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Thermal Degradation Study in the Process Development of Atorvastatin Calcium¶

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As a part of process development, thermal degradation pathway of atorvastatin calcium, an HMG-COA reductase, is studied. All the five compounds obtained in this process are fully characterized.

Key Words: Thermal degradation, Atorvastatin calcium.

INTRODUCTION

Atorvastatin calcium, [R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid hemicalcium salt has been approved by the USFDA for the treatment of serum dyslipidemia[1]. This active pharmaceutical ingredient has highest commercial importance among all the contemporary statins. Atorvastatin calcium competitively inhibits hydroxy methyl glutaryl-COA (HMG-COA) reductase[2], the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis. Inhibition of this enzyme has proven to be an effective means of lowering total and low-density lipoprotein cholesterol in human[3]. The ability of cholesterol-lowering drugs to reduce the incidence of coronary heart disease or delay its progression is well-established[4].

As a part of our process development of atorvastatin calcium, we have taken up its forced degradation studies to evaluate the overall thermal sensitivity of the material. Stress testing of the drug substance can help in identifying the likely degradation products, which can in turn establish the degradation pathways and the intrinsic stability of the atorvastatin calcium (**1**). This information can be used to validate analytical procedures. Amorphous atorvastatin calcium is known to photo degradation on prolonged UV irradiation to produce a mixture of three products[5].

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EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO, using Varian Gemini 400 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrometer. The mass spectrum (70 eV) was recorded on HP-5989A LC-MS spectrometer. The CHN analysis was carried out on a Perkin-Elmer model 2400S analyzer. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus and are uncorrected. The solvents and reagents were used without further purification.

Thermal degradation of 1: Atorvastatin calcium (**1**, 25 g) was taken in a 250 mL round bottom flask, heated to 180-200 ºC and maintained at similar temperature for a period of 0.5 h. After completion of heating, the reaction mass was cooled to room temperature dissolved in dichloromethane (250 mL), extracted with water (2 × 100 mL), separated the organic layer dried over anhydrous sodium sulphate and the solvent was removed under vacuum. As per the HPLC, the product is found to contain 25 % of **2** at retention time 34.7 min, 15 % of **3** at retention time 39 min, 25 % of **4** at retention time 45 min and remaining 25 % of **5** at retention time 36 min and 10 % of **6** at retention time 19 min. All these degradation compounds were separated through silica gel column using ethyl acetate and hexanes (25:75) mixture as mobile phase and further purified in toluene.

7-[2-(4-Fluoro-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-hepta-2,4-dienoic acid (3): m.p. 210-215 ºC; IR (Film, cm^{-1}) 3406 ν(NH), 1668 ν(C=O), 1632 ν(C=O) and 1600, 1562 ν(C=C); ^{1}H NMR ($CDCl_3$): δ 12.2 (s, -OH), 9.7 (S, -CONH-), 6.9-7.6 (m, 14H, Ar), 7.2 (m, 1H, -CH=CH-CH=CH-), 6.5 (t, 1H, -CH=CH-CH=CH-, *J* = 11.2Hz), 5.9 (m, 1H, olefinic -CH adjacent to methylene), 5.55 (d, 1H, -CH=CH-CH=CH-, *J* = 11.2 Hz), 3.8 (m, 2H, -N-CH_2), 3.2 (m, 1H, aliphatic CH), 2.3 (m, 2H, -CH_2), δ 1.37 (d, 6H, 2CH_3, *J* = 6.8 Hz), MS: m/e 523 M^+. m.f. $C_{33}H_{31}N_2O_3F$. Elemental analyses (%): Calcd.: C, 75.84; H, 5.98; N, 5.36; O, 9.18. Found: C, 75.82; H, 5.95; N, 5.34.

5-(4-Fluoro-phenyl)-1-hexa-3,5-dienyl-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide (4): m.p. 196-205 ºC; IR (Film, cm^{-1}) 3398 ν(NH), 1632 ν(C=O), 1595, 1530 ν(C=C); ^{1}H NMR ($CDCl_3$): δ 6.8-7.4 (m, 14H, Ar), 6.2 (m, 1H, CH of C=C), 5.9 (m, 1H, CH of C=C), 5.4 (m, 1H, CH of C=C), 5.0-5.1 (dd, 2H, -CH=CH_2), 3.9 (m, 2H,-N-CH_2), 3.6 (m, 1H, CH), 2.3 (m, 2H, CH of CHX), 1.6 (d, 6H, 2CH_3), MS: m/e 479.2 M^+. m.f. $C_{32}H_{31}N_2OF$. Elemental analyses (%): Calcd.: C, 80.31; H, 6.53; N, 5.85; O, 3.34. Found: C, 80.3; H, 6.5; N, 5.84.

