

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
17 January 2002 (17.01.2002)

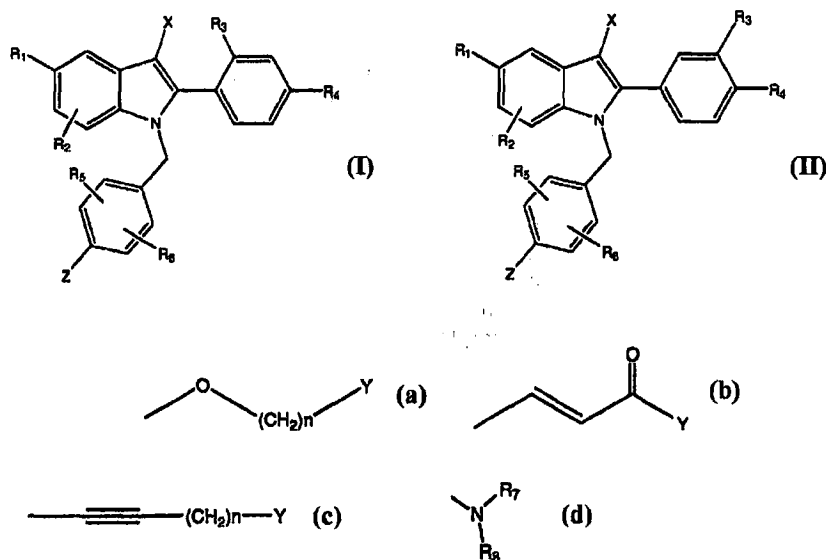
PCT

(10) International Publication Number
WO 02/03987 A2

- (51) International Patent Classification⁷: A61K 31/404, 9/20
- (21) International Application Number: PCT/US01/20993
- (22) International Filing Date: 29 June 2001 (29.06.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/216,192 6 July 2000 (06.07.2000) US
- (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 @ (US).
- (72) Inventors: BENJAMIN, Eric, Joel; 4 Hobbs Court, Pomona, NY 10970 (US). DULIN, Wendy, Ann; 25 Richard Street, Sloatsburg, NY 10974 (US). SURYAWAN-SHI, Jiwaji, Gulabrao; 5 Doreen Court, Rockaway, NJ 07866 (US).
- (74) Agents: MILOWSKY, Arnold, S., et al.; American Home Products Corporation, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report

[Continued on next page]

(54) Title: PHARMACEUTICAL COMPOSITIONS OF ESTROGENIC AGENTS



(57) Abstract: This invention comprises novel pharmaceutical carrier or excipient systems and oral pharmaceutical formulations comprising as an active ingredient raloxifene, amoxifen, droloxifene, arzoxifene, or analogs thereof, or a compound of formulae (I) or (II), wherein Z is a moiety selected from the group of formulae (a, b or c), wherein: R₁ is selected from H, OH or the C₁-C₁₂ esters alkyl ethers thereof, benzyloxy, or halogen; or C₁-C₄ halogenated ethers; R₂, R₃, R₄, R₅, and R₆ are H, OH or C₁-C₁₂ esters or alkyl ethers thereof, halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl, or CF₃, with the proviso that, when R₁ is H, R₂ is not OH; Y is the moiety: formulae (d), wherein R₇ and R₈ are alkyl or concatenated together to form an optionally substituted, nitrogen-containing ring; or a pharmaceutically acceptable salt thereof; and excipients chosen from pharmaceutical fillers, glidants, lubricants, wetting agents and antioxidants.

- 3 -

menopausal syndrome, cardiovascular-related pathological conditions and estrogen-dependent cancer.

U.S. 5,332,727 and U.S. 5,480,652 describe the use of antioxidants such as ascorbic acid in a solid pharmaceutical composition to stabilize the drug. In the case of NADH and NADPH formulations, the stabilizers added to the formulation include NaHCO₃ and PVP in addition to ascorbic acid and are not added to the formulation for an antioxidant effect per se. In the case of ibuprofen, the antioxidant must be in intimate contact with the active drug agent prior to its incorporation into the formulation in order to achieve its protective effect. This effect is only needed in the presence of alkaline carbonates in these effervescent formulations.

WO 96/21656 (Cameron et al.) teaches novel compounds, including CP 336156, and uses for treating or preventing obesity, breast cancer, osteoporosis, endometriosis, cardiovascular disease and prostatic disease.

Sawicka, J. "The influence of excipients and technological process on cholecalciferol stability and its liberation from tablets", *Pharmazie*, 46(1991), H. 7, pp. 519-521 describes the stabilization of cholecalciferol with various antioxidants in the solid state. The best antioxidant system described, however, yielded only 87.6% of the original content after 1 year of storage and the dissolution of the active material was also quite slow. Thus, improvements are required for stabilization of unstable solid drugs.

In light of the prior art, there is still a need to improve the solubility, stability and absorption qualities of poorly soluble pharmaceutical agents.

Description of the Invention

The present invention provides for orally administrable preparations that optimize the stability and enhance the dissolution of poorly soluble pharmaceutical agents, including estrogenic agents. Various formulations have been used to produce

- 4 -

rapid dissolution of poorly soluble drugs, such as solubilization form (e.g. softgel capsules) or a high-energy form (e.g. solid dispersions). These techniques use specialized equipment and/or processes. The present invention provides pharmaceutically useful compositions which produce a rapid dissolution of poorly soluble drugs from a pharmaceutical solid dosage formulation via commonly used components and processes.

This invention comprises novel pharmaceutical carrier or excipient systems useful in the formulation of solid oral dosage forms for poorly soluble pharmacological agents, including estrogenic pharmacological agents including, but not limited to, those in the art known as TSE-424, ERA-923, raloxifene, tamoxifen, droloxifene, and arzoxifene, as well as their analogs and pharmaceutically acceptable salts. These carrier or excipient systems comprise:

a) a filler and disintegrant component comprising from about 5% to about 82% by weight (wght) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants; and

b) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates and sodium chloride.

It will be understood that the percentages listed above for the filler and disintegrant component and lubricant are percentages each will comprise of a final pharmaceutical composition. The remainder of the final composition will be comprised of the active pharmacological agent(s) and a pharmaceutically acceptable surface covering, such as a coating or capsule, as described herein. In preferred

91
90

- 5 -

aspects of this invention, the active pharmacological agent(s) will comprise from about 0.5% to about 20%, by weight, of the final composition, more preferably from about 1% to about 5%, and the coating or capsule will comprise up to about 8%, by weight, of the formulation.

5

Considering the filler and disintegrant component and lubricant component above, solely and without reference to an active pharmacological agent or coating, the carrier or excipient system would comprise:

- 10 a) from about 5.4% to about 89%, by weight, of a filler or disintegrant component, preferably from about 32.5% to about 87%; and
- b) from about 0.22% to about 10.9% of a lubricant component.

15 The carrier or excipient systems or compositions herein may also optionally utilize pharmaceutically acceptable wetting agents, glidants and antioxidants. Such systems or compositions comprise:

- a) a filler and disintegrant component comprising from about 5% to about 20 82% by weight (wght) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

- b) optionally, a wetting agent comprising from about 0.2 to about 5% of 25 the composition (wght), such as selected from the group of sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, sugar esters of fatty acids and glycerides of fatty acids;

30

- c) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium

92
91

- 6 -

stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates and sodium chloride; and

- 5 d) optionally, a glidant comprising from about 0.1% to about 10% (wght) of the composition, the glidant selected from those known in the art, including from the group of silicon dioxide, talc, metallic stearates, calcium silicate, or metallic lauryl sulfates.

