pharmaceutically acceptable salt may be present in various forms, such as hydrates, solvates, polymorphs, etc. The bisphosphonic acid or its pharmaceutically acceptable salt in the pharmaceutical composition of the present invention includes such hydrates, solvates, polymorphs, etc, without any limitation.
- [22] The pharmaceutical composition according to the present invention can remarkably increase the bioavailability and thus expect desired pharmacological effects even at low dose. Therefore, the pharmaceutical composition according to the present invention may reduce the unit dose, thereby minimizing safety problems originated from receiving a high dose of the drug. The dose (and dosage) and administration route of the pharmaceutical composition of the present invention may be adjusted according to therapeutically effective amounts and patients' age, weight, susceptibility, or conditions. In an embodiment, when the pharmaceutical composition of the present invention is designed to a formulation for one-a-month administration (i.e., a formulation administered once per 4 weeks), the ibandronic acid or its pharmaceutically acceptable salt may be present in an amount ranging from 50 mg to 120 mg, preferably from 70 mg to 90 mg (for example, 70 mg, 80 mg or 90 mg) per unit dosage form.
- [23] The gelatin and/or polyvinylacetal diethylaminoacetate used as an absorption enhancer in the pharmaceutical composition of the present invention are biocompatible substances and may be used without safety problems. The absorption enhancer may be used in an amount sufficient for obtaining desired bioavailability. For example, when bisphosphonic acid or its salt (e.g., sodium ibandronate) is used, the weight ratio of bisphosphonic acid (the free acid form in case of using sodium ibandronate) and the ab-

sorption enhancer may be from 10:1 to 1:10, preferably from 2:1 to 1: 10.

- [24] The pharmaceutical composition of the present invention may further comprise an organic or inorganic acid, which reduces a dissolution time of the absorption enhancer and functions as a supplementary solubilizing agent. The organic or inorganic acid may be one or more selected from the group consisting of citric acid (including anhydrous form, monohydrate form, etc.), succinic acid, fumaric acid, acetic acid, phosphoric acid, sulfuric acid and hydrochloric acid. The organic or inorganic acid may be preferably acetic acid, hydrochloric acid, or citric acid; more preferably citric acid. The organic or inorganic acid may be used in an amount sufficient for accomplishing the said functions, i.e., reducing a dissolution time and/or functioning as a supplementary solubilizing agent. For example, the organic or inorganic acid may be used in an amount ranging from 0.05 to 10 parts by weight, preferably 0.1 to 5 parts by weight, based on 1 part by weight of the bisphosphonic acid.
- [25] And also, the pharmaceutical composition of the present invention may further comprise a surfactant or oil, which rapidly solubilizes the active ingredient and the absorption enhancer in the body and functions as a supplementary absorption enhancer of the active ingredient.
- [26] The surfactant may be one or more selected from polyoxyethylene-glycolated natural or hydrogenated castor oil; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene fatty acid esters; sugar fatty acid esters; polyoxyethylene-polyoxypropylene copolymers or block copolymers; sorbitan fatty acid esters; sterols or derivatives thereof; fatty acid or its derivatives or its salts such as capric acid, caprylic acid, sodium caprate, sodium lauryl sulfate; bile acid or its derivatives or its salts; phospholipids such as lecithin etc.; carnitine; betaine; docusate or its salt; caprylocaproyl macrogolglycerides; macrogol 15 hydroxystearate; vitamin E polyethylene glycol succinate, etc.
- [27] The oil may be one or more selected from vegetable or animal oil such as soybean oil, coconut oil, triglycerides, and wheat germ oil; and propyleneglycol fatty acid esters such as propyleneglycol dicaprylocaprate, propyleneglycol monolaurate, propylene glycol monocaprylate, oleic acid mono- or di-glyceride, isopropyl myristate, isopropyl palmitate, glyceryl linoleate, ethyl linoleate, ethyl oleate, oleic acid, linolenic acid, sorbitan oleate, monoolein, $C_8 \sim C_{10}$ mono- or di-glyceride extracted from coconut, $C_8 \sim C_{10}$ propyleneglycol diester extracted from coconut, liquid lecithin, etc.
- [28] Preferably, the surfactant or oil may be one or more selected from caprylocaproyl macrogolglycerides (for example, LabrasolTM), macrogol 15 hydroxystearate (for example, Solutol HS15TM), vitamin E polyethylene glycol succinate, propyleneglycol dicaprylocaprate (for example, Labrafac PGTM), propyleneglycol monolaurate (for example, Lauroglycol 90TM), and propyleneglycol monocaprylate (for example,

Capryol 90™). The surfactant or oil may be used in an amount ranging from 0.05 to 10 parts by weight, preferably from 0.1 to 5 parts by weight, based on 1 part by weight of the bisphosphonic acid, but not limited thereto.

