Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Pharmaceutical and Biomedical Analysis 41 (2006) 176–181
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Investigation on the photochemical stability of lercanidipine and its determination in tablets by HPLC–UV and LC–ESI–MS/MS☆

Jessica Fiori, Roberto Gotti, Carlo Bertucci, Vanni Cavrini *

Dipartimento di Scienze Farmaceutiche, Alma Mater Studiorum-Università di Bologna, Via Belmeloro 6, 40126 Bologna, Italy

Received 24 October 2005; accepted 15 November 2005
Available online 27 December 2005

Abstract

The photostability of lercanidipine, a dihydropyridine calcium-channel blocker used in the treatment of the hypertension, was studied. Drug substance and its solutions and formulations were exposed to UV-A radiations (solar simulator) and the photodegradation process was monitored by UV spectrophotometry, HPLC and HPLC–mass spectrometry. The effect of the solvent (ethanol and ethanol/PBS 1:1 v/v) on the photodegradation pathway and kinetic was evaluated.

Lercanidipine and its photodegradation products were separated by a selective reversed-phase HPLC method and the main photoproducts were characterized by HPLC–MS/MS analysis, using an electrospray ionization source (ESI) and an ion trap analyzer. Photochemical reactions, involved in the photodegradation of lercanidipine, include aromatisation of the dihydropyridine moiety, formation of nitrosoderivatives and *N*-dealkylation in the side chain. The developed stability-indicating HPLC method was then applied to the quality control of commercially available lercanidipine formulations (tablets).

Keywords: Lercanidipine; Photostability; HPLC; LC–MS/MS; Quality control; Tablets

1. Introduction

Lercanidipine, (±)2-[(3,3-diphenylpropyl)methylamino]-1, 1dimethylethyl methyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1-4-dihydropyridine-3,5-dicarboxylate monohydrochloride (Table 1), is a dihydropyridine calcium-channel blocker developed for an oral administration and used in the treatment of mild to moderate hypertension [1,2].

The chemical structure of lercanidipine is characterized by the presence of a side chain containing a 3,3-diphenylpropyl-methylamine-2-methyl-2-propyl group that was introduced to improve the lipophilic properties and the activity duration of the drug. From a physico-chemical point of view, lercanidipine is slightly soluble in water, but it is more soluble in some widely used solvents as well as ethanol and methanol, or mixture water–organic solvents. Lercanidipine is orally administered as racemate lercanidipine hydrochloride tablets. The drug is sensitive to light, according to the well-known photosensitivity of diihydropyridine class [3,4]. The photoreactivity of lercanidipine has been only in part investigated [4] and few methods, based on HPLC [4,5], spectrophotometry [6] and differential pulse voltammetry [7] have been developed for its determination in pharmaceutical dosage forms.

The aim of the present study was to investigate the photostability of lercanidipine in solutions and in pharmaceutical products, exposed to UV-A radiations, using a xenon arc lamp (solar simulator). The effect of the solvent (ethanol and ethanol/PBS 50:50) on the drug photostability and on the degradation kinetic was evaluated. Lercanidipine and its photodegradation products were separated by a selective liquid chromatographic (HPLC) method, under reverse phase conditions. The main photoproducts were characterized by LC–MS/MS analysis, using an electrospray ionization source (ESI) and an ion trap analyzer.

Therefore, a stability-indicating HPLC method was then developed and applied to the quality control of a commercial lercanidipine pharmaceutical formulation (tablets).

☆ Presented at 11th Meeting on RDPA 2005, Rimini (Italy), 25–28 September 2005.

* Corresponding author. Fax: +39 051 2099734.
E-mail address: vanni.cavrini@unibo.it (V. Cavrini).

