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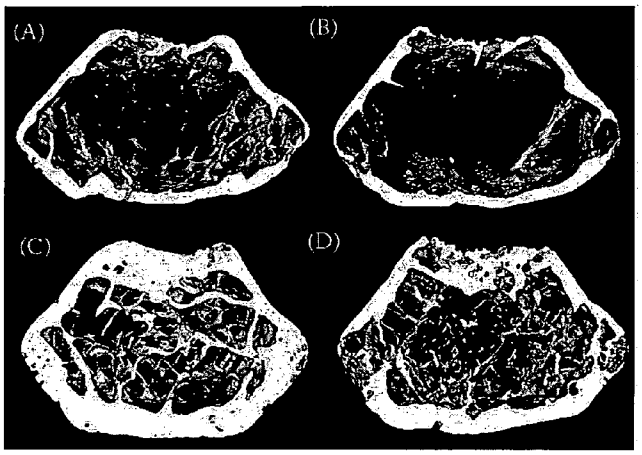
(54) **Title**: TRANSDERMAL DRUG DELIVERY SYSTEM AND PHARMACEUTICAL COMPOSITION FOR PREVENTING OR TREATING BONE DISEASES

Fig. 7a



(57) **Abstract**: The present invention relates to a transdermal drug delivery system comprising (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond, and a pharmaceutical composition comprising the drug delivery system for preventing or treating a bone disease. The novel approaches of the present invention is to decrease and increase hydrophilicity and hydrophobicity of bisphosphonate-based drugs, respectively, by forming ionic bonds with cationic amine compounds, contributing to dramatic increase in skin penetration into cell membrane. The present invention completely overcomes shortcomings associated with conventional bisphosphonate drugs for oral administration such as poor bioavailability (as much as 1%) and irritation of gastrointestinal tract.

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TRANSDERMAL DRUG DELIVERY SYSTEM AND PHARMACEUTICAL COMPOSITION FOR PREVENTING OR TREATING BONE DISEASES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a transdermal drug delivery system comprising (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond, and a pharmaceutical composition comprising the drug delivery system for preventing or treating a bone disease.

DESCRIPTION OF THE RELATED ART

Osteoporosis is a common disease characterized by low bone mass and structural deterioration of bone tissue, resulting in decreased bone strength and increased susceptibility to fractures. The risk of fragility fractures increases in the hips and spines of postmenopausal women suffering from osteoporosis. Hyperkyphosis, which refers to an accentuated concave curvature and loss of vertebrata height, commonly affects patients with osteoporosis due to a weakened vertebrate. The cause of osteoporosis is still unclear, but low body weight, low calcium intake, sedentary life style and declining estrogen levels at menopause can result in increased bone turnover and a loss of bone mass.

Several therapies and pharmaceutical compounds have demonstrated antifracture efficacy in the treatment of osteoporosis. Most of the compounds are bisphosphonate or other bone strengthening phosphonates [J.Y. Reginster et al., "Randomized Trial of the Effects of Risedronate on Vertebral Fractures in Women with Established Postmenopausal Osteoporosis," *Osteoporosis International*, 11:83-91(2000); and Steven T. Harris, MD et al., "Effects of Risedronate Treatment of Vertebral and Nonvertebral Fractures in Women With Postmenopausal Osteoporosis, A Randomized controlled Trial," *JAMA*, 282(14):1344-52(1999)]. Risedronate (chemical name, [1-hydroxy-2-(3-pyridinyl) ethylidene] bis [phosphonic acid] monosodium salt) is a member of the bisphosphonate family, which is the leading compound for the treatment of osteoporosis (U.S. Pat. No. 5,583,122).

Alendronate, marketed under the brand name FOSAMAX, is one of the nitrogen-

containing bisphosphonate agents that specifically inhibit bone resoption mediated by osteoclasts. FOSAMAX is known to be poorly absorbed and cause adverse effects on the gastrointestinal tract. Pamidronate disodium (AREDIA) is a commercially available drug for inhibiting bone resorption, usually administered as an intravenous infusion. Common side effects include pain, stiffening and irritation at the catheter insertion site, loss of appetite, vomiting, diarrhea, dyspepsia, esophagitis and stomatitis. Risedronate sodium (trade name ACTONEL) is water soluble but insoluble in organic solvents and has adverse effect on the upper gastrointestinal tract. Ibandronate sodium (trade name BONIVA) is a white/grey colored powder soluble in water but insoluble in organic solvents. This drug has adverse side effects in the upper GI tract. It is recommended that no food be taken for 2 hours after taking etidronate sodium (trade name DIDRONEL) due to its adverse gastrointestinal side-effects. Zoledronate (trade name ZOMETA) is the only bisphosphonate developed solely for use as an IV administration. However, fever, nausea, vomiting and higher incidents of upper GI disorders were reported in some patient groups.

Clinical studies suggested continuous and regular dosage of bisphosphonate alone or supplemented with parathyroid hormone, calcium and vitamin D, were an effective treatment method for osteoporosis [American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis, "Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis," *Arthritis & Rheumatism*, 44(7): 1496-1503 (2001); J.Y. Reginster, et al., "Randomized Trial of the Effects of Risedronate on Vertebral Fractures in Women with Established Postmenopausal Osteoporosis," *Osteoporosis International*, 11: 83-91 (2000); Steven T. Harris, MD, et al., "Effects of Risedronate Treatment of Vertebral and Nonvertebral Fractures in Women With Postmenopausal Osteoporosis, A Randomized controlled Trial," *JAMA*, 282 (14): 1344-52 (1999)].

Even though calcium supplementation is recommended to high risk or established osteoporosis patients, food containing calcium or calcium supplements can decrease the absorption and efficacy of bisphosphonate. These adverse side effects can be minimized by asking patients to take oral bisphosphonate on an empty stomach with sufficient plain water, and remaining in an upright position for at least 30 minutes. Patients are recommended to

take calcium supplement at a different time or day from bisphosphonate dosing [Hardman J.G. and Limbird L.E., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed., pp1733-1735 (1997)]. Strict adherence to treatment regimens could be difficult for patients undergoing long-term bisphosphonate treatment. Therefore, developing a simplified drug administration method would benefit the patient and help them adhere to their regimen of drug therapy.

Despite continued improvements in patient dosing regimens, patients experienced adverse GI tract events and noncompliance to daily dosing, strongly suggesting that an alternative delivery method to oral administration of bisphosphonate drug is needed.

Due to problems mentioned above, transdermal delivery may be a desirable alternative to oral treatment. A transdermal delivery system is beneficial when dealing with drugs that can cause adverse GI events or undergo liver metabolism, or for drugs that are poorly absorbed or easily disintegrated in GI. Transporting drugs across the skin layer is known to be an effective way to improve the bioavailability of the drug, and to reduce the potential GI adverse effects [*Clin. Pharmacol. Therapeutics* 58, 288-209 (1995)].

As mentioned above, bisphosphonates have low bioavailability and high upper GI adverse effects. Currently developed bisphosphonate-based drugs are highly charged, and have trouble penetrating the lipid bilayer. These drugs also have high affinity to polycationic metal ions, such as calcium ions, that form a water insoluble complex that is difficult to be absorbed by the cell membrane of the GI tract [Int J Pharm 21:143-154(1984)]. The acidic pH of the small intestine (pH 6-8) reduce the absorption of bisphosphonate drugs to less than 10% due to anionic character of bisphosphonate [Barry J. Gertz et al., "Studies of the oral bioavailability of alendronate," *Clin. Pharmacol. Therapeutics* 58: 288-209 (1995)].

Successful development of a transdermal delivery system of bisphosphonate-based drugs is expected to increase bioavailability and decreased the adverse side effects of the drug, therefore likely leading to increased patient compliance to the drug. Little information is available regarding transdermal delivery system of bisphosphonate throughout the world. This could be due to the low absorption rate of this drug in the patient body. Even oral administration of bisphosphonate shows less than 1% of bioavailability, therefore developing

an appropriate penetration activator could successfully enhance the efficacy of this low level of bisphosphonate delivery.

Vertebral fracture is a common consequence of osteoporosis if left untreated. This can lead to chronic pain and decreased quality of life, which in turn could be a great burden on government health care. A therapeutic intervention that decreases fracture risk is essential for reducing the consequences of this debilitating condition.

Successful commercialization of a transdermal delivery system for bisphosphonate using our accumulated knowledge could provide a novel therapeutic intervention of osteoporosis, which would reduce substantial economic burden on patients and government health care systems. The object of this invention is to develop a transdermal delivery system of risedronate and compare its efficacy with oral administration using animal models or healthy human subjects. The ultimate goal of this invention is to apply our accumulated pharmacokinetic and clinical trial data into commercializing of a novel transdermal delivery system for bisphosphonate. However, there is no description of or development of a transdermal delivery system for bisphosphonate in references presented in this invention. Based on our quantification and transdermal penetration experiments with bisphosphonate, we confirmed that a transdermal delivery system compromising bisphosphonate is a safe therapeutic method with a prolonged drug delivery capacity for osteoporosis, thus our invention satisfies the requirements as an alternative to oral drug administration for the treatment of osteoporosis.

Throughout this application, various patents and publications are referenced and citations are provided in parentheses. The disclosure of these patents and publications in their entities are hereby incorporated by references into this application in order to more fully describe this invention and the state of the art to which this invention pertains.