- [29] The pharmaceutical composition according to the present invention may be formulated to various dosage forms for oral administration, using conventional formulation methods, such as blending, kneading, grinding, sieving, filling, compressing, lyophilizing, spray-drying, fluid-bed drying, centrifugal granulating. The pharmaceutical composition of the present invention may have a dosage form of powders; granules; a tablet; a capsule; a syrup; a solution; or a freeze-drying formulation that is reconstituted into a suspension, an emulsion, or a solution at the time of administration. Preferably, the pharmaceutical composition of the present invention may have a tablet form.
- [30] In an embodiment, there is provided a pharmaceutical composition having a tablet form, the tablet form being obtained by formulating powders or granules comprising bisphosphonic acid or its pharmaceutically acceptable salt; an absorption enhancer; an organic or inorganic acid; and a surfactant or oil.
- [31] In the pharmaceutical composition in a tablet form, the formulating may be carried out by compressing a mixture of the powders or granules and a pharmaceutically acceptable excipient to form a tablet. The pharmaceutically acceptable excipient includes a diluent, a binder, a disintegrant, a coloring agent, a sweetening agent, a flavor, a preservative, a lubricant, etc. which are conventionally used in the field of pharmaceuticals. For example, the diluent includes lactose, dextrose, microcrystalline cellulose, starch, mannitol, etc.; the binder includes polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, dicalcium phosphate, sodium alginate, etc.; the disintegrant includes croscarmellose sodium, sodium starch glycolate, cross-linked polyvinylpyrrolidone (i.e., crospovidone), gelatinated starch, low-substituted hydroxypropyl cellulose, etc.; the coloring agent includes soluble dye, tar dye, etc.; the sweetening agent includes dextrose, sorbitol, mannitol, aspartame, acesulfame, citric acid, etc.; the flavor includes orange flavor powder, grape flavor powder, strawberry flavor powder, blueberry flavor powder, etc.; the preservative includes benzoic acid, methylparaben, ethylparaben, propylparaben, etc.; and the lubricant includes magnesium stearate, talc, light anhydrous silicic acid (for example, Aerosil 200, etc.), sodium stearyl fumarate, aluminum magnesium silicate, stearic acid, sucrose fatty acid ester, etc. Preferably, the pharmaceutically acceptable excipient may be a mixture of a diluent (such as lactose, starch, microcrystalline cellulose, or mannitol), a disintegrant (such as crospovidone, sodium starch glycolate, or croscarmellose sodium), and a lubricant (such as light anhydrous silicic acid, sodium stearyl fumarate, aluminum magnesium silicate, or

stearic acid).

[32] In the pharmaceutical composition in a tablet form, the powders may be obtained by (i) adding bisphosphonic acid or its pharmaceutically acceptable salt; an absorption enhancer; an organic or inorganic acid; a surfactant or oil; and optionally a lubricant (such as light anhydrous silicic acid) to water to provide a solution or a dispersion, and then (ii) drying the solution or the dispersion. The drying may be carried out according to conventional methods, including for example drying under reduced pressure, spray-drying, etc.

[33] And also, the granules may be obtained by (i') adding bisphosphonic acid or its pharmaceutically acceptable salt; an absorption enhancer; an organic or inorganic acid; and a surfactant or oil to water to provide a solution or a dispersion, and then (ii') spraying the solution or the dispersion onto a fluidizing pharmaceutically acceptable excipient in a fluid bed granulator. And also, the granulation may be performed by dividing the amount of bisphosphonic acid or its pharmaceutically acceptable salt into 2 parts, followed by using the one portion in the preparation of a solution or a dispersion and the other portion in the fluidization of the pharmaceutically acceptable excipient therewith. That is, the granules may be obtained by (i'') adding a portion of bisphosphonic acid or its pharmaceutically acceptable salt (A); an absorption enhancer; an organic or inorganic acid; and a surfactant or oil to water to provide a solution or a dispersion, and then (ii'') spraying the solution or the dispersion onto a fluidizing mixture of the remaining portion of bisphosphonic acid or its pharmaceutically acceptable salt (B) and a pharmaceutically acceptable excipient in a fluid bed granulator. At this time, the weight ratio of A and B is from 1:1 to 1:3, but not limited thereto. In the granulation process, the pharmaceutically acceptable excipient includes, as described in the above, a diluent, a binder, a disintegrant, a coloring agent, a sweetening agent, a flavor, a preservative, a lubricant, etc. which are conventionally used in the field of pharmaceuticals. Preferably, the pharmaceutically acceptable excipient may be a mixture of a diluent (such as lactose, starch or microcrystalline cellulose), a disintegrant (such as croscopolvidone or sodium starch glycolate), and a lubricant (such as light anhydrous silicic acid or sodium stearyl fumarate).

[34] In addition, if necessary, the pharmaceutical composition in a tablet form may further comprise an enteric coating layer on the tablet. The enteric coating layer may be formed according to conventional methods, using enteric coating agents conventionally used in the field of pharmaceuticals. If necessary, sub-coating layer may be formed using e.g., hydroxypropyl methylcellulose, prior to the enteric coating. The enteric coating agent includes, but not limited to, for example a copolymer of methyl methacrylate and methacrylic acid (1:1) (for example, Eudragit L, Rohm GmbH), a copolymer of methyl methacrylate and methacrylic acid (2:1) (for example, Eudragit S, Rohm GmbH), a

copolymer of ethyl acrylate and methacrylic acid (1:1) (for example, Eudragit LD-55, Rohm GmbH), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose acetate phthalate, shellac, zein, etc.

[35] The pharmaceutical composition according to the present invention is rapidly disintegrated in the stomach and then releases all of the active ingredient (i.e., bisphosphonic acid or its salt) within 1 hour, typically 30 minutes, from the dosage form. At this time, the absorption enhancer is rapidly dissolved and facilitates the membrane penetration of the drug.