0731-7085/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2005.11.018

2. Experimental

2.1. Materials

Lercanidipine standard was kindly supplied by Recordati Industria Chimica e Farmaceutica S.p.A (Milan, Italy). Zanedip® filmed tablets for oral administration, containing lercanidipine (9.4 mg/tab), were commercially available. Triethylamine (TEA) and acetic acid were from Sigma–Aldrich (Milan, Italy), solvents for chromatography were of HPLC grade from Romil Pure Chemistry (Cambridge, UK) and all other chemicals were of reagent grade from Carlo Erba Reagents (Milan, Italy). A Milli-Q® (Millipore, France) water purification system was used to obtain the purified water for photostability studies and HPLC analysis. Photodegradation studies were performed on drug solutions in ethanol and ethanol/phosphate buffer saline (PBS) 50:50 (v/v). PBS consisted of phosphate buffer (0.02 M; pH 7.4) containing 0.135 M sodium chloride.

2.2. Apparatus and experimental conditions

Tests on the photochemical stability were carried out using a xenon arc source to simulate the natural sunlight exposure. A 150 W xenon arc lamp (solar simulator, model 68805, Oriel Corporation, Stratford, CT, USA) was used, with a dichroic mirror (Oriel, model 81405) to block visible and IR radiation in order to minimize sample heating. An air-mass filter 1.5 (Oriel, model 81090) was used to simulate solar conditions and a UV-B-C blocking filter was employed to attenuate the UV-B component. The output beam was directed downward by a "beam-turning assembly", containing the dichroic mirror. The UV dose ($\mu W/cm^2$) from the Xe-arc lamp was measured using a Oriel Goldilux radiometer (model 70127), fitted with external interchangeable probes for UV-A (dose: 82.2 $\mu W/cm^2$ min) and UV-B (dose: 9.1 $\mu W/cm^2$ min).

Spectrophotometric analyses were performed on a HP 8453 UV–vis photodiode spectrophotometer (Agilent Technologies, Palo Alto, CA), using 1 cm quartz cells.

LC–MS analysis was carried out on a Jasco PU-1585 Liquid Chromatograph (Jasco Corporation, Tokyo, Japan) interfaced with a Jasco 1575 UV–vis detector ($\lambda = 265$ nm) and with a LCQ-Duo Mass Spectrometer (Thermo Finnigan, San Jose, CA, USA), by a splitting flow T-valve. The mass spectrometer was equipped with heated capillary interface and electrospray ionization (ESI) source, and operated with an Ion Trap analyser. ESI system employed a 4.5 kV (positive polarity) spray voltage and a heated capillary temperature of 220 °C. The sheath gas and the auxiliary gas (nitrogen) flow rates were set to 0.75 and 1.2 l/min, respectively. Electrospray ionization was optimised using lercanidipine as reference compounds. The mass chromatograms were acquired in total ion current (TIC) modality from 100 to 900 *m/z*, in MS/MS mode (relative collision energy 24–27%) on the ESI generated ions of lercanidipine and its photoproducts. Reverse phase chromatographic analysis were performed on a Phenomenex Luna C_{18}, 3.5 μm (2.0 × 150 mm i.d.) column, using a mobile phase consisting of methanol/TEA buffer (0.01 M) 60:40 (v/v), adjusted to pH 4 with acetic acid and a flow rate of 250 μl/min. The injector was a Rheodyne valve (model 7725i) with a 20 μl loop.

2.3. Photostability testing

Solutions of lercanidipine in ethanol and in the mixture ethanol/PBS 50:50 (v/v) at a concentration of 0.2 mg/ml were placed into quartz cells (1 cm path length) closed with screw caps. Quartz cells were placed horizontally and exposed to UV-A and -B radiations (Xe-arc lamp) for increasing time, corresponding to increasing UV doses. The photoexposed solutions were then analysed by both spectrophotometry, to detect any absorption spectral changes, and LC–MS analysis (after dilution 1:5 with mobile phase to the final concentration of 40 μg/ml), to follow the lercanidipine photodegradation rate and pathway. These analyses were also carried out on samples stored in darkness: sample solutions in quartz cells wrapped in aluminium foils were exposed to radiation exposure.