SUMMARY OF THE INVENTION

The present inventors have made intensive researches to enhance skin penetration and *in vivo* absorption rate of bisphosphonate-based drugs for prevention or treatment of bone diseases. As results, we have discovered that cationic amine compounds linked to

bisphosphonate-based drugs via an ionic bond makes the bisphosphonate-based drug less hydrophilic and more hydrophobic, thereby dramatically increasing its skin penetration rate.

Accordingly, it is an object of this invention to provide a transdermal drug delivery system.

It is another object of this invention to provide a pharmaceutical composition for preventing or treating bone disease via transdermal route.

It is still another object of this invention to provide a method for delivering a drug via transdermal route.

It is further object of this invention to a method for preventing or treating a bone disease via transdermal route.

Other objects and advantages of the present invention will become apparent from the detailed description to follow and together with the appended claims and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1a and 1b are graphs showing increased solubility of risedronate linked to diethylenetriamine (DETA) or L-arginine via ionic bonds in xylene or propylene carbonate.

Fig. 2a is a graph showing *in vitro* skin penetration of risedronate linked to L-arginine via ionic bonds.

Fig. 2b is a graph showing *in vitro* skin penetration of risedronate linked to L-lysine via ionic bonds.

Fig. 3 is a graph showing *in vitro* skin penetration of risedronate linked to diethylenetriamine (DETA) via ionic bonds.

Fig.4 is an image showing results of the skin irritation test performed using risedronate with viscosity by Xanthan gum aqueous solution.

Fig.5 is an image showing representative results of the skin irritation test performed using risedronate and L-arginine (molar ratio 1:2) ionic compound with viscosity by Xanthan gum aqueous solution.

Fig.6 is an image showing representative results of the skin irritation test performed using risedronate and diethylenetriamine (DETA, molar ratio 1:1) ionic compound with viscosity

by Xanthan gum aqueous solution.

Fig. 7a represents micro CT images of femur from ovariectomized mouse model treated with (a) Sham, (b) OVX-ctl, (c) OVX-0.2% or (d) OVX-2%. OVX-ctl, OVX-0.2% and OVX-2% represent the drug delivery system of this invention containing 0 wt% risedronate, 0.2 wt% risedronate and 2 wt% risedronate linked to L-arginine, respectively.

Fig. 7b represents two-dimensional micro CT images of femur from ovariectomized mouse model treated with (a) Sham, (b) OVX-ctl, (c) OVX-0.2% or (d) OVX-2%.

Figs. 8a-8e represent BMC (Bone mineral contents), BMD (mg/cc; Bone Mineral Density), TMC (mg; Total Mineral Contents), TMD (mg/cc; Total Mineral Density) and BVF (Bone volume fraction) of ovariectomized mouse model treated with (A) OVX-ctl, (B) OVX-0.2% or (C) OVX-2%.

DETAILED DESCRIPTION OF THIS INVETNION

In one aspect of this invention, there is provided a transdermal drug delivery system comprising (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond.

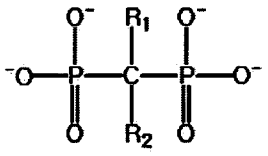
In another aspect of this invention, there is provided a method for delivering a drug via transdermal route, which comprises administering to a subject a composition comprising (i) a bisphosphonate-based drug; and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond.

The present inventors have made intensive research to enhance skin penetration and *in vivo* absorption rate of bisphosphonate-based drugs for prevention or treatment of bone diseases. As results, we have discovered that cationic amine compounds linked to bisphosphonate-based drugs via an ionic bond makes the bisphosphonate-based drug less hydrophilic and more hydrophobic, thereby dramatically increasing its skin penetration rate.

The term used herein "bisphosphonate" refers to a pyrophosphate analogue where the center oxygen atom in a P-O-P moiety is substituted with a carbon atom to from a P-C-P moiety. It should be noted that the term "bisphosphonate" as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates,

biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials.

According to a preferred embodiment, the bisphosphonate-based drug contained in the transdermal drug delivery system of the present invention is represented by the following Formula 1:



(1)

where R_1 is hydrogen, hydroxy or halo; R_2 is halo, C_{1-10} alkyl, C_{1-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{1-10} heteroaryl, C_{1-10} aryl or C_{1-10} arylalkyl; the alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl and heteroaryl are substituted with halo, sulfur, amino, C_{1-5} alkylamino or C_{1-5} dialkylamino and contains 1-3 nitrogen atoms.

The bisphosphonate-based compound carried by the drug delivery system of the present invention is represented by Formula 1. The term used herein "halo" means halogen atoms, for instance including fluoro, chloro, bromo, and iodo, preferably fluoro, chloro or bromo. The term "C_1-C_{10} alkyl" is defined herein to be a straight chain or branched chain saturated hydrocarbon groups containing 1-10 carbon atoms, including methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *n*-butyl, *t*-butyl, *n*-hexyl, *n*-octyl and *t*-octyl.

The term "cycloalkyl" used herein refers to cyclic hydrocarbon radicals containing 1-10 carbon atoms, preferably "C_3-C_8 cycloalkyl", including cyclopropyl, cyclobutyl and cyclopentyl and cyclooctyl. Cycloalkyl may be substituted with alkyl groups having 1-3 carbon atoms, preferably 1-methylcyclopropyl, 2-methylcyclopentyl and 2-methylcyclooctyl.

The term "heterocycloalkyl" used herein refers to cycloalkyl in which one or more of the atoms forming the ring is a heteroatom selected, independently from N, O, or S. Non-exclusive examples of heterocycloalkyl include piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl and the like.

The term used herein "aryl" means totally or partially unsaturated, substituted or unsubstituted monocylic or polycydic carbon rings, preferably phenyl, naphthyl, anthracene or

pyrene. Most preferably, the aryl group is substituted or unsubstituted phenyl, naphthyl or pyrene. The monoaryl group, *e.g.*, phenyl may be substituted with various substituents, preferably halo, hydroxy, nitro, cyano, C_1-C_4 alkyl and C_1-C_4 alkoxy group. More preferably, nitro and C_1-C_4 alkoxy groups. The term "alkoxy" means –O alkyl groups, preferably methoxy. Where substituted with C_1-C_4 substituted alkyl groups, halo, preferably chloro or fluoro substituted alkyl substituents may be used.

Where R_2 is biary, *e.g.* naphthyl, it may be substituted in various positions with various substituents, preferably halo, hydroxy, nitro, cyano, straight or branched, substituted or unsubstituted C_1-C_4 alkyl, straight or branched C_1-C_4 alkoxy, or substituted or unsubstituted amino groups, more preferably nitro or C_1-C_4 alkoxy.

The term "arylalkyl (aralkyl)" means aryl groups linked to a structure comprised of one or more alkyl groups, *e.g.* benzyl. More preferably, arylalkyl is alkylphenyl, alkylnaphthalene, alkyl anthracene, or alkylpyrene, most preferably, benzyl, methylnaphthalene or methylpyrene.

The term "heteroaryl" means heterocyclic aromatic groups containing heteroatoms such as N, O and S. Preferably, heteroaryl is heterobiaryl containing N atom as heteroatom.

The term "alkylamino" means alkyl groups having amino substituents. The term "dialkylamino" refers to two alkyl groups having amino substituents.

According to a preferred embodiment, the bisphosphonate-based drug is (4-amino-1-hydroxybutylidene)-bisphosphonate or 4-amine-1-hydroxybutane-1,1-bisphosphonic acid(alendronate); (dichloromethylene)-bisphosphonate (clodronate); (1-hydroxyethylidene)-bisphosphonate(etidronate); [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonate(evandronate); [(cycloheptylamino)-methylene] bisphosphonate (cimadronate, incadronate); [1-hydroxy-2-imidazo-(1,2-a) pyridine-3-ylethyledne] bisphosphonate (minodronate); (6-amino-1-hydroxyhexyleden) bisphosphonate (neridronate); [3-(dimethylamino)-hydroxy-propylidene] bisphosphonate (olpadronate); (3-amino-1-hydroxypropylidene) bisphosphonate (pamidronate); [1-hydroxy-2-(3-pyridinyl)-ethylidene] bisphosphonate [[(4-chlorophenyl)thio]-methylene] bisphosphonate (tiludronate); [1-hydroxy-2-(1H-imidazole-1-yl) ethylidene] bisphosphonate (zolendronate); dichloromethylene bisphosphonate (clodronate); paridronate; 5-amino-1-hydroxy pentane-1,1-bisphosphonic acid; or difluoro-methane bisphosphonic acid; or a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salts" means salts of the bisphosphonate-based drug which are pharmaceutically acceptable, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

In accordance with a preferred embodiment, the cationic amine compound used in the drug delivery system of this invention is selected from the group consisting of an amino acid, diethylenetriamine (DETA), spermine, ethylene diamine, triethylene tetramine and tris(2-aminoethyl amine). More preferably, the cationic amine compound is the amino acid.

The term used herein "amino acid" means compounds having both an amino group and carboxyl group. For example, the amino acid includes alanine, arginine, asparagine, aspartic acid, citrulline, cysteine, cystine, selenocysteine, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, hydroxy proline, γ-carboxyglutamate, or O-phosphoserine.

Each amino acid has its typical isoelectric point (pI) where its mean charge becomes zero. For instance, certain amino acids have higher pI values than the physiological pH value (pH 7.4) and are positively charged under physiological pH conditions.