2-(4-Fluoro phenyl)-3-phenyl-1*H*-pyrrole (6): IR (Film, cm^{-1}) 3467 ν(NH), 3026 ν(ArH), 1524 ν(C=C); ^1H NMR ($CDCl_3$): d 6.8-7.4 (m, 9H, Ar), 7.0 (d, 1H, α H of pyrrole), 5.9 (s, 1H, β H of pyrrole), 10.8 (s, 1H, NH); MS: m/e 238 M^+. m.f. $C_{16}H_{12}NF$. Elemental analyses (%): Calcd.: C, 80.99; H, 5.1; N, 5.9 Found: C, 80.97; H, 5.09; N, 5.87.

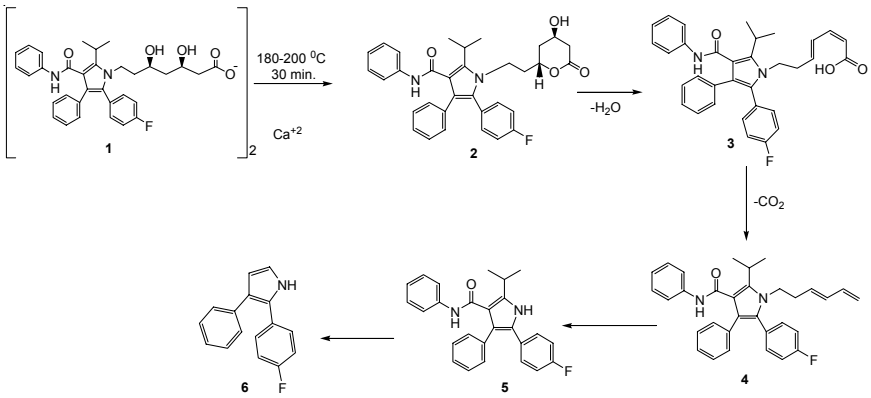
RESULTS AND DISCUSSION

In present investigation, we have taken up a thermal degradation study of atorvastatin calcium of both crystalline and amorphous forms. Atorvastatin calcium on heating at 180-200 ºC for 0.5 h followed by chromatographic separation using a silica column, furnished five compounds **2**, **3**, **4**, **5** and **6**. All compounds are fully characterized based on their IR, ^1H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

The major compound **2** which was formed to an extent of 25 % is characterized as (2R *trans*)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl]-1*H*-pyrrole-3-carboxamide[6], based on its spectral data and by comparison with an authentic sample.

The IR spectrum of compound **3** showed a broad NH absorption (3406 cm^{-1}) besides carbonyl (1668 cm^{-1}) and C=C (1562 cm^{-1}) absorptions, The ^1H NMR spectrum is characterized by the presence of δ 12.2 (s, -OH), 9.7 (S, -CONH-), 6.9-7.2 (m, 14H, Ar), 7.2 (m, 1H -CH=CH-CH=CH-), 6.5 (t, 1H, -CH=CH-CH=CH-, *J* = 11.2 Hz), 5.9 (m, 1H, olefinic -CH adjacent to methylene), 5.55 (d, 1H, -CH=CH-CH=CH-, *J* = 11.2 Hz), 3.8 (m, 2H, $-CH_2$), 3.2 (m, 1H, aliphatic CH), 2.3 (m, 2H, $-CH_2$), d1.37 (s, 6H, $2CH_3$, *J* = 6.8Hz) signals. Mass spectrum displays the molecular ion peak at 523 (M+1). IR, Mass, ^1H NMR and ^{13}C NMR of compound **3** is indicated its structure as 7-[2-(4-fluoro-phenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-1-yl]-hepta-2,4-dienoic acid.

Interestingly, compound **4**, 5-(4-fluoro-phenyl)-1-hexa-3,5-dienyl-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide, could be formed by the thermally induced decarboxylation of carboxylic acid[7-9] **3**. Such decarboxylation in carboxylic acid of statin is a unique phenomenon. Compound **5** characterized as 5-(4-fluoro-phenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide could be formed by the dealkylation of **4**. Pyrrole derivative **5** can be directly formed[10] from carboxylic acid **3**. Minor compound **6**, which is characterized as 2-(4-fluoro phenyl)-3-phenyl-1*H*-pyrrole could be possibly formed by the degradation of **5**. Assigned structures of new compounds, carboxylic acid **3**, its decarboxylation derivative **4** and diaryl pyrrole derivative **6** are further confirmed from their elemental analysis.



Scheme-I

Conclusion

Thermal degradation follows an interesting pathway leading to some unusual compounds. This forced degradation study of active pharmaceutical ingredient reflects its thermal behaviour.

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