- 10 This invention also comprises solid oral formulations or compositions of a pharmaceutically effective dose of an active pharmacological compound, or a pharmaceutically acceptable salt thereof, and a carrier or excipient system of this invention, as described above. Among the more preferred active pharmacological agents for use with these carrier or excipients systems are non-steroidal estrogenic
15 agents or tissues selective estrogenic agents. Examples of these compounds include, but are not limited to TSE-424, ERA-923, raloxifene, tamoxifen, droloxifene, arzoxifene or CP 336156, or a pharmaceutically acceptable salt of these compounds.

- While the formulations described herein may be used in an uncoated or non-
20 encapsulated solid form, preferably the final compositions are coated or encapsulated. The pharmacological compositions may be optionally coated with a film coating, preferably comprising from about 0.3% to about 8% by weight of the overall composition. Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant
25 and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may be included in film coating formulations to impart certain characteristics to the film coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

30

 The filler component listed above may utilize the filler or binder components known in the art for solid oral formulations. Pharmaceutically acceptable fillers or

93
92

- 7 -

binding agents selected from those known in the art including, but not limited to, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, or xylitol.

5 In conjunction with or in place of the materials listed above for the filler component, the present formulations utilize disintegrant agents. These disintegrants may be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other useful disintegrants include croscarmellose sodium, crospovidone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those
10 utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium
15 carbonate, etc.). The disintegrant(s) useful herein will comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%. Some components may have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, such a component may be referred to as a filler disintegrant and its
20 function in a specific formulation may be singular even though its properties may allow multiple functionality.

 The pharmaceutical formulations and carrier or excipient systems herein preferably also contain an antioxidant or a mixture of antioxidants, most preferably
25 ascorbic acid. Other antioxidants which may be used include sodium ascorbate and ascorbyl palmitate, preferably in conjunction with an amount of ascorbic acid. A preferable range for the antioxidant(s) is from about 0.5% to about 15% by weight, most preferably from about 0.5% to about 5% by weight.

- 14 -

group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;

5 and the pharmaceutically acceptable salts thereof.

In another embodiment of this invention, when R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group
10 containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

The invention includes sulfate, sulfamates and sulfate esters of phenolic groups for the active compounds described above. Sulfates can be readily prepared by the reaction of the free phenolic compounds with sulfur trioxide complexed with
15 an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfamates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the presence of a suitable base such as pyridine.
20 Additionally, this invention includes compounds containing phosphates at the phenol as well as dialkyl phosphates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkylphosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of
25 the phenol.

The invention includes acceptable salt forms of these compounds formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid,
30 nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methane-

administration will be from about 10 mg/day to about 600 mg/day in a single dose or in two or more divided doses. More preferably, administration will be from about 1 mg/day to about 200 mg/day in a single dose or in two or more divided doses. It will also be understood that these methods and regimens may be completed either
5 remedially or prophylactically in the treatment, prohibition, inhibition or alleviation of the causes and symptoms of the maladies in question.

When the active ingredient in the formulations and methods of this invention is 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol,
10 also known as TSE-424, or a pharmaceutically acceptable salt thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 50 mg, preferably from about 2.5 to about 40 mg per day.

When the active ingredient in the formulations and methods of this invention is 2-(4-hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol,
15 also known as ERA-923, or a pharmaceutically acceptable salt form thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 200 mg, preferably from about 2.5 to about 100 mg per day.

20 Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral suspensions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening
25 agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc,
30 sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate,

101
100

- 37 -

Wet granulation of the formulations as described in Table 1 may be carried out by mixing the drug and ascorbic acid with a portion of the lactose, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate. The sodium lauryl sulfate is dissolved in the water and used to granulate the mixture of powders in a high shear mixer. The granulation is dried in a fluid bed dryer to a moisture of 2-3%. The particle size of the dried granulation is controlled by passing through a mill equipped with knife-edged blades and using a 20- or 30-mesh screen. The silicon dioxide and remaining lactose, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate are mixed with the milled granulation in a tumble-type mixer. The final blend is prepared by adding magnesium stearate to the tumble-type mixer and mixing. Compression is carried out on a rotary tablet press using appropriate size tooling. Coating is performed in conventional coating pans and applying the coating suspension to achieve a suitable film coat.

Example 3. Modified TSE-424 formulation

%w/w

Ingredient	5% granulation
TSE-424 acetate, micronized ^a	5.00
Lactose NF	41.00
Microcrystalline Cellulose, NF	35.00
Pregelatinized Starch NF	10.00
Sodium Lauryl Sulfate NF	1.50
l-Ascorbic Acid USP	1.50
Sodium Starch Glycolate NF	5.50
Magnesium Stearate NF	0.50
Pur. Water USP ^b	qs

^a Amount in formula is adjusted for actual potency of TSE-424 as free base. Corresponding adjustment made with Lactose.

^b Used in process but does not appear in the final product.

Example 4. ERA-923 formulations

%w/w

Ingredient	10.86% granulation	11.19% granulation	17.5% granulation	17.9% granulation
ERA-923, micronized ^a	10.867	11.193	17.489	17.909
Lactose NF	29.000	29.000	17.380	18.000
Microcrystalline Cellulose, NF	40.633	42.807	38.000	39.090
Pregelatinized Starch NF	10.000	10.000	14.630	15.000
Sodium Lauryl Sulfate NF	2.500	--	2.500	--
l-Ascorbic Acid USP	1.500	1.500	1.500	1.500
Sodium Starch Glycolate NF	5.000	5.000	8.000	8.000
Magnesium Stearate NF	0.500	0.500	0.500	0.500
Pur. Water USP ^b	qs	qs	qs	qs

5 ^a As the Hydrochloride Monohydrate. Quantity is adjusted based on the actual potency (theory = 89.34%).

^b Used in process but does not appear in the final product.

ERA-923 tablets are compressed to a tablet weight of up to 640 mg to achieve the target dose (up to 100 mg). Tablets may then be film coated.

10 **Example 5. Stability with Ascorbic Acid as Antioxidant**

Formulations of this invention containing 1% active ingredient (TSE-424) were prepared for stability comparison of formulations with and without ascorbic acid present over periods of 1, 3 and 6 months at either 25°C and 60% relative humidity (RH) or 40°C and 75% relative humidity. The stability data for these formulations
15 are provided below, demonstrating that the ascorbic acid component provided protection of the estrogenic agent (TSE-424) versus oxidation in solid dosage formulations.

103
102

- 39 -

Storage Condition	1% capsule without Ascorbic Acid		1% tablet with Ascorbic Acid	
	Strength (% label claim)	Total degradation products	Strength (% label claim)	Total degradation products
Initial	101.4	0.20	100.5	0.46
25°C/60%RH 1 Month	101.7	0.85	97.2	0.99
25°C/60%RH 3 Months	99.3	1.63	98.6	0.55
25°C/60%RH 6 Months	98.2	2.22	99.6	0.77
25°C/60%RH 9 Months	95.7	2.77	99.1	0.88
40°C/75%RH 1 Month	101.0	0.87	97.8	0.96
40°C/75%RH 3 Months	97.8	1.86	98.5	0.55
40°C/75%RH 6 Months	99.8	2.49	98.8	0.75

Note: samples are stored in bottles.

Example 6. TSE-424 at 5 % Granulation

5

A preferred carrier or excipient system for formulating a granulation of from about 2 to about 8% by weight of one of the active pharmacological agents of this invention, preferably about 5%, may be produced utilizing the carrier or excipient components on a weight percentage; lactose from about 32% to about 38%, microcrystalline cellulose from about 32% to about 38%, pregelatinized starch from about 12% to about 16%, ascorbic acid from about 1% to about 2%, sodium lauryl sulfate from about 1% to about 2%, sodium starch glycolate from about 4% to about 8%, silicon dioxide from about 0.1% to about 0.2% and magnesium stearate from about 0.3% to about 0.7%.