In the present invention, the cationic amine compound is used to form ionic bonds with oxygen anions from phophonate groups of bisphosphonate drugs, decreasing hydrophilic properties of bisphosphonate drugs. Where the amino acids are used as cationic amine compounds, a suitable amino acid can be selected depending on pH values of solutions for preparation of materials having ion bonds (*i.e.*, drug delivery system of this invention).

The isoelectric point (pI) values of amino acids are: arginine (pI=10.76), lysine (pI=9.60), histidine (pI=7.60), proline (pI=6.30), glycine (pI=6.06), isoleucine (pI=6.05), alanine (pI=6.01), leucine (pI=6.01), valine (pI=6.00), tryptophan (pI=5.89), methionine (pI=5.74), serine (pI=5.68), glutamine (pI=5.65), tyrosine (pI=5.64), threonine (pI=5.60), selenocysteine (pI=5.50), phenylalanine (pI=5.49), asparagine (pI=5.41), cysteine (pI=5.05), glutamic acid (pI=3.15) and aspartic acid (pI=2.85).

For instance, where the solution for preparing the drug delivery system has a pH value of 2, all amino acids described above with pI values of above 2 are positively charged. Preferably, the solution for preparing the drug delivery system has a pH 4-9.

Given a physiological pH of about 7.4, the amino acid as cationic amine compound is preferably Arg or Lys.

Non-limiting examples of solvents for forming ion bonds between the bisphosphonate-based drug and the cationic amine compound include water, ethanol, 1,3-butylene glycol, glycerin, propylene glycol and combinations thereof.

According to a preferred embodiment, the drug delivery system has the molar ratio of the bisphosphonate-based drug and the cationic amine compound of 1:0.01-50, more preferably 1:1-40, most preferably 1:2-30. The molar ratio of 1:0.01-50 is advantageous for decreasing hydrophilic properties of bisphosphonate-based drugs by formation of ion bonds.

Where Arg is used as cationic amine compounds, the molar ratio of the bisphosphonate-based drug to the cationic amine compound is preferably 1:0.01-10, more preferably 1:1-6, most preferably 1:1-4. In the case of using diethylenetriamine (DETA) as

cationic amine compounds, the molar ratio of the bisphosphonate-based drug to the cationic amine compound is preferably 1:0.01-10, more preferably 1:0.1-6, most preferably 1:0.5-5.

According to a preferred embodiment, the bisphosphonate-based drug is contained in the amount of 0.01-20 wt% (more preferably 0.1-10 wt%, most preferably 1-5 wt%) based on the total weight of the drug delivery system. The amount of 0.01-20 wt% for bisphosphonate-based drugs is desirable for the decrease in hydrophilic properties of bisphosphonate-based drugs by formation of ion bonds.

The drug delivery system of the present invention is developed for overcoming shortcomings associated with oral and intravenous administration of bisphosphonate-based drugs and suggests transdermal administration as alternatives. The drug delivery system may be prepared in various forms such as solution, lotion, W/O emulsion, O/W emulsion, suspension, liposome, gel, hydrogel, cream, paste, patch or ointment.

The drug delivery system may be prepared in the form of liposomes using phospholipids.

The term "liposome" encompasses any compartment enclosed by a lipid bilayer. Liposomes are also referred to as lipid vesicles. In order to form a liposome the lipid molecules comprise elongated non-polar (hydrophobic) portions and polar (hydrophilic) portions. The hydrophobic and hydrophilic portions of the molecule are preferably positioned at two ends of an elongated molecular structure.

The term "phospholipids" used herein means any phospholipid capable of forming liposomes unless otherwise indicated, including lecithin (phosphatidyl choline), phosphatidyl serine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol and sphingomyelin, but not limited to. Preferably, phospholipids useful in this invention are lecithin, most preferably, hydrogenated lecithin. Lecithin can be made from egg, soybean and other plants, most preferably, soybean. Lecithin useful in this invention, which is synthetic, semi-synthetic or natural, includes, but not limited to, soybean lecithin, distearoylphosphatidylcholine, hydrogenated soybean lecithin, egg lecithin, dioleoylphosphatidylcholine, hydrogenated egg lecithin, dielaidoylphosphatidylcholine, dipalmitoylphosphatidylcholine and dimyristoylphosphatidylcholine. Most preferably, phospholipid used in this invention is hydrogenated soybean lecithin.

The liposomes may be prepared using high pressure homogenizer, sonicator, microfluidizer, extrusion apparatus or French press.

In addition, the drug delivery system may be fabricated in the form of hydrogel by using conventional materials for preparing hydrogel such as natural/synthetic hydrophilic polymers, cross-linking agents, skin softner, transdermal enhancer, preservatives, surfactant and pH modifier. Furthermore, for generating hydrogel, gelation agents may be used, including carbopol and/or xanthan gum, preferably carbopol 60 and/or xanthan gum.

In a specific example for preparing the drug delivery system in the form of hydrogel, polyethyleneglycol, xanthan gum, carbopol, carbomer and hydroxypropylcellulose are added in the amount of 0.01-20 wt% based the total weight to water to prepare hydrogel and then a bisphosphonate-based drug and a cationic amine compound are introduced in the amount of 0.01-20.00 wt%.

In still another aspect of this invention, there is provided a pharmaceutical composition for preventing or treating a bone disease via transdermal route, which comprises (a) a pharmaceutically effective amount of a drug delivery system containing (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond; and (b) a pharmaceutically acceptable carrier.

In further aspect of this invention, there is provided a method for preventing or treating a bone disease via transdermal route, which comprises administering to a subject a pharmaceutical comprising (a) a pharmaceutically effective amount of a drug delivery system containing (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond; and (b) a pharmaceutically acceptable carrier.

Since the present pharmaceutical composition comprises the drug delivery system described above, the common descriptions between them are omitted in order to avoid undue redundancy leading to the complexity of this specification.

According to a preferred embodiment, the drug delivery system is contained in the amount of 0.001-50 wt% (more preferably 0.1-40 wt%, most preferably 10-30 wt%) based on the total weight of the composition.

The pharmaceutical composition of this invention is provided in various forms such as solution, lotion, W/O emulsion, O/W emulsion, suspension, liposome, gel, hydrogel, cream, paste, patch or ointment.

According to a preferred embodiment, the bone disease prevented or treated by the present pharmaceutical composition includes osteoporosis, Paget's disease, rickets, osteopenia, rheumatoid arthritis, osteomalacia, renal osteodystrophy, osteogenesis imperfecta, hyperthyroidism, bone loss due to rheumatoid arthritis, inflammatory arthritis, subchondral osteosclerosis, subchondral osteocystoma, osteophytosis, athralgia, hyperparathyroidism, sarcoidosis and hypercalcemia, more preferably osteoporosis, Paget's disease, rickets, osteomalacia, renal osteodystrophy, hyperthyroidism and hyperparathyroidism, most preferably osteoporosis.

In the pharmaceutical compositions of this invention, the pharmaceutically acceptable carrier may be conventional one for formulation, including carbohydrates (e.g., lactose, amylose, dextrose, sucrose, sorbitol, mannitol, starch, cellulose), gum acacia, calcium phosphate, alginate, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, water, salt solutions, alcohols, gum arabic, syrup, vegetable oils (e.g., corn oil, cotton-seed oil, peanut oil, olive oil, coconut oil), polyethylene glycols, methyl cellulose, methylhydroxy benzoate, propylhydroxy benzoate, talc, magnesium stearate and mineral oil, but not limited to. The pharmaceutical compositions of this invention, further may contain wetting agent, sweetening agent, emulsifier, buffer, suspending agent, preservatives, flavors, perfumes, lubricant, stabilizer, or mixtures of these substances. Details of suitable pharmaceutically acceptable carriersand formulations can be found in Remington's Pharmaceutical Sciences (19th ed., 1995), which is incorporated herein by reference.

The pharmaceutical composition of this invention may be administered via transdermal route. The correct dosage of the pharmaceutical compositions of this invention will be varied according to the particular formulation, the mode of application, age, body weight and sex of the patient, diet, time of administration, condition of the patient, drug combinations, reaction sensitivities and severity of the disease. It is understood that the ordinary skilled physician will readily be able to determine and prescribe a correct dosage of this pharmaceutical compositions. Where the pharmaceutical compositions is administered via transdermal route,

suitable dosage unit for human host is to administer once a day with the composition of 0.001-100 mg/kg(body weight) per day.

According to the conventional techniques known to thoseskilled in the art, the pharmaceutical compositions of this invention can be formulatedwith pharmaceutical acceptable carrier and/or vehicle as described above, finally providing several forms including a unit dosage form.

The features and advantages of the present invention will be summarized as follows:

(a) The present invention provides drug delivery systems and pharmaceutical compositions ensuring trandermal administration of conventional bisphosphonate-based drugs by forming ionic bonds between bisphosphonate-based drugs and cationic amine compounds.

(b) The novel approaches of the present invention is to decrease hydrophilicity and increase hydrophobicity of bisphosphonate-based drugs by forming ionic bonds with cationic amine compounds, contributing to dramatic increase in skin penetration into cell membrane.

(c) The present invention completely overcomes shortcomings associated with conventional bisphosphonate drugs for oral administration such as poor bioavailability (as much as 1%) and irritation of gastrointestinal tract.

(d) The drug delivery systems and pharmaceutical compositions of this invention may be prepared in a relatively convenient fashion with no decrease in therapeutic effects of bisphosphonate drugs.

