Mechanism and Kinetics of Metal Ion-Mediated Degradation of Fosinopril Sodium

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Fosinopril sodium (I), a new angiotensin converting enzyme inhibitor, is a diester prodrug of the active moiety II. We report here a novel transformation of fosinopril into β-ketoamide, III, and a phosphonic acid, IV, mediated through metal ion participation. The interaction of fosinopril with magnesium ions was studied in a solution model system in which methanol was used as the solvent and magnesium acetate as the source of metal ions. Kinetic analysis indicated the degradation to be a bimolecular process, with the rate being first order in both metal ion and fosinopril concentration. The degradation products II, III, and IV effectively retarded the magnesium ion mediated reaction of fosinopril. Based on the results of 31P-NMR, 1H-NMR, Mn(II)-EPR spectroscopy experiments and mass spectrometry, a mechanism is postulated for this transformation. A key reactive intermediate has been characterized that supports the proposed mechanism. The results can account for the observed degradation profile of the fosinopril sodium in a prototype tablet formulation.

KEY WORDS: fosinopril sodium; magnesium ions; C-P bond cleavage; kinetics; mechanism; tablet formulation.

INTRODUCTION

Fosinopril, [1(S(R*)][2α,4β]-4-cyclohexyl-1-[(2-methyl-1-(1-oxopropoxy)-propoxyl)(4-phenylbutyl)phosphinyl]-acetyl]-1-proline, sodium salt (I) (Scheme I), is a new angiotensin converting enzyme inhibitor marketed under the trade name Monopril® (1). Fosinopril has four chiral centers and theoretically should exist in 16 isomeric forms. However, its synthesis is designed to give 99.9% SRS S S isomer. It is a prodrug which is converted in vivo into the active moiety II by the hydrolysis of the diester side chain (1). In this communication we report a novel metal ion mediated rearrangement that results in degradation of fosinopril into a β-ketoamide, III, and a phosphonic acid, IV. The degradation product III was isolated from the tablets undergoing accelerated stability testing and was characterized by 1H NMR and MS. Its structure was confirmed by unambiguous synthesis. Compound IV is reported in the literature (2). We show that the degradation/rearrangement of fosinopril is caused by several metal ions, in particular magnesium. A mechanism invoking metal chelation is proposed for the degradation of fosinopril sodium by this process. The kinetics of the metal ion-mediated degradation were studied by reacting fosinopril sodium with magnesium acetate tetrahydrate in methanol. The kinetic study established that the metal ion-mediated degradation was a second-order reaction between fosinopril and metal ion. The study helped to explain the degradation of fosinopril sodium in a prototype tablet formulation containing magnesium stearate as the lubricant.

MATERIALS AND METHODS

Materials

Fosinopril sodium was synthesized at Bristol-Myers Squibb Co. The following metal acetates were obtained from Aldrich Chemical Co.: magnesium acetate tetrahydrate, zinc acetate dihydrate, cobalt(II) acetate tetrahydrate, nickel(II) acetate tetrahydrate, barium acetate, and calcium acetate hydrate. The following metal acetate salts were obtained from Fischer Chemical Co.: potassium acetate, sodium acetate trihydrate, copper(II) acetate, and lithium acetate. Magnesium stearate and iron(II) chloride X·H2O was obtained from Mallinckrodt, Inc. Iron(III) chloride hexahydrate was obtained from J. T. Baker Chemical Co. All the salts were used as received from the manufacturer. All solvents were of HPLC grade and reagents of analytical purity. The names fosinopril and fosinopril sodium are used synonymously and interchangeably.

Degradation of Fosinopril Sodium by Metal Acetates in Methanol

Fosinopril sodium was dissolved in methanol at a concentration of 0.0017 M and reacted with each of the metal...
manner. Solutions of fosinopril sodium in methanol without any other additive served as blank controls. The data from these experiments were fitted to a second-order kinetic model (Table II).

Effect of Additives on Magnesium Ion-Mediated Degradation of Fosinopril

The effect of the II, III, and IV on the magnesium ion-mediated degradation of fosinopril was studied in methanol. Each additive was separately added to a methanolic solution of fosinopril sodium, followed by magnesium acetate in methanol. The molar ratio of the reactants was 1:1:1. The solutions were then placed in a constant-temperature bath at 24°C (±1°C). At periodic intervals, samples were withdrawn and analyzed by HPLC for fosinopril.

Synthesis of the Bis-Silylated Derivative of Intermediate (V)

The dibenzyl ester VI was prepared from the diacid II using DBU (1,8 diazabicyclo[5.4.0]undec-7-ene) and benzyl bromide (Scheme II). Compound VI was deprotonated with LDA (lithium diisopropylamide) and acylated with propionyl chloride to give the phosphonyldicarboxyl compound VII. Attempted hydrogenolysis of VII afforded an intractable mixture of compounds, however, in the presence of BSA [N,O-bis(trimethylsilyl)acetamide], provided the bis-silylated derivative VIII of the key intermediate V. The compound VIII was characterized by mass spectroscopy: ions at m/z = 564 [M + 1 – one Si(CH₃)₃]⁺, 492 [M + 1 – two Si(CH₃)₃]⁺, 562 [M – 1 – one Si(CH₃)₃]⁻, and 490 (M – 1 – two Si(CH₃)₃]⁻. ³¹P-NMR of VIII gave a signal at δ 35.9.

Synthesis of III

β-Ketoamide, III, was obtained by condensation of 4-cyclohexylproline with 3-oxopentanoic acid in the presence of anhydrous 1-hydroxybenzotriazole (HOBT) and N,N-dicyclohexylcarbodiimide (DCC) in methylene chloride. The product was isolated as the dicyclohexylammonium salt.

Scheme I. Pathways for degradation of fosinopril sodium. The degradation products II, III, and IV are shown in the form of magnesium ion chelates.

acetates at the same concentration. Acetate salts of calcium, barium, and manganese and magnesium stearate did not dissolve completely in methanol and were used as suspensions. The Fe(II) and Fe(III) salts were reacted as chlorides with potassium acetate added as a base. The reaction was allowed to proceed at 24°C (±1°C) for a specified time and then the contents of the flasks were withdrawn and analyzed by HPLC. Blank controls were solutions of fosinopril sodium in methanol at the same concentration. The data from these experiments were used to rank order the reactivity of each metal ion by calculating the pseudo-first-order rate constants for the degradation of fosinopril sodium.

Kinetics of Degradation of Fosinopril Sodium in the Presence of Magnesium Acetate in Methanol

For kinetic experiments equimolar stock solutions of fosinopril sodium (MW 585.6) and magnesium acetate tetrahydrate (MW 214.5) were prepared by dissolving separately 100 and 36.5 mg, respectively, in 100 mL of methanol. The two reactant solutions were mixed in a predetermined ratio in Teflon stoppered flasks and appropriately diluted with methanol. A series of flasks were then placed in a constant-temperature bath at 24°C (±1°C) and samples were periodically withdrawn and analyzed by HPLC.

Positive control experiments were performed by reacting fosinopril sodium with potassium acetate (anhydrous) or sodium acetate trihydrate dissolved in methanol in a similar manner.