15

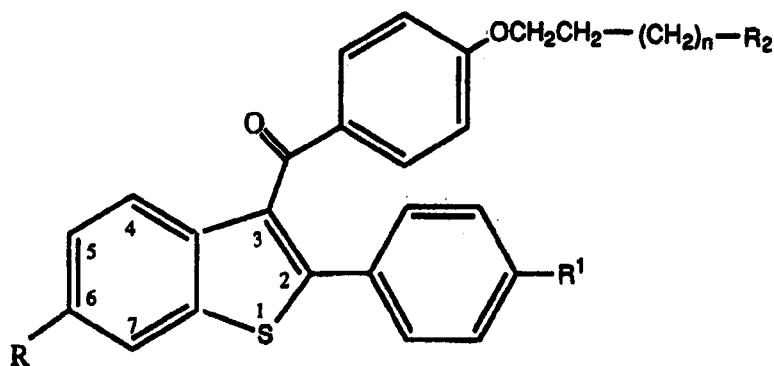
A formulation of this invention utilizing TSE-424 as the active ingredient at a 5% granulation was prepared utilizing the components listed below in a granulation part of components and a dry part.

125
164

5

10

15



(I)

wherein

n is 0, 1 or 2;

R and R^1 , independently, are hydrogen, hydroxyl, C_1 - C_6 -alkoxy, C_1 - C_6 -acyloxy, C_1 - C_6 -alkoxy- C_2 - C_6 -acyloxy, R^3 -substituted aryloxy, R^3 -substituted aroyloxy, R^4 -substituted carbonyloxy, chloro, or bromo;

R^2 is a heterocyclic ring selected from the group consisting of pyrrolidino, piperidino, or hexamethylenelmino;

R^3 is C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, hydrogen, or halo; and

R^4 is C_1 - C_6 -alkoxy or aryloxy; or

a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical formulation for use in inhibiting bone loss comprising a compound of formula I, wherein R , R^1 , R^2 , and n are as defined *supra*, in an amount that increases or retains bone density, together with a pharmaceutically acceptable carrier.

The current invention concerns the discovery that a group of 2-phenyl-3-arylbenzothiophenes (benzothiophenes) of formula I are useful in the treatment of osteoporosis. The benzothiophenes of formula I inhibit the loss of bone that results from a lack of endogenous estrogen such as occurs in women following cessation of menstruation due to natural, surgical, or other processes. The reduction of bone density and mass that more rarely occurs in men is also tied to the loss of hormonal regulation and is therefore also a target for therapy according to the methods of the current invention.

The benzothiophenes of formula I are a series of nonsteroidal compounds that exhibit high affinity for conventional estrogen receptors in primary sex target tissues. However, they elicit minimal estrogenic responses in those tissues, and actually serve as potent antagonists of natural estrogens such as estradiol. The benzothiophenes of formula I are able to antagonize classical estrogenic responses in primary sex target tissues without significantly reducing bone density when given to intact or estrogen treated animals, and they prevent bone loss in estrogen deficient animals. This dichotomy indicates selective agonist/antagonist actions on specific target cells which would appear to be highly desirable in treatment of the menopausal syndrome. Accordingly, the real benefit of the current discovery is that the benzothiophenes of formula I inhibit the loss of bone but do not elicit significant estrogenic responses in the primary sex target tissues. Thus, the current invention provides a method of inhibiting bone loss comprising administering to a human in need of treatment an amount of a compound of formula I that inhibits bone loss but does not significantly affect the primary sex target tissues. This combination of features allows for long-term treatment of the chronic ailment with a diminished risk of developing the undesirable effects of customary estrogen replacement therapy.

The biological action of the benzothiophenes of formula I is complex and may be unrelated to the detectable presence of the parent compound in the blood. Following oral administration of a preferred benzothiophene of this invention, raloxifene (administered as the hydrochloride salt), to human subjects in the clinic, the parent compound was not detected in the serum of those subjects. It was determined that following oral administration, the compound was extensively conjugated to the glucuronidated form and cleared quickly from the bloodstream. Although no biological endpoints were measured in the human recipients, there was concern that the compound was not bioavailable.

Experiments were undertaken to address the bioavailability issue in laboratory animals where biological activity could be assessed. The animal studies indicated that raloxifene was maximally active in inhibiting both uterine uptake of tritiated-estradiol and the normal uterotrophic response to estradiol, even under conditions where raloxifene was extensively conjugated in the plasma of the animals. Moreover, the conjugate, isolated

106
105

functionalities of particular substituents. Such modifications would be both apparent to, and readily ascertained by, those skilled in the art.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanolic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methane-sulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like.

In addition, some of the formula I compounds may form solvates with water or organic solvents such as ethanol. These solvates are also contemplated for use in the methods of this invention.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates and bicarbonates, as well as aliphatic and aromatic amines, aliphatic diamines and hydroxy alkylamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylene diamine, cyclohexylamine and ethanolamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

The current invention also provides pharmaceutical formulations useful for inhibiting bone loss comprising a formula I compound, or a pharmaceutically acceptable salt thereof, plus one or more pharmaceutically acceptable excipients. Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as agaragar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethylene glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to treat or inhibit bone loss according to this invention will depend upon the severity of the disease, its route of administration, and related factors that will be decided by the attending physician. Generally, an effective dose will be from about 0.1 to about 1000 mg of the formula I compound, typically from about 50 to about 400 mg, and most preferably about 50 to about 200 mg. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively inhibit the bone loss process.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is cus-

United States Patent [19]

Goertz et al.

[11] Patent Number: 4,801,460

[45] Date of Patent: Jan. 31, 1989

[54] PREPARATION OF SOLID PHARMACEUTICAL FORMS

[75] Inventors: Hans-Helmut Goertz, Freinsheim;
Roger G. Klimesch,
Alsbach-Haehnlein; Klaus
Laemmerhirt, Boehl-Iggelheim;
Siegfried Lang, Ludwigshafen; Axel
Sanner, Frankenthal; Reinhard
Spengler, Ludwigshafen, all of Fed.
Rep. of Germany

[73] Assignee: BASF Aktiengesellschaft, Fed. Rep.
of Germany

[21] Appl. No.: 34,938

[22] Filed: Apr. 6, 1987

[30] Foreign Application Priority Data

Apr. 11, 1986 [DE] Fed. Rep. of Germany 3612212

[51] Int. Cl.⁴ A61K 9/20

[52] U.S. Cl. 424/465; 424/467;
424/468; 424/80

[58] Field of Search 424/464, 80, 465, 486,
424/487, 467, 468

[56] References Cited

U.S. PATENT DOCUMENTS

3,089,818 5/1963 Stone 167/65
3,432,592 3/1969 Speiser 424/19
4,631,284 12/1986 Salpekar et al. 514/849 X
4,661,521 4/1987 Salpekar et al. 424/465 X

FOREIGN PATENT DOCUMENTS

1137009 9/1962 Fed. Rep. of Germany .
1388786 3/1975 United Kingdom .

OTHER PUBLICATIONS

P. Speiser, *Pharmaceutica Acta Helv.*, 41 (1966), 340.
R. Voight, *Lehrbuch der Pharmazeutischen Technologie*, 5th Edition, Verlag Chemie, Weinheim, 1984, pp. 221-222.

Tachibana & A. Nakamura, *Kolloid Zeitschrift and Zeitschrift fur Polymere*, 203 (1965), 130.