(e) The drug delivery systems and pharmaceutical compositions of this invention may be transdermally applied with much higher patient compliance suffering from bone diseases, particularly osteoporosis.

The present invention will now be described in further detail by examples. It would be obvious to those skilled in the art that these examples are intended to be more concretely illustrative and the scope of the present invention as set forth in the appended claims is not limited to or by the examples.

EXAMPLES

MATERIALS AND METHODS

Materials

Experimental animals

Male hairless mice (6-8 weeks old) purchased from Orientalbio, Inc. (Korea) were used in our *in vitro* experiment within one week of delivery.

Reagents

Risedronic acid, a potent bisphosphonate was provided by Lanfang Shinya Chemical. L-Arginine, L-Lysine and diethylenetriamine (DETA) serving as cationic binding partners were purchased from Sigma Chemical (St. Louis, MO, USA). Sodium chloride as receptor media was purchased from Daejung (Korea). Pyrophosphate sodium (Samchun, Korea), tetrabutyl ammonium hydroxide (TBAH; Sigma Chemical Co., St Louis, MO, USA) and phosphoric acid (Sigma Chemical Co., St Louis, MO, USA) were used as HPLC buffer. HPLC grade acetonitril (Fischer, USA) was used. Water used in these experiments was distilled and purified through ultra water purification system.

Equipment and apparatus

High performance liquid chromatography (HPLC; Agilent 1100 series, USA) and Franz Cell Permeation system (Labotech, Korea) were used in these experiments.

Preparation of risedronate ionic compound

Risedronate and diethylenetriamine (DETA) each dissolved in distilled water were homogeneously mixed at molar ratio of 1:1, 1:2 or 1:4 and kept to stand at room temperature for 1 hr. This facilitates the ionic bonding between anionic risedronate and cationic diethylenetriamine (DETA). L-Arginine, L-Lysine were used also to form an ionic bond with risedronate. The concentration of the risedronate ionic complex was 2 wt% and the solution was adjusted to pH 6.

Preparation of transdermal delivery system (hydrogel) comprising risedronate ionic complex

As formulation examples for this invention, hydrogel containing risedronate ionic compound were prepared in accordance with formulations presented in Table 1. First,

hydrogel was prepared by dissolving polyethylene glycol (PEG), Xanthan gum, carbopol, carbomer and hydroxypropyl cellulose (HPC) in the water solution according to the formula presented below. Then, the active compound, risedronate was added according to the weight ratio shown below. Risedronate ionic compound in Table 1 had a molar ratio of risedronate: DETA of 1:1.

TABLE 1

Composition	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Example 8
Risedronate ionic compound	1	1	1	1	2	2	2	2
Xanthan gum	1	1	-	-	1	1	-	-
Polyethylene glycol	-	10	-	10	-	10	-	10
Hydroxypropyl cellulose	-	-	1	-	-		1	
Glycerol	-	-	10	-	-		10	
Carbopol	-	-	-	0.5	-	-	-	0.5
Carbomer	-	-	0.1	-	-	-	0.1	
Water	98	88	87.9	88.5	97	87	87.9	87.5
Total	100 wt%	100 wt%	100 wt%	100 wt%	100 wt%	100 wt%	100 wt%	100 wt%

Skin penetration test of risedronate ionic compound

(1) Skin extraction

The dorsal skin of 6 week old hairless mouse was excised and used for this experiment. Hairless mouse was anesthetized with ether and fixed on the surgical table. Subcutaneous fat layer, tissue and blood vessel was carefully removed from epidermal layer.

(2) Skin penetration test

The skin excised from hairless mouse, as mentioned above, were loaded with 200 μl of risedronate ionic compound, attached and mounted on Franz Cell Permeation System. Ten ml of 0.9% sodium chloride were added to the receptor cell. 0.5 ml of permeated solution was

collected from receptor cell at 2, 4, 8, 12 and 24 hrs. The receptor cell was supplemented with the same volume of 0.9% sodium chloride. Thirty μl of sample was injected and the accumulated penetration amount was calculated by integrating the peak area from the HPLC chromatogram.

(3) Quantification of risedronate by HPLC

A C-18 column (5 μm diameter particle size, 150 x 4.6 mm dimensions, Waters) was used for separation. A 93/7 of buffer A/bufferB were used as mobile phase, where buffer A consisted of 0.005M pyrophosphate sodium, 0.005M tetrabutyl ammonium hydroxide at the ratio of 1:1, adjusted to pH 7 using phosphoric acid, and buffer B was HPLC grade acetonitrile. The column was operated at a flow rate of 1 ml/min and eluted samples were detected at the UV absorbance at 262 nm with a UV spectrophotometer. Samples were quantified by calibrating the relative area of the sample peaks from the chromatogram. This result is presented in Fig. 2 and Fig. 3.

(4) Skin irritation test

Three 6-week old mice were used for each formulation group. Control group used solely risedronate. In two experiment groups (i) the first group used risedronate and L-arginine ionic compound (molar ratio 1:2) and (ii) the second group used risedronate and DETA ionic compound (molar ratio 1:1). Reagents were mixed homogenously with 1% xanthan gum solution. This solution was applied onto the same size of mouse skin for 30 min, rinsed and monitored for 72 hrs before measuring the skin irritation by taking pictures. The concentration of risedronate was 2 wt %; Xanthan gum was used to increase the viscosity of the solution.

Ovariectomized mouse model

Following a 1 week of adaptation, 14 week old mice underwent ovariectomy. Four days after surgery, drug treatment was initiated once every 2 days, for four weeks. Sham- operated surgical controls underwent laparotomy to give the same stress level as the ovariectomy performed experimental group. The back hair on mice was removed using animal electrical clipper and a shave. After 4 weeks of treatment, mouse femurs were sampled and scanned

with micro-CT. The range of drug concentration used for the treatment based on risedronate was 0.2 wt% (lowest) to 2 wt% (highest) that were linked with L-arginine via ionic bond. The molar ratio of risedronate to L-arginine is 1:2.

RESULTS

At optimal pH, anionic risedronate and cationic DETA or amino acids like L-arginine and L-lysine form an ionic compound that makes risedronate less hydrophilic and becomes more hydrophobic, thereby increasing its solubility in organic solvents. In Figs. 1a and 1b, as the ratio of added DETA or L-arginine is increased, there was an increase in the amount of risedronate dissolved in a solvent such as xylene (Fig. 1a) and propylene carbonate (Fig. 1b).

Fig. 2a shows *in vitro* skin penetration experiment of risedronate ionic compound, which were previously separated by HPLC. Experimental group containing risedronate: L-arginine at molar ratio of 1:1, 1:2 and 1:4 showed a time dependent increase in skin penetration. Control group containing risedronate alone alone showed negligent increase of skin penetration during the observation period. Risedronate: L-arginine at the molar ratio of 1:2 showed greater penetration than those at a ratio of 1:4.

Fig. 2b shows *in vitro* skin penetration of risedronate linked to L-lysine via ionic bonds. Experimental groups containing risedronate: L-lysine at molar ratios of 1:2 and 1:4 showed a time dependent increase in skin penetration. Control group containing risedronate alone showed negligent increase of skin penetration during the observation period. Risedronate: L-lysine at the molar ratio of 1:4 showed greater penetration than those of at a ratio of 1:2.

In addition, as shown in Fig. 3, the experimental group containing risedronate: DETA at molar ratio of 1:1 and 1:4 showed a time dependent increase in penetration. Control groups containing risedronate alone did not show any increase of transdermal penetration during the time observed.

As shown in Figs. 4-6, no skin irritation was observed in either control or experiment groups.

Ovariectomized mouse experiment showed an increase in both cortical and cancellous bone area in risedronate treated experimental groups. Experimental group treated with 0.2 wt% risedronate-Arg ionic complex showed a significant increase in bone density, especially in

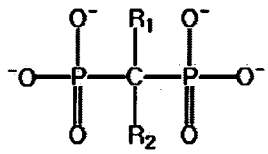
cancellous bone density as shown in micro CT images of Figs. 7a and 7b. Total bone mineral content, total mineral density and bone volume fraction showed highest increase in 0.2 wt% risedronate-Arg ionic complex treatment group (Figs. 8a-8e). This increase was higher than that of the sham-operated surgical group, suggesting that bisphosphonate drugs (e.g. risedronate) linked to cationic amine compounds (e.g. Arg) via ion bonds have significant therapeutic effects on osteoporosis by transdermal administration.

Having described a preferred embodiment of the present invention, it is to be understood that variants and modifications thereof falling within the spirit of the invention may become apparent to those skilled in this art, and the scope of this invention is to be determined by appended claims and their equivalents.

What is claimed is:

1. A transdermal drug delivery system, comprising (i) a bisphosphonate-based drug; and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond.

2. The transdermal drug delivery system according to claim 1, wherein the bisphosphonate-based drug is a compound represented by the following Formula 1:



(1)

where R_1 is hydrogen, hydroxy or halo; R_2 is halo, C_{1-10} alkyl, C_{1-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{1-10} heteroaryl, C_{1-10} aryl or C_{1-10} arylalkyl; the alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl and heteroaryl are substituted with halo, sulfur, amino, C_{1-5} alkylamino or C_{1-5} dialkylamino and contains 1-3 nitrogen atoms.