[36] The pharmaceutical composition of the present invention may further comprise vitamin D3 as an active ingredient, for improving the calcium absorption. Vitamin D3 may be present in an amount necessary for improving the calcium absorption. For example, in case of a formulation for once-a-month administration, the vitamin D3 may be present in an amount ranging from 12,000 IU to 24,000 IU in a unit dosage form. The pharmaceutical composition of the present invention further comprising vitamin D3 may further comprise a surfactant or oil as described in the above; may be formulated into powders, granules, a tablet, a capsule, a syrup, a solution, or a freeze-drying formulation that is reconstituted into a suspension, an emulsion, or a solution at the time of administration. Therefore, according to an embodiment, there is provided a pharmaceutical composition having a tablet form, the tablet form being obtained by formulating powders or granules comprising bisphosphonic acid or its pharmaceutically acceptable salt; vitamin D3; an absorption enhancer; an organic or inorganic acid; and a surfactant or oil. The formulating may be carried out by compressing a mixture of the powders or granules and a pharmaceutically acceptable excipient to form a tablet. In addition, the pharmaceutical composition in a tablet form may further comprise an enteric coating layer on the tablet.

[37] The present invention will be described in further detail with reference to the following examples and experimental examples. These examples and experimental examples are for illustrative purposes only and are not intended to limit the scope of the present invention.

[38]

[39] **Example 1: Preparation of a solution**

[40] 113 mg of Sodium ibandronate (corresponding to 100 mg as ibandronic acid), 1,000 mg of gelatin (210B(F), Geltech Co., Ltd.), and 500 mg of citric acid were dissolved in 50 mL of distilled water to obtain a solution.

[41]

[42] **Example 2: Preparation of a powder formulation**

[43] 563 mg of Sodium ibandronate (corresponding to 500 mg as ibandronic acid) and 1 g

of citric acid were dissolved in 100 g of distilled water. 2.5 g of Polyvinylacetal diethylaminoacetate was completely dissolved in the solution. 0.5 g of Labrafac PG and 0.5 g of Labrasol were added to the solution under stirring at 300 rpm. 0.15 g of Aerosil 200 was added to the solution, which was then stirred at 300 rpm. The resulting dispersion was spray-dried using a spray-dryer (Mini spray dryer, Buchi 190), at the conditions of 120~130°C of inlet temperature and 80~90°C of outlet temperature, to obtain powders.

[44]

[45] **Example 3: Preparation of a powder formulation**

[46] 563 mg of Sodium ibandronate (corresponding to 500 mg as ibandronic acid) and 1 g of citric acid were dissolved in 100 g of distilled water. 2.5 g of Polyvinylacetal diethylaminoacetate was completely dissolved in the solution. 0.5 g of Capryol 90 and 0.5 g of Labrasol were added to the solution under stirring at 300 rpm. 0.15 g of Aerosil 200 was added to the solution, which was then stirred at 300 rpm. The resulting dispersion was spray-dried at the same conditions of Example 2 to obtain powders.

[47]

[48] **Example 4: Preparation of a powder formulation**

[49] 563 mg of Sodium ibandronate (corresponding to 500 mg as ibandronic acid) and 1 g of citric acid were dissolved in 100 g of distilled water. 2.5 g of gelatin (210B(F), Geltech Co., Ltd.) was completely dissolved in the solution. 0.5 g of Labrafac PG and 0.5 g of Labrasol were added to the solution under stirring at 300 rpm. 0.15 g of Aerosil 200 was added to the solution, which was then stirred at 300 rpm. The resulting dispersion was spray-dried at the same conditions of Example 2 to obtain powders.

[50]

[51] **Example 5: Preparation of a powder formulation**

[52] 16.88 g of Sodium ibandronate (corresponding to 15 g as ibandronic acid), 10 g of polyvinylacetal diethylaminoacetate and 4 g of citric acid were completely dissolved in 120 g of distilled water under stirring. 2 g of Labrafac PG and 2 g of Labrasol were added to the solution under stirring. 3 g of Aerosil 200 was dispersed in the solution under stirring. The resulting dispersion was spray-dried at the same conditions of Example 2 to obtain powders.

[53]

[54] **Example 6: Preparation of a powder formulation**

[55] 16.88 g of Sodium ibandronate (corresponding to 15 g as ibandronic acid), 10 g of gelatin (210B(F), Geltech Co., Ltd.) and 4 g of citric acid were completely dissolved in 100 g of distilled water under stirring. 2 g of Labrafac PG and 2 g of Labrasol were added to the solution under stirring. 3 g of Aerosil 200 was dispersed in the solution under stirring. The resulting dispersion was spray-dried at the same conditions of

Example 2 to obtain powders.

[56]

[57] **Example 7: Preparation of a powder formulation**

[58] 16.88 g of Sodium ibandronate (corresponding to 15 g as ibandronic acid), 10 g of gelatin (210B(F), Geltech Co., Ltd.) and 3 g of citric acid were completely dissolved in 100 g of distilled water under stirring. 2 g of Lauroglycol 90 and 2 g of Labrasol were added to the solution under stirring. 3 g of Aerosil 200 was dispersed in the solution under stirring. The resulting dispersion was spray-dried at the same conditions of Example 2 to obtain powders.

[59]

[60] **Example 8: Preparation of a powder formulation**

[61] 16.88 g of Sodium ibandronate (corresponding to 15 g as ibandronic acid), 10 g of gelatin (210B(F), Geltech Co., Ltd.) and 4 g of citric acid were completely dissolved in 150 g of distilled water under stirring. 2 g of Labrafac PG and 2 g of vitamin E polyethylene glycol succinate were added to the solution under stirring. 3 g of Aerosil 200 was dispersed in the solution under stirring. The resulting dispersion was spray-dried at the same conditions of Example 2 to obtain powders.