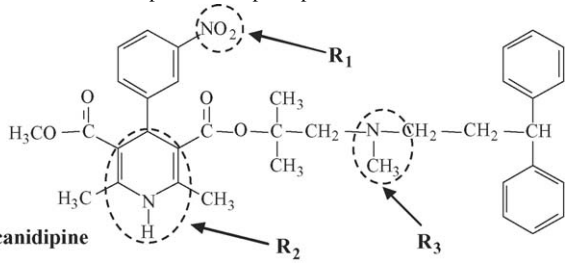
To gain information on the kinetics of the process, solutions of lercanidipine (0.1 mg/ml) in ethanol and in the mixture ethanol/PBS 50:50 (v/v) were exposed to UV radiations and the disappearance of the drug was evaluated by HPLC–UV. Aliquots of 100 μl of the exposed solutions were withdrawn every 10 min (total time 45 min) for ethanolic solutions and every 30 min (total time 360 min) for solutions in ethanol/PBS. The photoexposed solutions were previous diluted with the mobile phase to the final concentration of 20 μg/ml before injection in HPLC apparatus.

Photostability at the solid state was also evaluated by exposing lercanidipine drug substance and lercanidipine commercial preparation Zanedip®, as entire and powdered tablets, to UV radiations for increasing time. Each tablet was turned upside down every hour to have the tablets surface exposed homogeneously. The solid forms were then analysed by LC–MS. Photoexposed tablets were treated as described in Section 2.5; photoexposed lercanidipine substance was dissolved in ethanol (0.2 mg/ml) and the resulting solution was diluted with the mobile phase to the final concentration of 40 μg/ml.

2.4. Photoproducts characterization: LC–ESI–MS/MS analysis

The photoexposed solutions in ethanol and in ethanol/PBS, diluted 1:5 with mobile phase, and the irradiated solid forms, treated as described in Section 2.5, were subjected to LC–MS analysis using the following conditions. The mass spectra were recorded within 100–900 *m/z* full scan (positive polarity), providing the total ion current (TIC) chromatograms (Fig. 2) and the pseudomolecular mass of the analytes. The MS/MS spectra of lercanidipine and its photoproducts, named PP (in the mixture ethanol/PBS) and PE (in ethanol) were also obtained by on-line LC–ESI–MS analyses. An explicative MS/MS spectrum of lercanidipine and a representative scheme of the fragmentation pattern, in agreement with literature data [8] is presented in Fig. 4. This fragmentation was found to be valid also for the photoproducts (Table 1), as below reported.

Table 1
Structures of lercanidipine and its photoproducts



Lercanidipine

Photoproduct	R_1	R_2	R_3
PP1–PE1	—OH	Pyridine	—NH—
PP2	—NO	1,4-dihydropyridine	$-NCH_3-$
PP3–PE2	$-NO_2$	Pyridine	—NH—
PP4	—NO	Pyridine	—NH—
PP5–PE3	$-NO_2$	1,4-dihydropyridine	—NH—
PP6–PE4	—NO	1,4-dihydropyridine	—NH—
PP7–PE5	$-NO_2$	Pyridine	$-NCH_3-$
PP8	—NO	Pyridine	$-NCH_3-$

PP: photoproducts in ethanol/PBS 1:1 solution; PE: photoproducts in ethanol solution.