3. The transdermal drug delivery system according to claim 1 or 2, wherein the bisphosphonate-based drug is (4-amino-1-hydroxybutylidene)-bisphosphonate or 4-amine-1-hydroxybutane-1,1-bisphosphonic acid(alendronate); (dichloromethylene)-bisphosphonate (clodronate); (1-hydroxyethylidene)-bisphosphonate(etidronate); [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonate(evandronate); [(cycloheptylamino)-methylene] bisphosphonate (cimadronate, incadronate); [1-hydroxy-2-imidazo-(1,2-a) pyridine-3-ylethyledne] bisphosphonate (minodronate); (6-amino-1-hydroxyhexyleden) bisphosphonate (neridronate); [3-(dimethylamino)-hydroxy-propylidene] bisphosphonate (olpadronate); (3-amino-1-hydroxypropylidene) bisphosphonate (pamidronate); [1-hydroxy-2-(3-pyridinyl)-ethylidene] bisphosphonate [[(4-chlorophenyl)thio]-methylene] bisphosphonate (tiludronate); [1-hydroxy-2-(1H-imidazole-1-yl) ethylidene] bisphosphonate (zolendronate); dichloromethylene bisphosphonate (clodronate); paridronate; 5-amino-1-hydroxy pentane-1,1-bisphosphonic acid; or difluoro-methane bisphosphonic acid; or a pharmaceutically acceptable salt thereof.

4. The transdermal drug delivery system according to claim 1, wherein the cationic amine compound is selected from the group consisting of an amino acid, diethylenetriamine (DETA), spermine, ethylene diamine, triethylene tetramine and tris(2-aminoethyl amine).

5. The transdermal drug delivery system according to claim 4, wherein the cationic amine compound is the amino acid.

6. The transdermal drug delivery system according to claim 5, wherein the amino acid is arginine or lysine.

7. The transdermal drug delivery system according to claim 1, wherein the drug delivery system has the molar ratio of the bisphosphonate-based drug and the cationic amine compound of 1:0.01-50.

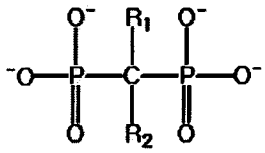
8. The transdermal drug delivery system according to claim 1, wherein the bisphosphonate-based drug is contained in the amount of 0.01-20 wt% based on the total weight of the drug delivery system.

9. The transdermal drug delivery system according to claim 1, wherein the drug delivery system is in the form of solution, lotion, W/O emulsion, O/W emulsion, suspension, liposome, gel, hydrogel, cream, paste, patch or ointment.

10. A pharmaceutical composition for preventing or treating a bone disease via transdermal route, which comprises (a) a pharmaceutically effective amount of a drug delivery system containing (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond; and (b) a pharmaceutically acceptable carrier.

11. The pharmaceutical composition according to claim 10, wherein the bisphosphonate-based drug is a compound represented by the following Formula 1:

22



(1)

where R_1 is hydrogen, hydroxy or halo; R_2 is halo, C_{1-10} alkyl, C_{1-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{1-10} heteroaryl, C_{1-10} aryl or C_{1-10} arylalkyl; the alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl and heteroaryl are substituted with halo, sulfur, amino, C_{1-5} alkylamino or C_{1-5} dialkylamino and contains 1-3 nitrogen atoms.

12. The pharmaceutical composition according to claim 10 or 11, wherein the bisphosphonate-based drug is (4-amino-1-hydroxybutylidene)-bisphosphonate or 4-amine-1-hydroxybutane-1,1-bisphosphonic acid(alendronate); (dichloromethylene)-bisphosphonate (clodronate); (1-hydroxyethylidene)-bisphosphonate(etidronate); [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonate(evandronate); [(cycloheptylamino)-methylene] bisphosphonate (cimadronate, incadronate); [1-hydroxy-2-imidazo-(1,2-a) pyridine-3-ylethyledne] bisphosphonate (minodronate); (6-amino-1-hydroxyhexyleden) bisphosphonate (neridronate); [3-(dimethylamino)-hydroxy-propylidene] bisphosphonate (olpadronate); (3-amino-1-hydroxypropylidene) bisphosphonate (pamidronate); [1-hydroxy-2-(3-pyridinyl)-ethylidene] bisphosphonate [[(4-chlorophenyl)thio]-methylene] bisphosphonate (tiludronate); [1-hydroxy-2-(1H-imidazole-1-yl) ethylidene] bisphosphonate (zolendronate); dichloromethylene bisphosphonate (clodronate); paridronate; 5-amino-1-hydroxy pentane-1,1-bisphosphonic acid; or difluoro-methane bisphosphonic acid; or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition according to claim 10, wherein the cationic amine compound is selected from the group consisting of an amino acid, diethylenetriamine (DETA), spermine, ethylene diamine, triethylene tetramine and tris(2-aminoethyl amine).

14. The pharmaceutical composition according to claim 13, wherein the cationic amine compound is the amino acid.

15. The pharmaceutical composition according to claim 14, wherein the amino acid is arginine or lysine.

16. The pharmaceutical composition according to claim 10, wherein the drug delivery system has the molar ratio of the bisphosphonate-based drug and the cationic amine compound of 1:0.01-50.

17. The pharmaceutical composition according to claim 10, wherein the bisphosphonate-based drug is contained in the amount of 0.01-20 wt% based on the total weight of the drug delivery system.

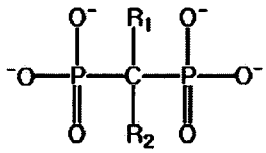
18. The pharmaceutical composition according to claim 10, wherein the drug delivery system is contained in the amount of 0.001-50 wt% based on the total weight of the composition.

19. The pharmaceutical composition according to claim 10, wherein the composition is solution, lotion, W/O emulsion, O/W emulsion, suspension, liposome, gel, hydrogel, cream, paste, patch or ointment.

20. The pharmaceutical composition according to claim 10, wherein the bone disease is osteoporosis, Paget's disease, rickets, osteopenia, rheumatoid arthritis, osteomalacia, renal osteodystrophy, osteogenesis imperfecta, hyperthyroidism, bone loss due to rheumatoid arthritis, inflammatory arthritis, subchondral osteosclerosis, subchondral osteocystoma, osteophytosis, athralgia ,hyperparathyroidism, sarcoidosis or hypercalcemia.

21. A method for delivering a drug via transdermal route, which comprises administering to a subject a composition comprising (i) a bisphosphonate-based drug; and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond.

22. The method according to claim 21, wherein the bisphosphonate-based drug is a compound represented by the following Formula 1:



(1)

where R_1 is hydrogen, hydroxy or halo; R_2 is halo, C_{1-10} alkyl, C_{1-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{1-10} heteroaryl, C_{1-10} aryl or C_{1-10} arylalkyl; the alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl and heteroaryl are substituted with halo, sulfur, amino, C_{1-5} alkylamino or C_{1-5} dialkylamino and contains 1-3 nitrogen atoms.

23. The method according to claim 21 or 22, wherein the bisphosphonate-based drug is (4-amino-1-hydroxybutylidene)-bisphosphonate or 4-amine-1-hydroxybutane-1,1-bisphosphonic acid(alendronate); (dichloromethylene)-bisphosphonate (clodronate); (1-hydroxyethylidene)-bisphosphonate(etidronate); [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonate(evandronate); [(cycloheptylamino)-methylene] bisphosphonate (cimadronate, incadronate); [1-hydroxy-2-imidazo-(1,2-a) pyridine-3-ylethyledne] bisphosphonate (minodronate); (6-amino-1-hydroxyhexyleden) bisphosphonate (neridronate); [3-(dimethylamino)-hydroxy-propylidene] bisphosphonate (olpadronate); (3-amino-1-hydroxypropylidene) bisphosphonate (pamidronate); [1-hydroxy-2-(3-pyridinyl)-ethylidene] bisphosphonate [[(4-chlorophenyl)thio]-methylene] bisphosphonate (tiludronate); [1-hydroxy-2-(1H-imidazole-1-yl) ethylidene] bisphosphonate (zolendronate); dichloromethylene bisphosphonate (clodronate); paridronate; 5-amino-1-hydroxy pentane-1,1-bisphosphonic acid; or difluoro-methane bisphosphonic acid; or a pharmaceutically acceptable salt thereof.

24. The method according to claim 21, wherein the cationic amine compound is selected from the group consisting of an amino acid, diethylenetriamine (DETA), spermine, ethylene diamine, triethylene tetramine and tris(2-aminoethyl amine).

25. The method according to claim 24, wherein the cationic amine compound is the amino acid.

26. The method according to claim 25, wherein the amino acid is arginine or lysine.

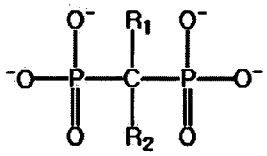
27. The method according to claim 21, wherein the drug delivery system has the molar ratio of the bisphosphonate-based drug and the cationic amine compound of 1:0.01-50.

28. The method according to claim 21, wherein the bisphosphonate-based drug is contained in the amount of 0.01-20 wt% based on the total weight of the drug delivery system.

29. The method according to claim 21, wherein the drug delivery system is in the form of solution, lotion, W/O emulsion, O/W emulsion, suspension, liposome, gel, hydrogel, cream, paste, patch or ointment.

30. A method for preventing or treating a bone disease via transdermal route, which comprises administering to a subject a pharmaceutical comprising (a) a pharmaceutically effective amount of a drug delivery system containing (i) a bisphosphonate-based drug and (ii) a cationic amine compound linked to the bisphosphonate-based drug via an ionic bond; and (b) a pharmaceutically acceptable carrier.