[62]

[63] **Example 9: Preparation of a powder formulation**

[64] 16.88 g of Sodium ibandronate (corresponding to 15 g as ibandronic acid), 10 g of polyvinylacetal diethylaminoacetate and 4 g of hydrochloric acid were completely dissolved in 150 g of distilled water under stirring. 2 g of Capryol 90 and 2 g of Solutol HS15 were added to the solution under stirring. 3 g of Aluminum magnesium silicate was dispersed in the solution under stirring. The resulting dispersion was spray-dried at the same conditions of Example 2 to obtain powders.

[65]

[66] **Example 10: Preparation of a powder formulation**

[67] 563 mg of Sodium ibandronate (corresponding to 500 mg as ibandronic acid) and 2 g of citric acid were completely dissolved in 100 g of distilled water. 5 g of Polyvinylacetal diethylaminoacetate was completely dissolved in the solution. The resulting solution was spray-dried at the same conditions of Example 2 to obtain powders.

[68]

[69] **Comparative Example 1: Preparation of a solution**

[70] 113 mg of Sodium ibandronate (corresponding to 100 mg as ibandronic acid) was dissolved in 50 mL of distilled water to obtain a transparent solution.

[71]

[72] **Comparative Example 2: Preparation of a solution**

[73] 113 mg of Sodium ibandronate (corresponding to 100 mg as ibandronic acid) and 500 mg of citric acid were dissolved in 50 mL of distilled water to obtain a transparent solution.

[74]

[75] **Experimental Example 1: Evaluation of bioavailability in rats**

[76] The solutions and the powders obtained in Examples 1 to 4 and Comparative Examples 1 and 2 were orally administered to rats and then evaluated the bioavailabilities thereof. Sprague-Dawley rats (body weight: 200 to 230 g) fasted for 12 hours were divided into 6 groups, each group having 4 rats (i.e. n=4). The solution (obtained in Example 1, Comparative Example 1, or Comparative Example 2) and the powders (obtained in Examples 2 to 4) were orally administered to rats of each group. The powders were dispersed in distilled water and then administered. The administrations were carried out using an oral zonde in a dose of 10 mg/kg as a ibandronic acid, respectively. About 0.3 ml of blood was collected using a heparin-treated injector, at the time of 0.25, 0.5, 1, 1.5, 2, 3, and 5 hours after the administration. The collected blood was centrifuged at 10,000 rpm for 1 minute, and then the separated serum was stored at -20 °C for analysis. The concentration of ibandronic acid in the serum was analyzed with LC/MS/MS. The pharmacokinetic parameters obtained from blood concentration profiles are presented in Table 1 below.

[77] <Table 1>

	AUC _{0-5hr} (ng·hr/mL)	Cmax (ng/mL)
Example 1	894.5±313.7	978.3±345.9
Example 2	1665.6±582.6	1705.4±607.1
Example 3	1326.2±567.7	1132.8±507.2
Example 4	1515.1±516.9	1211.3±444.3
Comparative Example 1	200.9±46.5	242.3±60.0
Comparative Example 2	228.3±82.4	250.7±70.8

[79]

[80] As shown in Table 1, the formulations of Examples 1 to 4 prepared according to the present invention exhibited about 2 to 8 times higher absorption rate than the formulations of Comparative Example 1 having no absorption enhancer. And also, the formulations prepared according to the present invention exhibited remarkably excellent absorption rate, in comparison with the formulation having only an acid (Comparative Example 2).

[81]

[82] **Example 11: Preparation of a tablet**

[83] The mixture of 15.15 g of the powders prepared in Example 5, 0.8 g of lactose, 1.6 g of microcrystalline cellulose, 2.85 g of crospovidone, 0.4 g of Aerosil 200, and 0.4 g of sodium stearyl fumarate was compressed with a single-punch tablet-press machine to

obtain tablets, each containing 150 mg as ibandronic acid.

[84]

[85] **Example 12: Preparation of a tablet**

[86] The mixture of 15.15 g of the powders prepared in Example 6, 0.8 g of lactose, 1.6 g of microcrystalline cellulose, 2.85 g of crospovidone, 0.4 g of Aerosil 200, and 0.4 g of sodium stearyl fumarate was compressed with a single-punch tablet-press machine to obtain tablets, each containing 150 mg as ibandronic acid.

[87]

[88] **Example 13: Preparation of a tablet**

[89] The mixture of 15.15 g of the powders prepared in Example 7, 0.8 g of lactose, 1.6 g of microcrystalline cellulose, 2.85 g of sodium starch glycolate, 0.4 g of Aerosil 200, and 0.4 g of stearic acid was compressed with a single-punch tablet-press machine to obtain tablets, each containing 150 mg as ibandronic acid.

[90]

[91] **Example 14: Preparation of a tablet**

[92] The mixture of 15.15 g of the powders prepared in Example 8, 0.8 g of starch, 1.6 g of mannitol, 2.85 g of croscarmellose sodium, 0.4 g of Aerosil 200, and 0.4 g of stearic acid was compressed with a single-punch tablet-press machine to obtain tablets, each containing 150 mg as ibandronic acid.