M. Mayersohn et al., *J. Pharm. Sci.* 55 (1966), 1323.

W. Scholten, *Arzn. Forschung* 14 (1964), 469.

El-Egakey, Soliva, and Speiser, *Pharmaceutica Acta Helvetiae*, vol. 46, (1971), 31-54.

Primary Examiner—Michael Lusignan

Attorney, Agent, or Firm—Keil & Weinkauff

[57] ABSTRACT

Process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible, pharmacologically tolerated binders and, if required, other conventional pharmaceutical auxiliaries, at from 50° to 180° C., and subjecting the mixture to injection molding or extrusion and shaping, wherein the fusible binder used is a NVP polymer which contains not less than 20% by weight of NVP as copolymerized units, and, where they are present, all of whose comonomers contain nitrogen and/or oxygen.

9 Claims, No Drawings

PREPARATION OF SOLID PHARMACEUTICAL FORMS

The present invention relates to a process for the preparation of solid pharmaceutical forms which in an n-vinylpyrrolid-2-one(NVP) polymer as a binder, by injection molding or extrusion and shaping.

Conventional tableting machines operate by a cyclic process using punches and dies. The process requires thoroughly premixed and specially prepared tableting materials and the overall process is therefore a multi-stage one and is expensive. The production of solid pharmaceutical forms with controlled release of active compound is particularly expensive. This may require retardation measures on the one hand and measures for improving the absorption of active compounds on the other hand.

One possible method for improving the absorption of sparingly soluble active compounds is to use solid solutions of the active compounds in water-soluble polymers. The known solid solutions of this type in NVP polymers were prepared by dissolving the active compound and the polymer together in an organic solvent and removing the latter. As a rule, in order to dissolve both the hydrophobic compound and the hydrophilic polymer, chlorohydrocarbons were required. Complete removal of these solvents is very expensive. In order to avoid environmental pollution, the solvents must again be removed as completely as possible from the waste air, which in turn is very expensive. Processes of this type are described in, for example, U.S. Pat. No. 3,089,818; T. Tachibana and A. Nakamura, *Kolloid Zeitschrift und Zeitschrift für Polymere*, 203 (1965), 130; Japanese Patent No. 24,379; M. Mayersohn et al., *J. Pharm. Sci.* 55 (1966), 1323; DE-B-11 37 009; and W. Scholten, *Arzn. Forschung* 14 (1964), 469.

The extrusion of active compound/polymer mixtures has already been described (cf. for example DE-A No.12 29 248; P. Speiser, *Pharmaceutica Acta Helv.*, 41 (1966), 340 and *ibid.* 46 (1971, 31). However, in no case were solvent-free NVP polymers melted, let alone extruded, without being mixed with other polymers or with water, and in no case is the formation of a solid solution of a sparingly water-soluble active compound in a water-soluble polymer described.

In R. Voigt, *Lehrbuch der pharmazeutischen Technologie*, 5th Edition, Verlag Chemie, Weinheim, 1984, pages 221-222, the preparation of solid pharmaceutical formulations by injection molding or extrusion shaping of active compound/thermoplastic mixtures is described in general form but without any specific information, in particular about the type of polymers which are suitable for this purpose. The polymers in question here were without a doubt not highly hydrophilic polymers, such as NVP polymers, since, in the pharmaceutical sector to date, these have been processed not via the dry melt but always as a base with solvents (as a rule water) (cf. for example, British Patent No. 1,388,786).

It is an object of the present invention to provide a simple process for the preparation of solid pharmaceutical forms, preferably with controlled release of active compound.

We have found that this object is achieved by a process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible, pharmacologically tolerated binders and, if required, other conventional

pharmaceutical auxiliaries, at from 50° to 180° C., preferably from 60° to 160° C., and subjecting the mixture to injection molding or extrusion and shaping, wherein the fusible binder used is a solvent-free NVP polymer which has a water content of not more than 3.5% by weight and contains not less than 20, preferably not less than 60, in particular 100, % by weight of NVP as copolymerized units, and, where they are present, all of whose comonomers contain nitrogen and/or oxygen, and, at least when the glass transition temperature of the mixture is above 120° C., an NVP polymer is used which is obtained by polymerization in an organic solvent or using an organic peroxide as an initiator in aqueous solution, and the mixture does not contain any thermoplastics which are sparingly soluble in gastric juice (less than 10% dissolving in 6 hours).

The NVP polymers should contain not less than 20, preferably not less than 60, in particular 100, % by weight of NVP as copolymerized units and have a Fikentscher K value (*Cellulose-Chemie* 13 (1932), 58-64 and 71-74) of from 10 to 70, preferably from 10 to 50, particularly preferably from 12 to 40, in particular from 12 to 35 and, in the case of NVP homopolymers, preferably from 12 to 35, in particular from 12 to 17.

The polymeric binder must soften or melt in the total mixture of all components at from 50 to 180° C., preferably from 60° to 130° C., so that the melt can be extruded. The glass transition temperature of the mixture must therefore in any case be less than 180° C., preferably less than 130° C. If necessary, it is reduced by conventional pharmacologically acceptable plasticizers, such as long-chain alcohols, ethylene glycol, propylene glycol, trimethylolpropane, triethylene glycol, butanediols, pentanols, hexanols, polyethylene glycols, aromatic carboxylates (eg. dialkyl phthalates, trimellitates, benzoates or terephthalates), aliphatic dicarboxylates (eg. dialkyl adipates, sebacates, azelates, citrates or tartrates) or fatty acid esters. The plasticizer preferably accounts for no more than 20% by weight, based on the polymer. Particularly preferred NVP polymers are those which do not require additives of this type, ie. those which, as a mixture with the active ingredient and, if required, conventional pharmaceutical auxiliaries, melt or soften in the desired temperature range even without additives having a specific plasticizing effect. Melting or softening below a certain temperature may be necessary because of possible thermal and/or oxidative damage not only to the active ingredient but also to the NVP polymer. The latter may undergo yellowing on extrusion, and it is for this reason that NVP polymers have not usually been extruded to date. However, there is little danger at extrusion temperatures below 180° C., especially below 130° C., if the polymer has not been prepared in aqueous solution using hydrogen peroxide as an initiator, but has been obtained in an organic solvent or in water using an organic peroxide as an initiator, for example by the process according to German Patent application No. P 36 42 633.4 or by the process described in U.S. Pat. Nos. 4,520,179 and 4,520,180.

If the K value is greater than 17, in particular greater than 30 or even 40 (up to a maximum of 70), and no highly plasticizing component is present, the only suitable copolymers are those having a glass transition temperature Tg of less than 120° C., preferably less than 100° C., or the NVP polymer (including homopolymers) must not have been prepared in water containing H₂O₂ as an initiator. This would give rise to polymer

108
(07)

109
108

terminal groups which result in yellowing at elevated temperatures.

Suitable comonomers are unsaturated carboxylic acids, eg. methacrylic acid, crotonic acid, maleic acid and itaconic acid, and their esters with alcohols of 1 to 12, preferably 1 to 8, carbon atoms, as well as hydroxyethyl or hydroxypropyl acrylate and methacrylate, (meth) acrylamide, the anhydrides and half esters of maleic acid and itaconic acid (the half esters preferably not being formed until after the polymerization), N-vinylcaprolactam and vinyl propionate.

Preferred comonomers are acrylic acid and in particular vinyl acetate. Preferred NVP polymers are therefore those which either contain only NVP or vinyl acetate as the only comonomer or contain not less than 10, preferably not less than 30% by weight thereof as copolymerized units. Some or all of the vinyl acetate and vinyl propionate may be hydrolysed after the polymerization.