31. The method according to claim 30, wherein the bisphosphonate-based drug is a compound represented by the following Formula 1:



(1)

where R_1 is hydrogen, hydroxy or halo; R_2 is halo, C_{1-10} alkyl, C_{1-10} cycloalkyl, C_{1-10} heterocycloalkyl, C_{1-10} heteroaryl, C_{1-10} aryl or C_{1-10} arylalkyl; the alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl and heteroaryl are substituted with halo, sulfur, amino, C_{1-5} alkylamino or C_{1-5} dialkylamino and contains 1-3 nitrogen atoms.

32. The method according to claim 30 or 31, wherein the bisphosphonate-based drug is (4-amino-1-hydroxybutylidene)-bisphosphonate or 4-amine-1-hydroxybutane-1,1-bisphosphonic acid(alendronate); (dichloromethylene)-bisphosphonate (clodronate); (1-hydroxyethylidene)-bisphosphonate(etidronate); [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonate(evandronate); [(cycloheptylamino)-methylene] bisphosphonate (cimadronate, incadronate); [1-hydroxy-2-imidazo-(1,2-a) pyridine-3-ylethyledne] bisphosphonate (minodronate); (6-amino-1-hydroxyhexyleden) bisphosphonate (neridronate); [3-(dimethylamino)-hydroxy-propylidene] bisphosphonate (olpadronate); (3-amino-1-hydroxypropylidene) bisphosphonate (pamidronate); [1-hydroxy-2-(3-pyridinyl)-ethylidene] bisphosphonate [[(4-chlorophenyl)thio]-methylene] bisphosphonate (tiludronate); [1-hydroxy-2-(1H-imidazole-1-yl) ethylidene] bisphosphonate (zolendronate); dichloromethylene bisphosphonate (clodronate); paridronate; 5-amino-1-hydroxy pentane-1,1-bisphosphonic acid; or difluoro-methane bisphosphonic acid; or a pharmaceutically acceptable salt thereof.

33. The method according to claim 30, wherein the cationic amine compound is selected from the group consisting of an amino acid, diethylenetriamine (DETA), spermine, ethylene diamine, triethylene tetramine and tris(2-aminoethyl amine).

34. The method according to claim 33, wherein the cationic amine compound is the amino acid.

35. The method according to claim 34, wherein the amino acid is arginine or lysine.

36. The method according to claim 30, wherein the drug delivery system has the molar ratio of the bisphosphonate-based drug and the cationic amine compound of 1:0.01-50.

37. The method according to claim 30, wherein the bisphosphonate-based drug is contained in the amount of 0.01-20 wt% based on the total weight of the drug delivery system.

38. The method according to claim 30, wherein the drug delivery system is contained in the amount of 0.001-50 wt% based on the total weight of the composition.

39. The method according to claim 30, wherein the composition is solution, lotion, W/O emulsion, O/W emulsion, suspension, liposome, gel, hydrogel, cream, paste, patch or ointment.

40. The method according to claim 30, wherein the bone disease is osteoporosis, Paget's disease, rickets, osteopenia, rheumatoid arthritis, osteomalacia, renal osteodystrophy, osteogenesis imperfecta, hyperthyroidism, bone loss due to rheumatoid arthritis, inflammatory arthritis, subchondral osteosclerosis, subchondral osteocystoma, osteophytosis, athralgia ,hyperparathyroidism, sarcoidosis or hypercalcemia.

Fig. 1a

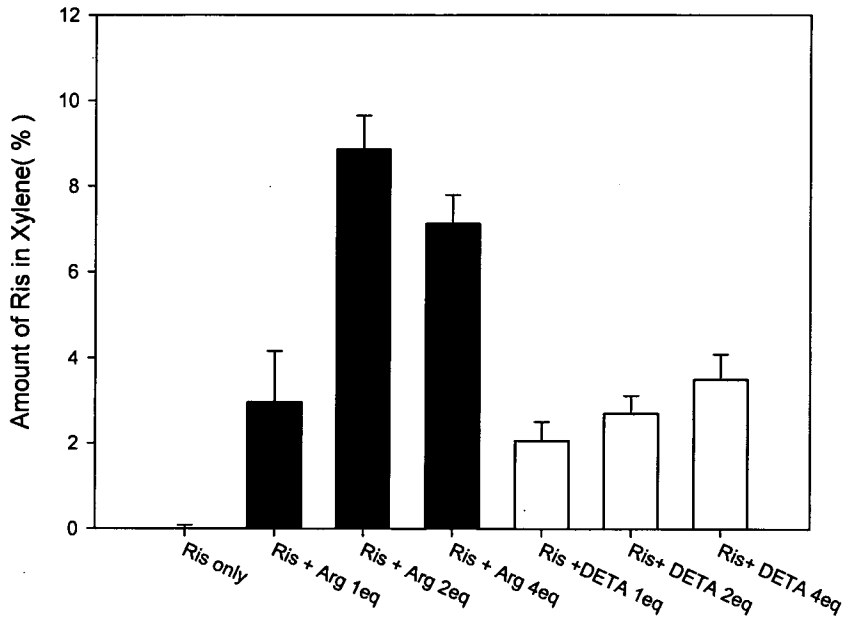

Amount of Ris in Xylene(%)
12
10
8
6
4
2
0
Ris only
Ris + Arg 1eq
Ris + Arg 2eq
Ris + Arg 4eq
Ris +DETA 1eq
Ris+ DETA 2eq
Ris+ DETA 4eq

Fig. 1b

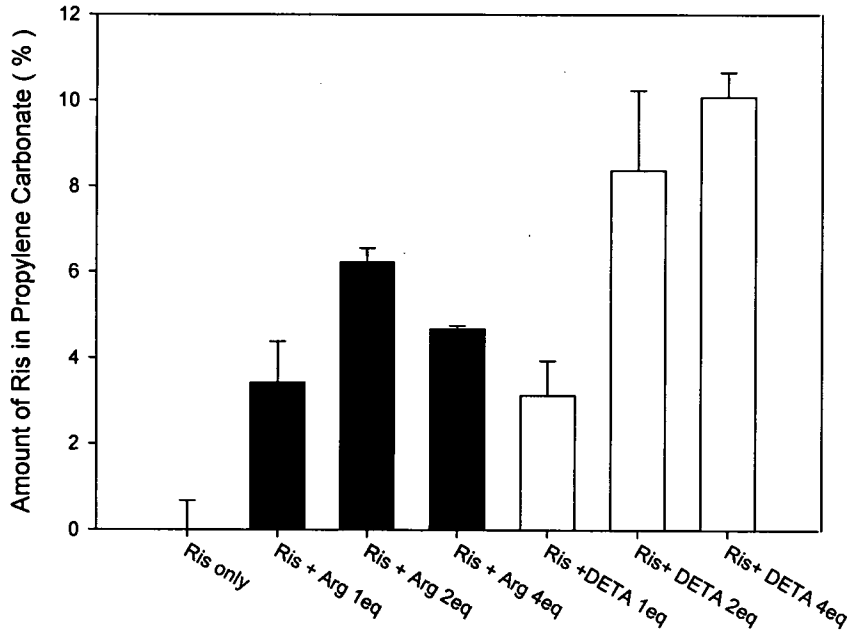

Amount of Ris in Propylene Carbonate (%)
12
10
8
6
4
2
0
Ris only
Ris + Arg 1eq
Ris + Arg 2eq
Ris + Arg 4eq
Ris +DETA 1eq
Ris+ DETA 2eq
Ris+ DETA 4eq

Fig. 2

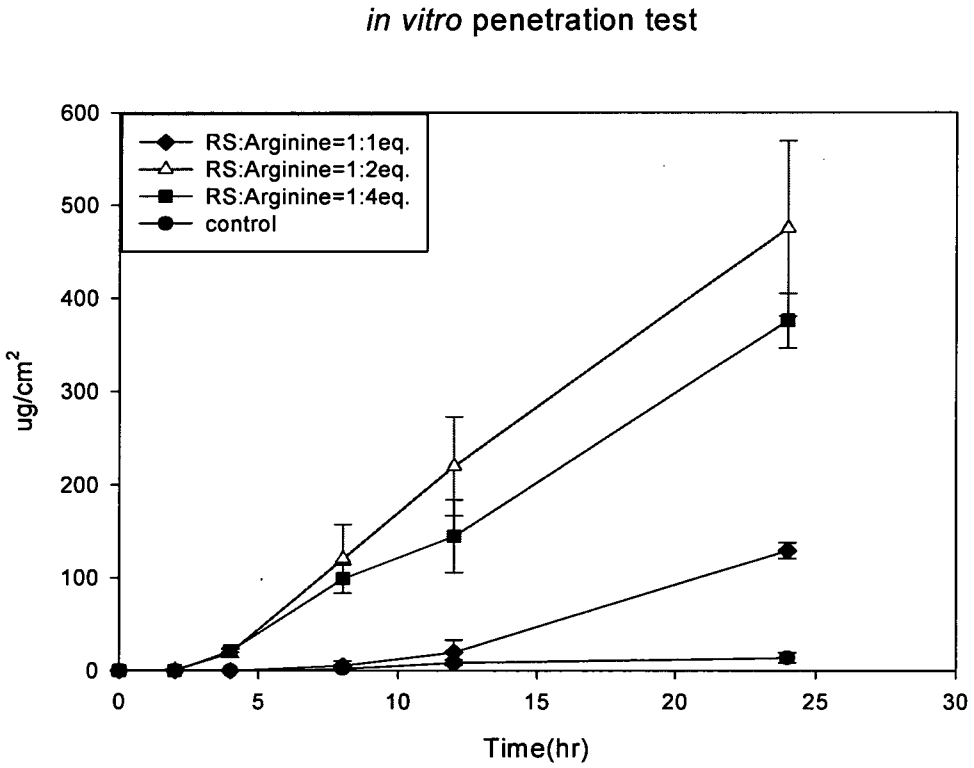

in vitro penetration test
RS:Arginine=1:1eq.
RS:Arginine=1:2eq.
RS:Arginine=1:4eq.
control
ug/cm2
600
500
400
300
200
100
0
0
5
10
15
20
25
30
Time(hr)