[93]

[94] **Experimental Example 2: Evaluation of bioavailability in beagle dogs**

[95] The bioavailabilities of the tablets prepared in Examples 11 and 12 were evaluated using beagle dogs. The commercially available Bonviva™ Tablet (GlaxoSmithKline PLC) was used as a comparative formulation. Beagle dogs (body weight: about 10 kg) fasted for 12 hours were divided into 3 groups, each group having 5~6 dogs (i.e. n=5~6). The dogs of Group 1 were orally administered with Bonviva™ Tablet (GlaxoSmithKline PLC). The dogs of Group 2 and 3 were orally administered with the tablets prepared in Examples 11 (Group 2) and 12 (Group 3), respectively. The blood was collected using a heparin-treated injector, at the time of 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours after the administration. The collected blood was centrifuged at 3,000 rpm for 5 minutes, and then the separated serum was stored at -20 °C for analysis. The concentration of ibandronic acid in the serum was analyzed with LC/MS/MS. The blood concentration profiles are shown in FIG. 1; and the pharmacokinetic parameters are presented in Table 2 below.

[96] <Table 2>

[97]

Parameters	Comparative formulation	Example 11	Example 12
Contents of active ingredient	150 mg	150 mg	150 mg
AUC _{0-24hr} (ng·hr/ml)	8413.5±1406.1	32361.7±7287.3	27728.9±8017.2
C _{max} (ng/ml)	3183.3±377.5	7200.0±835.7	5198.8±1513.3
T _{max} (hr)	1.2±0.2	1.6±0.6	1.8±0.4

[98]

[99]

As shown in FIG. 1 and Table 2, the tablets prepared according to the present invention exhibited about 2.3 times and 1.6 times higher C_{max} and about 3.7 times and 3.3 times higher AUC_{0-24hr} than the comparative formulation, respectively. From these results, it can be seen that the pharmaceutical composition of the present invention remarkably increase bioavailability of ibandronic acid.

[100]

[101]

Example 15: Preparation of a granular formulation

[102]

48 g of Sodium ibandronate, 48 g of polyvinylacetal diethylaminoacetate, 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Labrasol and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 114 g of sodium ibandronate, 30 g of microcrystalline cellulose, 12 g of lactose, 12 g of Aerosil 200 and 48 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain the spray-dried granules. The conditions of the fluid bed granulator were as follows; Inlet air temperature: 60~75°C, atomizing pressure: 0.5~1.5 bar.

[103]

[104]

Example 16: Preparation of a granular formulation

[105]

48 g of Sodium ibandronate, 48 g of polyvinylacetal diethylaminoacetate, 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Labrasol and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 73.5 g of sodium ibandronate, 70.5 g of microcrystalline cellulose, 12 g of lactose, 12 g of Aerosil 200 and 48 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[106]

[107]

Example 17: Preparation of a granular formulation

[108]

56.3 g of Sodium ibandronate, 70 g of polyvinylacetal diethylaminoacetate, 30 g of citric acid were completely dissolved in 875 g of distilled water. 10 g of Labrasol and 10 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 128.8 g of microcrystalline

cellulose, 35 g of lactose, 10 g of Aerosil 200 and 50 g of crospovidone in a fluid bed granulator (GPCG-1, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[109]

[110] **Example 18: Preparation of a granular formulation**

[111] 48 g of Sodium ibandronate, 48 g of gelatin (210B(F), Geltech Co., Ltd.), 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Solutol HS15 and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 114 g of sodium ibandronate, 30 g of microcrystalline cellulose, 12 g of lactose, 12 g of Aerosil 200 and 48 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[112]

[113] **Example 19: Preparation of a granular formulation**

[114] 48 g of Sodium ibandronate, 48 g of gelatin (210B(F), Geltech Co., Ltd.), 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Solutol HS15 and 12 g of Lauroglycol 90 were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 114 g of sodium ibandronate, 30 g of microcrystalline cellulose, 12 g of lactose, 12 g of Aerosil 200 and 48 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[115]

[116] **Example 20: Preparation of a granular formulation**

[117] 48 g of Sodium ibandronate, 48 g of polyvinylacetal diethylaminoacetate, 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Labrasol and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 60 g of sodium ibandronate, 90 g of microcrystalline cellulose, 30 g of lactose, 12 g of Aerosil 200 and 24 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[118]

[119] **Example 21: Preparation of a granular formulation**

[120] 48 g of Sodium ibandronate, 48 g of polyvinylacetal diethylaminoacetate, 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Labrasol and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting

dispersion was spray-dried onto the fluidizing mixture of 46.5 g of sodium ibandronate, 103.5 g of microcrystalline cellulose, 30 g of lactose, 12 g of Aerosil 200 and 24 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[121]

[122] **Example 22: Preparation of a granular formulation**

[123] 48 g of Sodium risedronate, 24 g of polyvinylacetal diethylaminoacetate, 12 g of citric acid were completely dissolved in 600 g of distilled water. 4.8 g of Labrasol and 4.8 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 117.4 g of sodium risedronate, 17 g of microcrystalline cellulose, 6 g of lactose, 6 g of Aerosil 200 and 12 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[124]

[125] **Example 23: Preparation of a granular formulation**

[126] 48 g of Sodium risedronate, 24 g of polyvinylacetal diethylaminoacetate, 12 g of citric acid were completely dissolved in 600 g of distilled water. 4.8 g of Labrasol and 4.8 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 62.2 g of sodium risedronate, 72.2 g of microcrystalline cellulose, 6 g of lactose, 6 g of Aerosil 200 and 12 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[127]

[128] **Example 24: Preparation of a granular formulation**

[129] 48 g of Sodium alendronate, 48 g of polyvinylacetal diethylaminoacetate, 24 g of citric acid were completely dissolved in 600 g of distilled water. 12 g of Labrasol and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 39.6 g of sodium alendronate, 44.4 g of microcrystalline cellulose, 12 g of lactose, 12 g of Aerosil 200 and 48 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[130]

[131] **Example 25: Preparation of a granular formulation**

[132] 48 g of Sodium alendronate, 48 g of polyvinylacetal diethylaminoacetate, 24 g of

citric acid were completely dissolved in 600 g of distilled water. 12 g of Labrasol and 12 g of Labrafac PG were dispersed in the solution under stirring. The resulting dispersion was spray-dried onto the fluidizing mixture of 12 g of sodium alendronate, 72 g of microcrystalline cellulose, 12 g of lactose, 12 g of Aerosil 200 and 48 g of crospovidone in a fluid bed granulator (mini Glatt, Glatt Corporation) to obtain spray-dried granules. The conditions of the fluid bed granulator were the same as in Example 15.