Solvent-free means that no organic solvent, in particular no chlorohydrocarbon, is added. Furthermore, thermoplastics which are poorly soluble in gastric juice should not be admixed, and the water content of the NVP polymer should not exceed 3.5% by weight. (This water content is due to spontaneous absorption of moisture from the air and not the intentional addition of water.) Higher water contents are harmful in that evaporation of the water after the polymer/active compound extrudate emerges from the die results in porous moldings or may even produce moldings possessing cracks in the surface.

The novel process is suitable, for example, for processing the following active compounds: betamethasone, thiotic acid, sotalol, salbutamol, norfenefrine, silymarin, dihydroergotamine, buflomedil, etofibrate, indometacin, oxazepam, β -acetyl-digoxin, piroxicam, haloperidol, ISMN, amitriptylin, diclofenac, nifedipine, verapamil, pyritinol, nitrendipin, doxycycline, bromhexine, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxin, tamoxifen, metildigoxin, o-(β -hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, paracetamol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, tramadol, bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol, enalaprilhydrogen maleate, bezafibrate, ISDN, gallopamil, xantinol nicotinate, digtoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam, flunarizin, erythromycin, metoclopramide, acemetacin, ranitidin, biperiden, metamizole, doxepin, dipotassium chlorazepate, tetrazepam, estramustine phosphat, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamide, cefaclor, etilefrine, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainid, mgpyridoxal 5-phosphate glutamate, himechromone, etofylline clofibrate, vincamine, cinnarizine, diazepam, ketoprofen, flupentixol, molsimine, glibornuride, dimetinden, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepide, kallidinogenase, oxyfedrine, baclofen, carboxymethylcysteine, thioridazine, betahistine, L-tryptophan, myrtol, bromelaine, prenylamine, salazosulfapyridine, astemizol, sulpiride, benzerazide, dibenzepine, acetylsalicylic acid, miconazol, nystatin, ketoconazole, Na picosulfate, colestyramine, gemfibrocil, rifampicin, fluocortolone, mexiletin, amoxicillin, terfenadrin, mucopolysaccharide polysulfate, triazolam,

mianserin, tiaprofenic acid, amezinium metilsulfate, mefloquine, probucol, quinidine, carbamazepine, mg L-aspartate, penbutolol, piretanide, amitriptyline, cyproterone, Na valproinate, mebeverine, bisacodyl, 5-aminosalicylic acid, dihydralazine, magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine, methyldopa, auranofine, estriol, nadolol, levomepromazine, doxorubicin, medofenoxate, azathioprine, flutamide, norfloxacin, fendiline, prajmalium bitartrate and aescin.

Solid solutions of the following active compounds are particularly preferred: acetaminophen (paracetamol), acetoexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β -carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin, digoxin, dihydroergotamine, drotaverine, flunitrazepam, furosemide, gramicidin, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydrofluormethiazide, indomethacin, ketoprofen, lonetil, medazepam, mefruside, methandrostenolon e, methylprednisolone, methylsulfadiazine (sulfaperin), nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nystatin, estradiol, papaverine, phenacetin, pheno-barbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactone, streptomycin, sulfadimidine (sulfamethazine), sulfamethizole, sulfamethoxazole, sulfamethoxydiazine (sulfameter), sulfaperin, sulfathiazole, sulfoxazole, testosterone, tolazamide, tolbutamide, trimethoprim and tyrothricin.

The term solid solutions is familiar to the skilled worker, for example from the literature cited at the outset. In solid solutions of pharmaceutical active compounds in polymers, the active compound is present in the polymer in molecular disperse form.

The formation of solid solutions of the stated active compounds in NVP polymers was not to be foreseen and is all the more surprising since many active compounds which are sparingly soluble in water do not form (molecular disperse) solid solutions in other polymers but are incorporated in the particular polymer in the form of solid particles which can be detected under the electron microscope. In the case of crystalline active compounds, they also exhibit a Debye-Scherrer pattern, in contrast to the solid solutions.

If, in addition to the binders employed according to the invention, further water-soluble, fusible binders are used, the amount of the first-mentioned binders should be not less than 50, preferably not less than 70% by weight, based on all fusible binders used.

For the purposes of the present invention, solid pharmaceutical forms are, for example, tablets, tablet cores, granules and suppositories.

For the purposes of the present invention, pharmaceutical active compounds are all substances which have a pharmaceutical effect and have a very low level of side effects, provided that they do not decompose under the processing conditions. The amount of active compound per dosage unit and the concentration can vary within wide limits, depending on the activity and the rate of release. The only condition is that they are sufficient for achieving the desired effect. For example, the concentration of active compound may be from 0.1 to 95, preferably from 20 to 80, in particular from 30 to 70, % by weight. Combinations of active compounds may also be used. For the purposes of the present invention, vitamins too are active compounds. Active compounds which are sparingly soluble in water are those

whose absorption in the gastro intestinal tract is usually unsatisfactory owing to their low solubility.

The active compound or compounds can be mixed with the binders and, where relevant, other conventional pharmaceutical additives before or after melting of the polymeric binder, by a method conventionally used in industry. Mixing is preferably carried out in an extruder having a mixing zone, preferably a twin-screw extruder, or in the screw zone of an injection molding machine.

Shaping may be effected by injection molding or by extrusion followed by shaping of the plastic extrudate, for example by hotface cutting to give granules or molding to give tablets, for example by passing the extrudate between two rollers which are driven in opposite directions and have depressions opposite one another in the roller shell, the form of these depressions determining the tablet shape. Cold-face cutting is also suitable and may be followed by pressing of the granules to give tablets. For the purpose of the present invention, the extrusion includes injection molding.

By varying the type and amount of comonomer, the NVP polymer can, depending on the intended use, be made sufficiently strongly or weakly hydrophilic for the tablets prepared from it to dissolve (rapidly or with a delay) in the mouth (buccal tablets) or in the stomach or not until they reach the intestine, or to swell so that they release the active compound. They are sufficiently swellable when they absorb more than 10% by weight of water on storage at 90% relative humidity. If it is desirable for carboxyl-containing binders to release the active compound only when they reach the alkaline medium of the intestine, the above water absorption applies only to the neutralized form (salt form) of the polymer (in which some or all of the protons of the carboxyl groups have been replaced by ammonium, sodium or potassium ions).

Examples of conventional pharmaceutical auxiliaries, whose total amount may be up to 100% by weight, based on the polymer are extenders, such as silicates or silica, stearic acid or its salts with, for example, magnesium or calcium, methylcellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal or corn starch, potato flour or polyvinyl alcohol, as well as wetting agents, preservatives, disintegrating agents, adsorbents, colorants and flavorings (cf. for example H. Sucker et al., *Pharmazeutische Technologie*, Thieme-Verlag, Stuttgart 1978).

If desired, the solid pharmaceutical form may also be provided with a conventional coating to improve the appearance and/or the flavor (coated tablets) or additionally to delay the release of active compound. For oral tablets with sustained release of active compound, it may be advantageous to prepare the tablet by one of the known techniques in a closed-cell porous form so that it floats in the stomach and consequently remains there longer.

In the case of solid pharmaceutical forms with rapid release of active compound, the novel process permits substantially freer design of the pharmaceutical form than does the conventional tablet pressing technique. For example, the tablets can be engraved for designation, or virtually any shapes, which are clearly identifiable even by those with impaired vision, may be produced. Certain shapes, for example hemispheres may also be suitable for achieving certain characteristics of active compound release. By extrusion or hot or cold face cutting of the extrudate, it is possible to produce

very small-particled and uniformly shaped granules in a simple manner, for example for multiple-unit forms.

In the Examples which follow, parts and percentages are by weight. The active compound release time was determined by the half-change test method.