Fig. 3

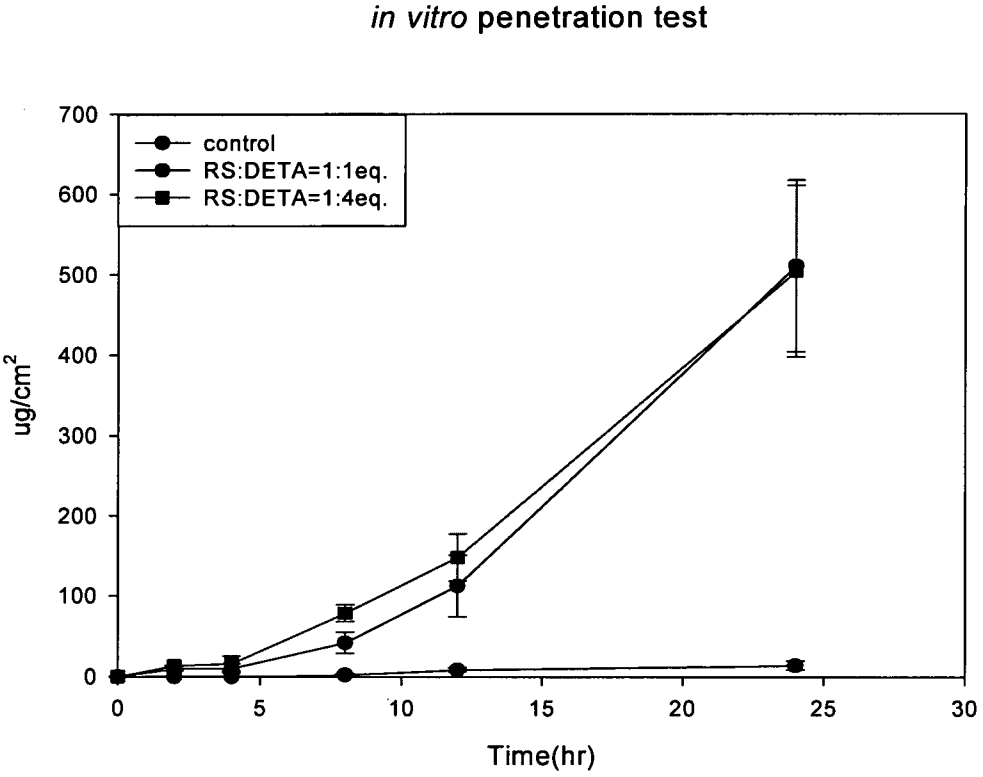

in vitro penetration test
control
RS:DETA=1:1eq.
RS:DETA=1:4eq.
ug/cm2
Time(hr)
0
100
200
300
400
500
600
700
0
5
10
15
20
25
30