[133]

[134] **Examples 26 to 32: Preparation of a tablet**

[135] Tablets were prepared using the granules obtained in Examples 15 to 17 and 19 to 21. The tables were prepared in the same procedures as in Example 11, according to the components and amounts shown in Table 3 below. Each amount in Table 3 represents the amount of the respective component per one tablet.

[136] <Table 3>

[137]

	Example						
	26	27	28	29	30	31	32
Granules of Example 15	300						
Granules of Example 16		300					
Granules of Example 17			400				
Granules of Example 19				300	300		
Granules of Example 20						300	
Granules of Example 21							300
Microcrystalline cellulose	95	100	40	110	100	95	100
Crospovidone	40	40	50		20	20	40
Sodium starch glycolate				30	20	20	
Aerosil	5					5	
Sodium stearyl fumarate	10	10	10	10	10	10	10
Total weight	450	450	500	450	450	450	450

[138]

[139] **Examples 33 to 36: Preparation of a tablet**

[140] Tablets were prepared using the granules obtained in Examples 22 to 25. The tables were prepared in the same procedures as in Example 11, according to the components and amounts shown in Table 4 below. Each amount in Table 4 represents the amount of the respective component per one tablet.

[141] <Table 4>

[142]

	Example 33	Example 34	Example 35	Example 36
Granules of Example 22	210			
Granules of Example 23		210		
Granules of Example 24			250	
Granules of Example 25				250
Microcrystalline cellulose	10	10	60	60
Crospovidone	25	25	30	30
Aerosil	5	5		
Sodium stearyl fumarate			10	10
Total weight	250	250	350	350

[143]

[144] **Example 37**

[145] A 10% solution of hydroxypropyl methylcellulose (HPMC) was sprayed onto the tablet prepared in Example 27, using a High Coater, to obtain tablets sub-coated with 2% of HPMC (inlet air temperature: 55~70°C, outlet air temperature: 40~45°C). A 10% enteric coating solution (Eudragit L 30 D-55 : triethyl citrate : talc = 416.7 : 12.5 : 62.5) was sprayed onto the subcoated tablets, using a High Coater, to obtain tablets coated with about 9% of enteric coating agent, i.e., Eudragit L 30 D-55 (inlet air temperature: 50~60°C, outlet air temperature: 35~45°C).

[146]

[147] **Example 38**

[148] A 10% solution of hydroxypropyl methylcellulose (HPMC) was sprayed onto the tablet prepared in Example 31, using a High Coater, to obtain tablets sub-coated with 2% of HPMC (inlet air temperature: 55~70°C, outlet air temperature: 40~45°C). A 10% enteric coating solution (Eudragit L 30 D-55 : triethyl citrate : talc = 416.7 : 12.5 : 62.5) was sprayed onto the subcoated tablets, using a High Coater, to obtain tablets coated with about 9% of enteric coating agent, i.e., Eudragit L 30 D-55 (inlet air temperature: 50~60°C, outlet air temperature: 35~45°C).

[149]

[150] **Example 39**

[151] A 10% solution of hydroxypropyl methylcellulose (HPMC) was sprayed onto the tablet prepared in Example 34, using a High Coater, to obtain tablets sub-coated with 2% of HPMC (inlet air temperature: 55~70°C, outlet air temperature: 40~45°C). A 10% enteric coating solution (Eudragit L 30 D-55 : triethyl citrate : talc = 416.7 : 12.5 : 62.5) was sprayed onto the subcoated tablets, using a High Coater, to obtain tablets coated with about 9% of enteric coating agent, i.e., Eudragit L 30 D-55 (inlet air temperature: 50~60°C, outlet air temperature: 35~45°C).

[152]

[153] **Example 40**

[154] A 10% solution of hydroxypropyl methylcellulose (HPMC) was sprayed onto the

tablet prepared in Example 36, using a High Coater, to obtain tablets sub-coated with 2% of HPMC (inlet air temperature: 55~70°C, outlet air temperature: 40~45°C). A 10% enteric coating solution (Eudragit L 30 D-55 : triethyl citrate : talc = 416.7 : 12.5 : 62.5) was sprayed onto the subcoated tablets, using a High Coater, to obtain tablets coated with about 9% of enteric coating agent, i.e., Eudragit L 30 D-55 (inlet air temperature: 50~60°C, outlet air temperature: 35~45°C).

[155]

[156] **Experimental Example 3: Dissolution Test**

[157] The dissolution tests of the tablets prepared in Examples 26 and 27 were performed according to the 'Dissolution Test 2 (Paddle Method)' of the Korean Pharmacopeia. 900 ml of water was used as a dissolution medium and the dissolution test was performed at 37 ± 0.5 °C and at the paddle rotation rate of 50 rpm. A 4 ml aliquot was taken from the dissolution medium at the time of 5, 10, 15, 30, 45, and 60 minutes, respectively. Each aliquot was filtered with a 0.45 μm syringe filter. The resulting filtrate was analyzed with HPLC. The results are presented in FIG. 2.