EXAMPLE 1

45 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 5 parts of stearyl alcohol and 50 parts of theophylline were processed to tablet cores in an injection molding machine at 100° C. The tablet cores obtained were stable to mechanical effects and did not show any abrasion during transportation and packaging. In the half-change test (cf. for example R. Voigt, *Lehrbuch der pharmazeut. Technologie*, 5th Edition, Verl. Chemie. Weinheim; Deerfield Beach, Florida; Basel, 1984, page 627) in conjunction with the paddle method according to USP 21, the active compound was completely released in the course of from 6 to 8 hours.

EXAMPLE 2

50 parts of the copolymer of example 1 and 50 parts of theophylline were processed to oblong tablets having a length of 1 cm in an injection molding machine at 120° C. In this case too, the tablets thus obtained were stable to mechanical effects and released the active compound completely in the course of from 1 to 2 hours.

EXAMPLE 3

47.5 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 2.5 parts of crosslinked polyvinylpyrrolidone (PVP) as a tablet disintegrator and 50 parts of theophylline were mixed and extruded in a twinscrew extruder. The temperature of each of the five shots was 120° C. The die was at 130° C. The still plastic extrudate was pressed to give oblong tablets with the aid of the apparatus described in the parallel German Application No. P 36 12 211.4. The tablets were stable to mechanical effects and the active compound was released in the course of from 30 to 45 minutes.

EXAMPLE 4

50 parts of a copolymer of 30% by weight of N-Weinheim; vinylpyrrolidone and 70% by weight of vinyl acetate, having a K value of 52, and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. The temperatures of the five shots were 30, 60, 100, 100 and 120° C. The die was likewise heated to 120° C. The still plastic extrudate was pressed to give mechanically stable oblong tablets as described in Example 3. The active compound was completely released in the course of 8 hours.

EXAMPLE 5

47.5 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 2.5 parts of stearyl alcohol and 50 parts of theophylline were melted in an injection molding machine at 100° C. and processed to tablet cores. The mold was left at room temperature. The tablet cores thus produced were stable to mechanical effects, and the active compound was completely released in the course of 6 hours.

In each of the Examples 6 to 11, a mixture of 50% by weight of an NVP homopolymer (PVP) having a Fikentscher K value of from 12 to 60 and 50% by weight

of theophylline was processed in a single-screw extruder at the following temperatures:

Example	K value	T [°C.]					Die
		1st	2nd	3rd shot	4th	5th	
6	12	115	125	135	135	135	145
7	17	125	125	135	145	145	155
8	25	145	155	165	175	175	175
9	30	150	160	160	170	180	180
10	60	150	160	160	170	180	180
11	60	80	100	130	140	150	160

The active compound in the tablets thus obtained dissolved completely (in simulated gastric juice) in less than 30 minutes in the case of Examples 6 and 7, in the course of from 1 to 2 hours in the case of Examples 8 and 9, and after more than 2 hours in the case of Example 10. In Example 11, the PVP contained 10% by weight of stearyl alcohol. In this case, the time of release was 8 hours.

EXAMPLES 12 TO 14

36 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 4 parts of stearyl alcohol, 40 parts of theophylline and 20 parts of starch in Example 12, lactose in Example 13 and sucrose in Example 14

were mixed in a 6-shot twin-screw extruder and shaped into tablets similarly to Example 1. The temperatures of the shots were 90°, 100°, 110°, 120°, 130° and 130° C., and the temperature of the die was 135° C. The active compound dissolved completely out of the tablets in the course of 6 hours.

EXAMPLE 15

50 parts of the copolymer of Examples 12 to 14 and 50 parts of lithium carbonate were processed to tablets on the same apparatus and at the same temperatures as in Examples 12 to 14. These tablets released the active compound (in simulated gastric juice) completely in the course of from 15 to 20 minutes.

EXAMPLE 16

50 parts of the copolymer of Examples 12 to 14 and 50 parts of verapamil were shaped into tablets as described in Examples 12 to 14. The active compound was released in this case in about 3 hours.

The copolymers used for the preparation of solid solutions had the following compositions and K values:

(A) 60% by weight of NVP and 40% by weight of vinyl acetate; K value about 33.

(B) 100% by weight of NVP; K value 30.

(C) 100% by weight of NVP; K value 12.

(D) 100% by weight of NVP; K value 12.

The polymers B, C and D were prepared according to German Patent Application P 36 42 633.4 in water using an organic peroxide as the initiator.

EXAMPLE 17

3 parts of copolymer A and 1.5 parts of benzocaine were premixed in a plowshare mixer and were extruded in a simple, 6-shot extruder, the individual shots having the following temperatures, proceeding toward the die: 30°, 30°, 40°, 50°, 60° and 70° C. The die temperature was likewise 70° C. The extrudate consisted of a solid solution, as was shown by the DebyeScherrer photograph, which did not give the slightest indication of crystallinity. A similar procedure was used for the remaining Examples (cf. Table), and the same result was obtained.

Example no.	Active compound	Polymer	Active comp./polymer							Die temp. °C.
			Weight ratio	T1	T2	T3	T4	T5	T6	
17a	Benzocaine	A	1:3	20	30	40	40	50	50	50
18	Paracetamol	C	1:3	60	80	100	120	120	120	120
19	Phenytoin	C	1:3	60	80	100	120	120	120	120
20	Benzocaine	C	1:3	50	50	60	60	70	80	90
21	Indomethacin	A	1:3	50	60	70	80	80	80	80
22	Indomethacin	A	1:3	60	80	100	120	120	120	120
23	Anipamil	A	1:3	30	30	40	50	50	60	60
24	Anipamil	C	1:3	30	30	40	50	50	60	60
25	Benzocaine	A	1:1	30	30	40	500	50	60	60
26	Benzocaine	B	1:1	30	30	40	500	50	60	60
27	Benzocaine	C	1:1	30	30	40	50	50	60	60
28	Phenytoin	A	1:3	60	80	100	120	120	120	130
29	Paracetamol	A	1:3	60	80	100	120	120	120	130
30	Sulfathiazole	A	1:1	70	90	100	100	100	100	130
31	Benzocaine	A	1:3	50	50	60	60	70	80	90
32	Benzocaine	C	1:3	50	50	60	60	70	80	80
33	Sulfathiazole	C	1:3	70	90	100	100	100	100	120
34	Benzocaine	A	1:9	30	40	50	60	60	70	70
35	Benzocaine	A	1:6	50	60	70	80	85	85	85
36	Benzocaine	C	1:9	30	30	40	50	60	60	60
37	Benzocaine	C	1:6	30	40	60	60	70	70	70
38	Benzocaine	B	1:9	60	70	90	90	90	100	100
39	Benzocaine	B	1:6	60	80	80	100	120	120	120
40	Benzocaine	B	1:3	60	80	80	100	120	120	120
41	Benzocaine	B	1:1	60	80	95	100	120	135	140
42	Phenytoin	A	1:9	60	70	90	90	90	100	100
43	Phenytoin	A	1:6	60	70	90	100	100	100	100
44	Phenytoin	C	1:9	60	70	90	90	90	100	100
45	Phenytoin	C	1:6	60	70	90	100	100	100	100
46	Phenytoin	B	1:9	60	80	110	130	150	150	150
47	Phenytoin	B	1:6	60	80	110	130	150	160	160
48	Phenytoin	B	1:3	60	80	110	120	150	160	170

-continued

Example no.	Active compound	Polymer	Active comp./ polymer Weight ratio	T1	T2	T3	T4	T5	T6	Die temp. °C.
49	Phenytoin	B	1:1	60	80	125	150	160	175	180

T1 to T6 are the temperatures of shots 1 to 6 in °C.