Fig. 4

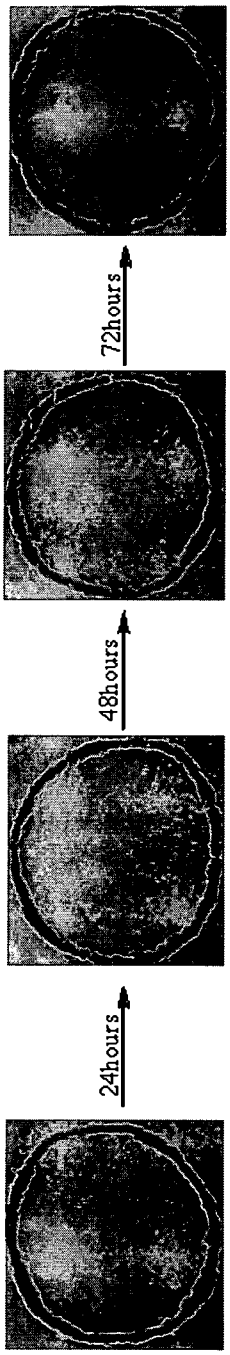


Fig. 5

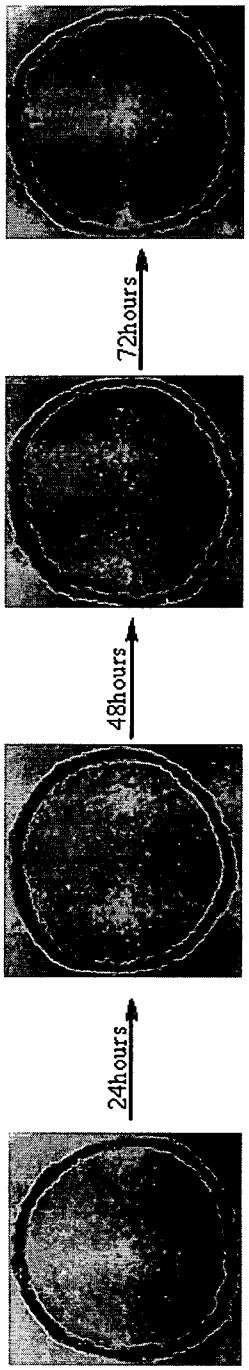


Fig. 6

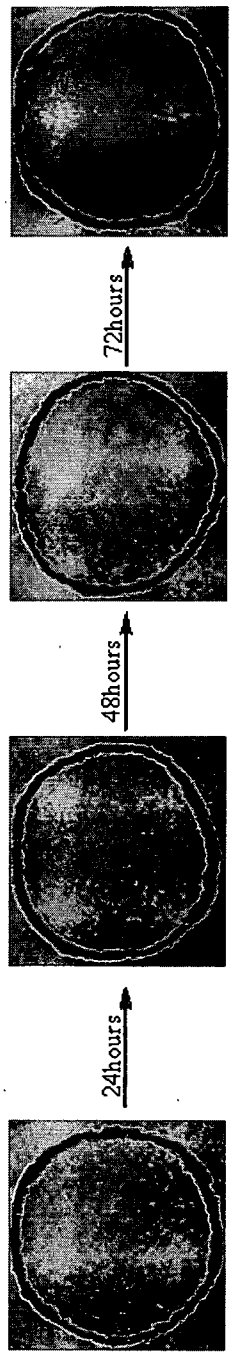


Fig. 7a

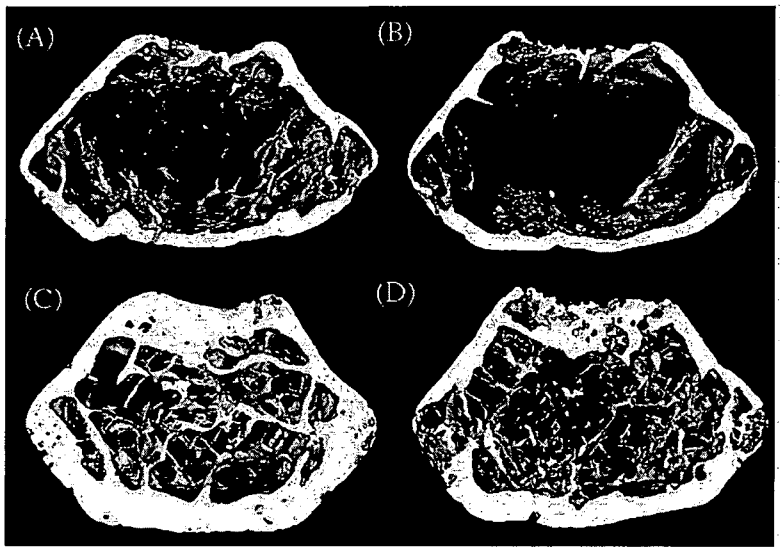


Fig. 7b

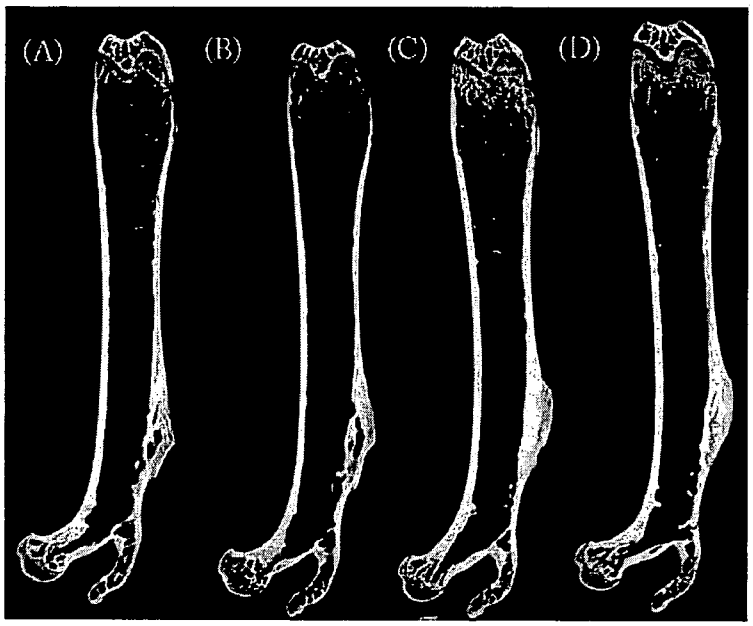


Fig. 8a

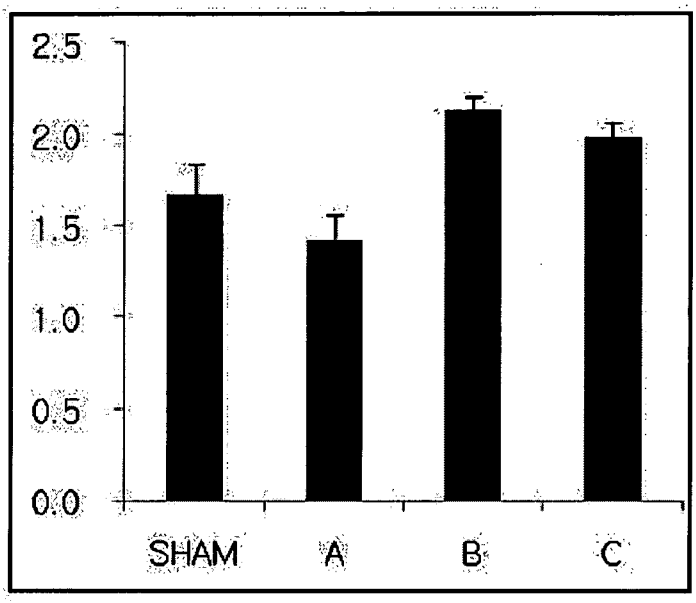


Fig. 8b

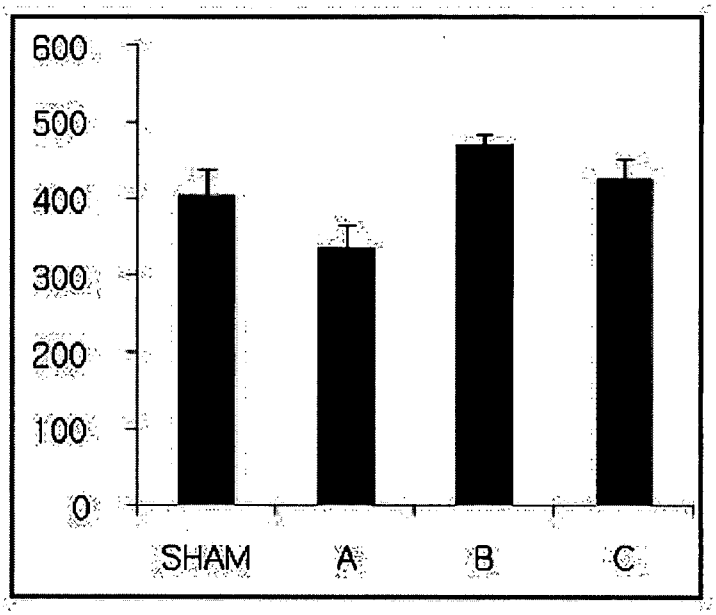


Fig. 8c

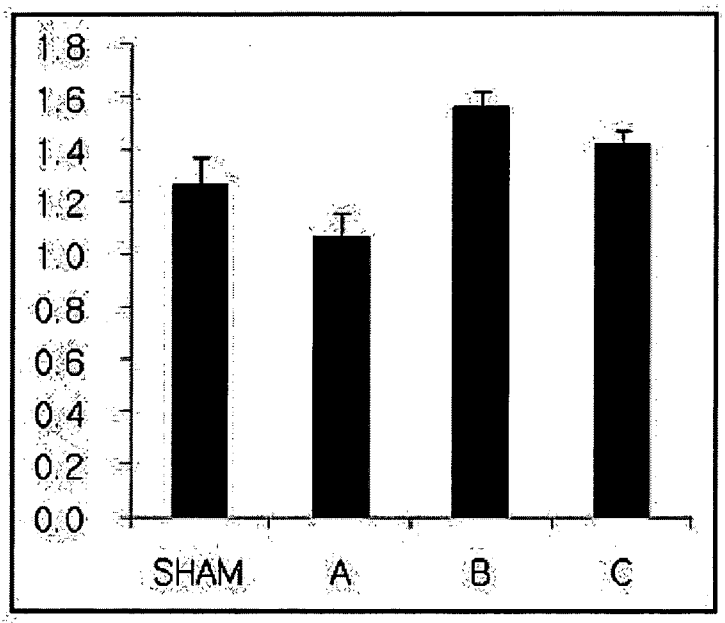

1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
SHAM
A
B
C

Fig. 8d

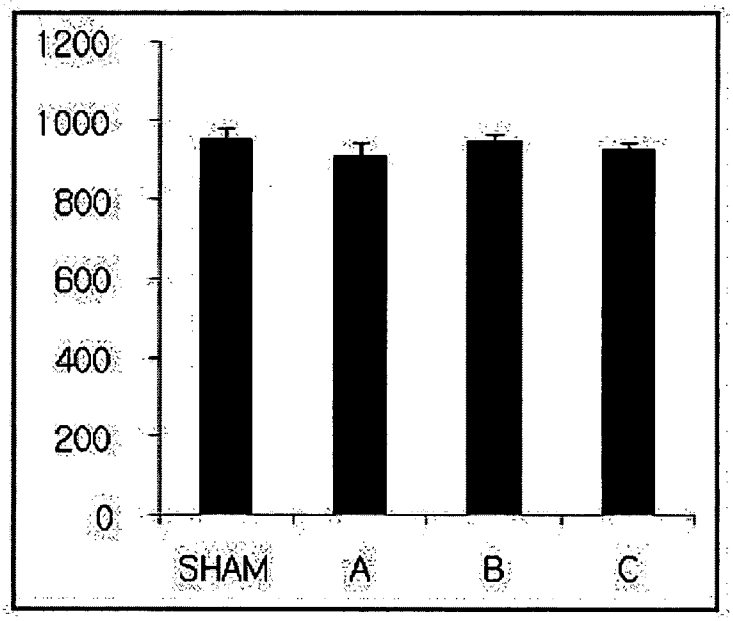
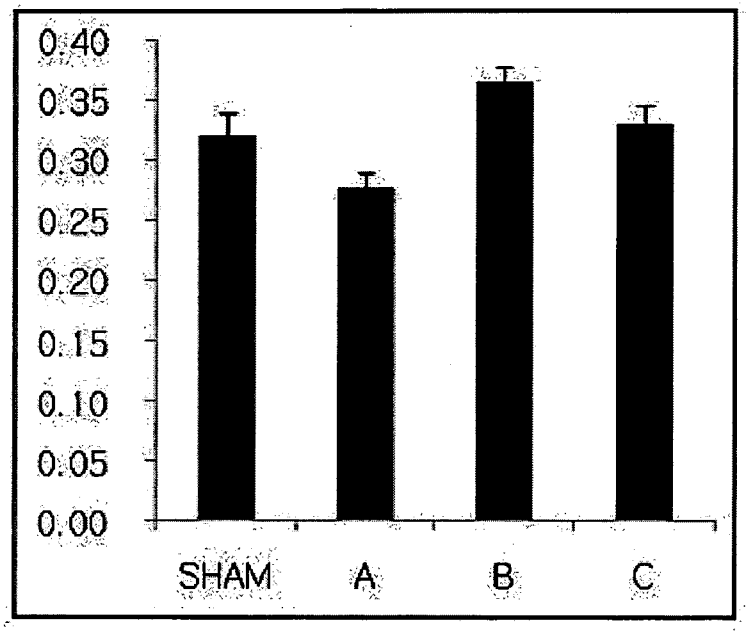

1200
1000
800
600
400
200
0
SHAM
A
B
C

Fig. 8e



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2010/005890

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/06(2006.01)i, A61K 9/50(2006.01)i, A61K 31/663(2006.01)i, A61P 19/00(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 9/06; A61K 31/5575; A61K 31/66; A61K 9/70; A61K 47/04; A61K 9/08

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), GOOGLE, PUBMED

Keywords: TRANSDERMAL, DRUG DELIVERY, BISPHOSPHONATE, ALENDRONATE, BONE DISEASE, AMINE, LYSINE, ARGININE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 10-2006-0087568 A (NOVARTIS AG) 02 August 2006 See abstract; page 2, line 46-page 3, line 11; claims 1-40.	1-20
X	KR 10-2008-0000647 A (ONO PHARMACEUTICAL CO., LTD.) 02 January 2008 See abstract; claims 1-18; [0090], [0094], [0150]-[0153].	1-20
A	JP 08-092101 A (TEIJIN LTD) 09 April 1996 See the whole document.	1-20
A	US 6638920 B2 (THOMPSON, D. R.) 28 October 2003 See the whole document.	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 JUNE 2011 (20.06.2011)	**20 JUNE 2011 (20.06.2011)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
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Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

HAN, Jung Hee

Telephone No. 82-42-481-5604

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2010/005890

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21-40
because they relate to subject matter not required to be searched by this Authority, namely:
The subject-matter of claims 21-40 pertain to the method for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2010/005890

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