[158]

[159] **Experimental Example 4: Evaluation of bioavailability in beagle dogs**

[160] The bioavailabilities of the tablets prepared in Examples 26, 37 and 38 were evaluated using beagle dogs. The commercially available Bonviva™ Tablet (GlaxoSmithKline PLC) was used as a comparative formulation. Beagle dogs (body weight: about 10 kg) fasted for 12 hours were divided into 4 groups, each group having 10 dogs (i.e. n=10). The dogs of Group 1 were orally administered with Bonviva™ Tablet (GlaxoSmithKline PLC). The dogs of Group 2 to 4 were orally administered with the tablets prepared in Examples 26 (Group 2), 37 (Group 3) and 38 (Group 4), respectively. The blood was collected using a heparin-treated injector, at the time of 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24 hours after the administration. The collected blood was centrifuged at 3,000 rpm for 5 minutes, and then the separated serum was stored at -20 °C for analysis. The concentration of ibandronic acid in the serum was analyzed with LC/MS/MS. The pharmacokinetic parameters obtained from the blood concentration profiles are presented in Table 5 below.

[161] <Table 5>

[162]

Parameters	Comparative formulation	Example 26	Example 37	Example 38
Contents of active ingredient	150mg	120mg	90mg	80mg
AUC _{0-24hr} (ng·hr/ml)	6035.2±2103.9	6350.0±1440.6	10130.0±1086.4	8024.7±1860.6
C _{max} (ng/ml)	1898.2±575.7	2051.3±412.2	3548.0±333.0	3155.0±519.4
T _{max} (hr)	1.0±0.5	1.4±0.8	2.1±0.7	2.0±0.2

[163]

[164] As shown in Table 5, the tablet of Example 26 containing 120 mg of ibandronic acid showed an equivalent bioavailability to the comparative formulation (Bonviva™ Tablet) containing 150 mg of ibandronic acid. And also, the tablet of Example 38 containing 80 mg of ibandronic acid exhibited about 1.7 times higher C_{max} and about 1.3 times higher AUC_{0-24hr} than the comparative formulation (Bonviva™ Tablet). From these results, it can be seen that the pharmaceutical composition of the present invention has high bioavailability and show equivalent effects even at significantly low amount (e.g., not higher than 80 mg of ibandronic acid) to the commercially available formulation.

Claims

- [Claim 1] A pharmaceutical composition for oral administration, comprising bisphosphonic acid or its pharmaceutically acceptable salt; and gelatin, polyvinylacetal diethylaminoacetate, or a mixture thereof as an absorption enhancer.
- [Claim 2] The pharmaceutical composition for oral administration according to claim 1, wherein the bisphosphonic acid is selected from the group consisting of ibandronic acid, risedronic acid, alendronic acid, pamidronic acid, and zoledronic acid.
- [Claim 3] The pharmaceutical composition for oral administration according to claim 2, wherein the bisphosphonic acid is ibandronic acid.
- [Claim 4] The pharmaceutical composition for oral administration according to claim 3, wherein the ibandronic acid or its pharmaceutically acceptable salt is present in an amount ranging from 50 mg to 120 mg per a unit dosage form; and the unit dosage form is for once-a-month administration.
- [Claim 5] The pharmaceutical composition for oral administration according to claim 1, wherein a weight ratio of the bisphosphonic acid and the absorption enhancer is from 10:1 to 1:10.
- [Claim 6] The pharmaceutical composition for oral administration according to claim 1, further comprising one or more organic or inorganic acid selected from the group consisting of citric acid, succinic acid, fumaric acid, acetic acid, phosphoric acid, sulfuric acid and hydrochloric acid.
- [Claim 7] The pharmaceutical composition for oral administration according to claim 6, wherein the organic or inorganic acid is present in an amount ranging from 0.05 to 10 parts by weight, based on 1 part by weight of the bisphosphonic acid.
- [Claim 8] The pharmaceutical composition for oral administration according to claim 1, further comprising a surfactant or oil.
- [Claim 9] The pharmaceutical composition for oral administration according to claim 8, wherein the surfactant or oil is one or more selected from the group consisting of caprylocaproyl macroglycerides, macrogol 15 hydroxystearate, vitamin E polyethylene glycol succinate, propylene glycol dicaprylocaprate, propylene glycol monolaurate, and propylene glycol monocaprylate.
- [Claim 10] The pharmaceutical composition for oral administration according to claim 8, wherein the surfactant or oil is present in an amount ranging

from 0.05 to 10 parts by weight, based on 1 part by weight of the bisphosphonic acid.

[Claim 11] The pharmaceutical composition for oral administration according to claim 1, wherein the pharmaceutical composition has a dosage form of powders; granules; a tablet; a capsule; a syrup; a solution; or a freeze-drying formulation that is reconstituted into a suspension, an emulsion, or a solution at the time of administration.

[Claim 12] The pharmaceutical composition for oral administration according to claim 1, wherein the pharmaceutical composition has a tablet form obtained by formulating powders or granules comprising bisphosphonic acid or its pharmaceutically acceptable salt; the absorption enhancer; an organic or inorganic acid; and a surfactant or oil.