EXAMPLE 50

Examples 18, 19 and 20 were repeated on an injection molding machine at a die temperature of 130° C. Tablets consisting of solid solutions were obtained.

EXAMPLE 51

Vitamin C, as the active compound, was mixed in a weight ratio of 1:1 with the following NVP polymers in a twin-screw extruder, the mixture was extruded at the temperatures stated in the Table for shots 1 to 6 and for the die, and the extrudate was shaped into tablets via a calender, according to the parallel German application No. P 36 12 211.4.

(a) Copolymer of 60% by weight of NVP and 40% by weight of vinyl acetate; K value about 33.

(b) 90% by weight of copolymer (a) and 10% by weight of stearyl alcohol.

(c) Homopolymer of NVP; K value 17.

	T1	T2	T3	T4	T5	T6	Die
(a)	60	80	100	110	120	120	120° C.
(b)	60	80	80	100	100	110	110° C.
(c)	60	80	100	110	120	120	125° C.

In all three cases, the vitamin was liberated in water in the course of from 1 to 2 hours. During the processing described, it did not undergo any decomposition at all and, in this form, was protected from the effects of light and atmospheric oxygen when stored for a prolonged period.

We claim:

1. A process for the preparation of a solid pharmaceutical form by mixing one or more pharmaceutical active compounds with one or more fusible pharmacologically tolerated binders and subjecting the mixture to injection molding or extrusion and shaping at from 50° to 180° C., wherein the fusible binder used is a solvent-free N-vinylpyrrolidone polymer which has a water content of not more than 3.5% by weight and contains not less than 20% by weight of N-vinylpyrrolid-2-one (as copolymerized units, all copolymerized comonomers contain) nitrogen and/or oxygen and, at least when the glass transition temperature of the mixture is above 120° C., N-vinylpyrrolidone polymer is used which is obtained by polymerization in an organic solvent or using an organic peroxide as an initiator in aqueous solution, and the mixture does not contain any thermoplastics which are sparingly soluble in gastric juice.

2. A process as defined in claim 1, wherein the polymeric binder used contains not less than 60% by weight of N-vinylpyrrolidone as copolymerized units.

3. A process as defined in claim 1, wherein plasticizers are used in an amount of not more than 20% by weight, based on the N-vinylpyrrolidone polymer.

4. A process as defined in claim 1, wherein a polymeric binder used consists of N-vinylpyrrolidone or contains, in addition to N-vinylpyrrolidone, only vinyl acetate as copolymerized units.

5. A process as defined in claim 1, wherein a polymeric binder is used whose comonomers are selected from the following group: acrylic acid, methacrylic acid, crotonic acid, maleic acid, maleic anhydride, itaconic acid, itaconic anhydride and esters of the stated acids or half esters of the stated dicarboxylic acids with alcohols of 1 to 12 carbon atoms, and hydroxyethyl and hydroxypropyl acrylate and methacrylate, acrylamide, methacrylamide, N-vinylcaprolactam and vinyl propionate.

6. A process as defined in claim 1, wherein the active compound used is sparingly soluble in water, dissolves in the polymer melt without the addition of a solvent or water to give a molecular disperse solution, and forms a solid solution after the melt solidifies.

7. A process as defined in claim 1, wherein one or more active compounds from the following group are used: acetaminophen (paracetamol), acetoacetamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β -carotene, chloramphenicol, chlorthalidone, chlorthalidone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin, digoxin, dihydroergotamine, drotaverine, flunitrazepam, furosemide, gramicidin, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydrofluoromethiazide, indomethacin, ketoprofen, lonetil, medazepam, mefruside, methandrostenolone, methylprednisolone, methylsulphadiazine (sulfapyridine), nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nystatin, estradiol, papaverine, phenacetin, phenobarbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactone, streptomycin, sulfadimidine (sulfamethazine), sulfamethizole, sulfamethoxazole, sulfamethoxydiazine (sulfamer), sulfaperin, sulfathiazole, sulfisoxazole, testosterone, tolazamide, tolbutamide, trimethoprim, tyrothricin.

8. A process as defined in claim 1, wherein a N-vinylpyrrolidone polymer having a Fikentscher K value of from 10 to 50 is used.

9. A process as defined in claim 1, wherein a N-vinylpyrrolidone polymer having a Fikentscher K value of from 12 to 35 is used.

* * * * *

Reivindicaciones 3-7: un método para preparar la sal de la reivindicación 1.

Reivindicaciones 9-17, 22 y 26: una dispersión sólida que comprende la sal de la reivindicación 1 y un agente dispersante.

Reivindicaciones 18-21 y 23-25: métodos para preparar la dispersión sólida de la reivindicación 19.

Reivindicación 27: una composición farmacéutica que comprende la dispersión sólida de la reivindicación 9 y un vehículo farmacéuticamente aceptable.

Reivindicaciones 28-34: relacionadas con métodos de tratamiento.

Reivindicación 35: el uso de un compuesto.

Clasificación Internacional de Patentes (IPC): C07D 209/12, A61K31/55, A61P5/24.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Se caracteriza inadecuadamente un compuesto por su método de preparación (reivindicación 8), ya que un compuesto (ascorbato de bazedoxifeno) solo debe caracterizarse por su fórmula, estructura química o nombre genérico.

Se caracteriza inapropiadamente una dispersión sólida por ser preparada mediante un método dado (reivindicaciones 22 y 26), puesto que la dispersión sólida debe caracterizarse por los elementos que la comprenden como son compuesto activo y agente dispersante.

4. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

De acuerdo con los artículos anteriores, la reivindicación 35, relacionada con el uso de un compuesto, no se considera objeto de protección porque el uso no es un producto o un procedimiento tecnológico. Por lo que es recomendable que sea eliminada del alcance de la invención.

a. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las reivindicaciones 28-34, relacionadas con un método de tratamiento, están exceptuadas de patentabilidad de acuerdo con el artículo anterior; por lo que es recomendable eliminarlas del alcance de la solicitud.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que se reivindica prioridad es 08-04-2004, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO0203987	Pharmaceutical compositions of estrogenic agents	17-01-2002
D2	EP0584952	Improvements in or relating to benzothiophenes	02-03-1994
D3	US4801460	Preparation of solid pharmaceutical foms	31-01-1989

Anterioridad D1 en folios 86-103, D2 en folios 104-106, D3 en folios 107-112.

6. Análisis de patentabilidad (artículo 14 D486)

6.1. Nivel inventivo (artículo 18 D486)

- Se solicita en la reivindicación 1 y 8 una sal de ácido ascórbico de bazedoxifeno y en la 2 una composición farmacéuticamente que la contiene junto con un vehículo farmacéuticamente aceptable.

El estado de la técnica más cercano es D1 que divulga el compuesto TSE-424 (bazedoxifeno) y sus sales orgánicas farmacéuticamente aceptables (folios 94-97; pág. 14-15, 23 y 28), especialmente la sal de acetato de TSE-424 así como composiciones farmacéuticas que la contienen junto con excipientes farmacéuticamente aceptables (folios 99; pág. 35).

La diferencia de la solicitud con D1 es que señala específicamente una sal de ascorbato de bazedoxifeno.

El efecto técnico que logra tal diferencia es obtener otra sal orgánica (ascorbato) de bazedoxifeno, útil también en la preparación de composiciones farmacéuticas.

Así, el Problema Técnico Objetivo de esta solicitud esta relacionado con la necesidad de obtener otras sales orgánicas farmacéuticamente aceptables de bazedoxifeno (como la de ascorbato), que sean útiles en la preparación de composiciones farmacéuticas.

Sin embargo, para un experto en la materia la existencia de otras sales orgánicas farmacéuticamente aceptables de bazedoxifeno (como la de ascorbato) diferentes a las ya señaladas en D1 que sean adecuadas en composiciones farmacéuticas no es considerado como inesperado, puesto que D1 señala que cualquier sal orgánica farmacéuticamente aceptable de bazedoxifeno puede ser usada en las composiciones farmacéuticas de bazedoxifeno, tal como lo reitera D2 al señalar que las sales de ascorbato de compuestos activos se encuentran dentro de las sales frecuentemente usadas en el área farmacéutica por ser fisiológicamente aceptables - por ej. sales de ascorbato de compuestos moduladores estrogénicos de formula (I) análogos a los de la solicitud- (folios 105-106; pág. 3,5); por lo que se considera que la materia solicitada (una sal de ácido ascórbico de bazedoxifeno y una composición farmacéuticamente que la contiene) es una alternativa a la materia divulgada por D1 y no tiene nivel inventivo.

- En las reivindicaciones 3-7 se solicita un método para preparar una sal de ácido ascórbico de bazedoxifeno, caracterizado por combinar la base libre de bazedoxifeno y el ácido ascórbico, en cantidades aproximadamente equimoleculares de los mismos y en un solvente como un alcohol.

El estado de la técnica más cercano es D1 que divulga la formación de sales orgánicas de bazedoxifeno por una reacción de adición de un ácido orgánico aceptable al compuesto base en un solvente orgánico (folio 94-97; pág. 14-15, 23 y 28).

La solicitud se diferencia de D1 en que señala específicamente el ácido ascórbico como el ácido orgánico que se utiliza en la formación de la sal de bazedoxifeno.

El efecto técnico que proporciona tal diferencia es obtener una sal de ascorbato de bazedoxifeno.

No obstante, para un experto en la materia la obtención de sales orgánicas de ascorbato de bazedoxifeno es obvia acorde con la divulgación de D1 (reacción entre el compuesto base y un ácido orgánico farmacéuticamente aceptable) y D2 que señala la formación de sales de ascorbato de un compuesto modulador estrogénico mediante la reacción típica del compuesto base con una cantidad equimolecular o en exceso del ácido orgánico en un solvente mutuo (folios 105-106; pág. 4-5); por lo que el proceso reivindicado no tiene nivel inventivo.

- Se solicita en las reivindicaciones 9-17, 22 y 26 una dispersión sólida que comprende una sal de ácido ascórbico de bazedoxifeno y un agente dispersante (como polivinilpirrolidona entre otros), y en la 27 una composición farmacéutica que comprende tal dispersión sólida y un vehículo farmacéuticamente aceptable.

El estado de la técnica más cercano es D1 que señala la formación de dispersiones solidas de compuestos pobremente solubles (agentes estrogénicos como tamoxifeno y el TSE-424 ó *bazedoxifeno* y sus sales farmacéuticamente aceptables como la de acetato) para mejorar la disolución de los mismos, que permiten proveer composiciones farmacéuticas que alcanzan una rápida disolución del fármaco pobremente soluble desde una forma de dosificación sólida (folios 89-90; pág. 3-4).

La diferencia de la solicitud con D1 es que señala específicamente que es la sal de ascorbato del fármaco (bazedoxifeno) y que el agente dispersante es un polímero como polivinilpirrolidona (acorde con lo soportado en la descripción folio 36-37; pág. 22-23, ej. 5).

El efecto técnico que logra tal diferencia es obtener una dispersión solida en polivinilpirrolidona de una sal de ascorbato bazedoxifeno, que permite aumentar la solubilidad del activo en medio acuoso.

Así, el Problema Técnico Objetivo esta relacionado con la necesidad de obtener una dispersión sólida de de una sal de bazedoxifeno, que permita aumentar la solubilidad del fármaco (bazedoxifeno).

Sin embargo, para un experto en la materia la obtención de una dispersión sólida de una sal farmacéuticamente aceptable de bazedoxifeno en un agente dispersante como polivinilpirrolidona no es inesperado puesto que D1 ya señala la formación de dispersiones solidas del fármaco o de sus sales farmacéuticamente aceptables como una forma de mejorar la solubilidad y amentar la velocidad de disolución del fármaco y D3 enseña que polímeros NVP (n-vinilpirrrolidin-2-ona) como polivinilpirrolidona, son usados como agentes dispersantes en la formación de dispersiones solidas de compuestos activos escasamente solubles (como tamoxifeno un modulador estrogénico) para aumentar la solubilidad y mejorar su absorción (folios 108-109; col

1, 3-4); por lo que la materia solicitada (una dispersión de ascorbato de bazedoxifeno en polivinilpirrolidona y composiciones farmacéuticas que la contienen) no tiene nivel inventivo.

➤ Se solicita en las reivindicaciones 18-21 y 23-25 métodos para preparar una dispersión sólida que comprende una sal de ácido ascórbico de bazedoxifeno y un agente dispersante, caracterizados por:

- b. Combinar la sal y el agente dispersante en solución (solvente orgánico) y
- c. Remover el solvente para dar la dispersión sólida.

ó

- a. Combinar la sal con un agente dispersante fundido para formar una mezcla líquida y
- b. Solidificar la mezcla líquida para dar la dispersión sólida.

El estado de la técnica más cercano es D1 que señala la formación de dispersiones solidas de compuestos pobremente solubles (agentes estrogénicos como tamoxifeno y el TSE-424 ó *bazedoxifeno* y sus sales farmacéuticamente aceptables)) para mejorara la disolución de los mismos mediante procesos comúnmente conocidos (folio 89-90; pág. 3- 4).

La solicitud se diferencia de D1 en que señala específicamente dos métodos concretos: 1. Combinar la sal y el agente dispersante en un solvente orgánico y remover luego el solvente y 2. Combinar la sal con el agente fundido formando una mezcla líquida y luego enfriarla, para formar la dispersión sólida.

El efecto técnico que proporciona tal diferencia es obtener una dispersión solida de la sal ascorbato de bazedoxifeno en el agente dispersante polivinilpirrolidona (acorde con lo soportado en la descripción folio 36-37; pág. 22-23, ej. 5).

Así, el problema técnico objetivo es cómo obtener una dispersión solida de la sal ascorbato de bazedoxifeno en un agente dispersante (como polivinilpirrolidona)

No obstante y a pesar de que en D1 no se señalan los métodos conocidos para formar las dispersiones solidas allí señaladas, un experto en la materia ya conoce los dos métodos aplicados en la solicitud para obtener dispersiones solidas, tal como lo demuestra D3 que divulga que soluciones ó dispersiones solidas de compuestos activos ligeramente solubles (agentes estrogénicos como tamoxifeno) en un agente dispersante como polivinilpirrolidona pueden ser preparadas mediante:

1. Disolución conjunta del compuesto activo y del agente dispersante [polímero NVP (n-vinilpirrolidin-2-ona) como polivinilpirrolidona] en un solvente orgánico y posterior remoción del solvente (folios 108; col 1, lín. 22) ó
2. Disolución del compuesto activo en el polímero fundido [un NVP (n-vinilpirrolidin-2-ona) como polivinilpirrolidona] para logara la solución o dispersión solida después de que la masa fundida se solidifique (folio 112; col 10, lín. 30).

En consecuencia, para un experto en la materia acorde con la información de D1 (obtención de dispersiones solidas de bazedoxifeno o una de sus sales farmacéuticamente aceptables) y teniendo en cuenta que un experto en la materia ya conoce los dos métodos aplicados en la solicitud para obtener dispersiones solidas tal como lo ejemplifica D3, los métodos solicitados, de obtención de dispersiones solidas de ascorbato de bazedoxifeno en un agente dispersante, no tienen nivel inventivo.