[Claim 13] The pharmaceutical composition for oral administration according to claim 12, wherein the formulating is carried out by compressing a mixture of the powders or granules and a pharmaceutically acceptable excipient to form a tablet.

[Claim 14] The pharmaceutical composition for oral administration according to claim 13, wherein the pharmaceutically acceptable excipient is a mixture of a diluent, a disintegrant, and a lubricant.

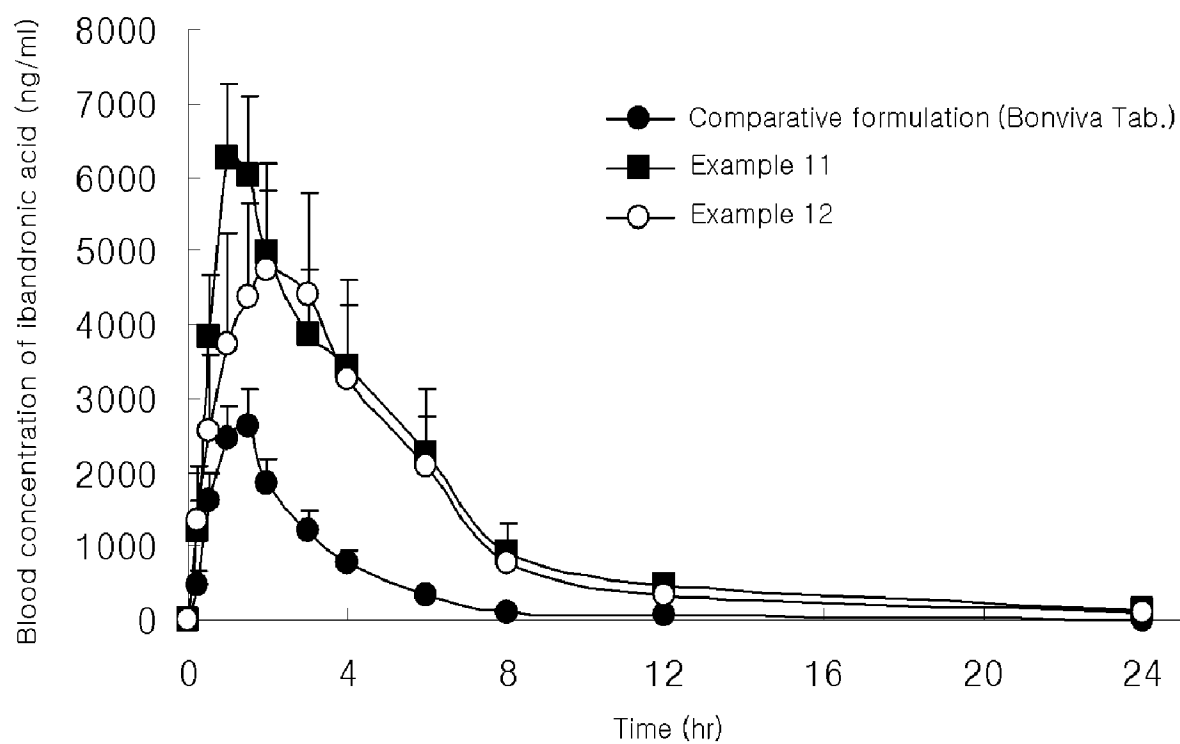
[Claim 15] The pharmaceutical composition for oral administration according to claim 12, wherein the powders are obtained by (i) adding bisphosphonic acid or its pharmaceutically acceptable salt; the absorption enhancer; the organic or inorganic acid; the surfactant or oil; and optionally a lubricant to water to provide a solution or a dispersion, and then (ii) drying the solution or the dispersion.

[Claim 16] The pharmaceutical composition for oral administration according to claim 12, wherein the granules are obtained by (i') adding bisphosphonic acid or its pharmaceutically acceptable salt; the absorption enhancer; the organic or inorganic acid; and the surfactant or oil to water to provide a solution or a dispersion, and then (ii') spraying the solution or the dispersion onto a fluidizing pharmaceutically acceptable excipient in a fluid bed granulator.

[Claim 17] The pharmaceutical composition for oral administration according to claim 12, wherein the granules are obtained by (i'') adding a portion of bisphosphonic acid or its pharmaceutically acceptable salt (A); the absorption enhancer; the organic or inorganic acid; and the surfactant or oil to water to provide a solution or a dispersion, and then (ii'') spraying the solution or the dispersion onto a fluidizing mixture of the remaining

- portion of bisphosphonic acid or its pharmaceutically acceptable salt (B) and a pharmaceutically acceptable excipient in a fluid bed granulator, and wherein the weight ratio of A and B is from 1:1 to 1:3.
- [Claim 18] The pharmaceutical composition for oral administration according to claim 16, wherein the pharmaceutically acceptable excipient is a mixture of a diluent, a disintegrant, and a lubricant.
- [Claim 19] The pharmaceutical composition for oral administration according to claim 17, wherein the pharmaceutically acceptable excipient is a mixture of a diluent, a disintegrant, and a lubricant.
- [Claim 20] The pharmaceutical composition for oral administration according to claim 12, further comprising an enteric coating layer on the tablet.
- [Claim 21] The pharmaceutical composition for oral administration according to any one of claims 1 to 20, further comprising vitamin D3 as an active ingredient.
- [Claim 22] The pharmaceutical composition for oral administration according to claim 21, wherein the vitamin D3 is present in an amount ranging from 12,000 IU to 24,000 IU in a unit dosage form.

[Fig. 1]



[Fig. 2]