MS/MS data: m/z (relative abundance). PP1–PE1: 568 (10) $[M+H]^+$, 357 (5) $[M-HN(CH_2)_2CH(Ar)_2]^+$, 285 (40) $[M-OC(CH_3)_2CH_2NH(CH_2)_2CH(Ar)_2]^+$, 284 (100) [M − (CO-4-substituted pyridine)]$^+$, 266 (45) [M − (OCO-4-substituted pyridine)]$^+$;
PP2: 596 (20) $[M+H]^+$, 371 (10) $[M-CH_3N(CH_2)_2CH(Ar)_2]^+$, 298 (50) [M − (CO-4-substituted 1,4-dihydropyridine)]$^+$, 280 (100) [M − (OCO-4-substituted 1,4-dihydropyridine)]$^+$;
PP3–PE2: 596 (15) $[M+H]^+$, 385 (10) $[M-HN(CH_2)_2CH(Ar)_2]^+$, 313 (5) $[M-OC(CH_3)_2CH_2NH(CH_2)_2CH(Ar)_2]^+$, 266 (100) [M − (OCO-4-substituted pyridine)]$^+$;
PP4: 580 (5) $[M+H]^+$, 369 (10) $[M-HN(CH_2)_2CH(Ar)_2]^+$, 297 (5) $[M-OC(CH_3)_2CH_2NH(CH_2)_2CH(Ar)_2]^+$, 266 (100) [M − (OCO-4-substituted pyridine)]$^+$;
PP5–PE3: 598 (15) $[M+H]^+$, 387 (10) $[M-HN(CH_2)_2CH(Ar)_2]^+$, 315 (5) $[M-OC(CH_3)_2CH_2NH(CH_2)_2CH(Ar)_2]^+$, 284 (100) [M − (CO-4-substituted 1,4-dihydropyridine)]$^+$, 266 (65) [M − (OCO-4-sobstituted 1,4-dihydropyridine)]$^+$;
PP6–PE4: 582 (5) $[M+H]^+$, 371 (5) $[M-HN(CH_2)_2CH(Ar)_2]^+$, 299 (5) $[M-OC(CH_3)_2CH_2NH(CH_2)_2CH(Ar)_2]^+$, 284 (100) [M − (CO-4-substituted 1,4-dihydropyridine)]$^+$, 266 (40) [M − (OCO-4-substituted 1,4-dihydropyridine)]$^+$;
PP7–PE5: 610 (5) $[M+H]^+$, 385 (30) $[M-CH_3N(CH_2)_2CH(Ar)_2]^+$, 313 (45) $[M-OC(CH_3)_2CH_2NCH_3(CH_2)_2CH(Ar)_2]^+$, 280 (100) [M − (OCO-4-substituted pyridine)]$^+$;
PP8: 594 (30) $[M+H]^+$, 369 (30) $[M-CH_3N(CH_2)_2CH(Ar)_2]^+$, 297 (25) $[M-OC(CH_3)_2CH_2NCH_3(CH_2)_2CH(Ar)_2]^+$, 280 (100) [M − (OCO-4-substituted pyridine)]$^+$.

2.5. Assay procedure

Tablets containing lercanidipine (9.4 mg/tab, corresponding to 10 mg of lercanidipine hydrochloride) were analysed by HPLC, in order to verify identity, content and photostability of the drug in the solid pharmaceutical formulation.

Five tablets of Zanedip® were powdered and an accurately weighted amount of about 100 mg was treated with 50 ml of ethanol and sonicated for 15 min. An aliquot (2 ml) of this solution was then filtrated and diluted 1:10 with the mobile phase, to a final concentration of lercanidipine of approximately 20 μg/ml. The sample solution was then analysed by HPLC.

2.6. Calibration graph

Working standard solutions of lercanidipine (5–40 μg/ml) were prepared in ethanol and diluted with the mobile phase to the required concentration. These solutions were analysed by HPLC under isocratic conditions, using UV detection at 265 nm. Calibration graph for lercanidipine was then constructed by plotting the peak area of the drug versus the corresponding drug concentration.

3. Results and discussion

The photostability studies on lercanidipine were aimed at: (a) determination of the photochemical properties of the drug, (b) structural characterization of the main photoproducts, (c) evaluation of content and photochemical stability of lercanidipine in commercial pharmaceutical formulations. To this end a xenon arc lamp was used as solar simulator for photostability studies, according to the option 1 of ICH guidelines [9]. Moreover, the photoreactivity of lercanidipine was studied in different conditions of solvent, to gain general information on drug handling and storage.

3.1. Photochemical behaviour of lercanidipine in solution

Lercanidipine exhibits a very low solubility in aqueous solutions, therefore, after preliminary experiments, the photostability was evaluated on drug solutions in ethanol and in mixture ethanol/PBS 50:50 (v/v). The drugs solutions in quartz cells, the pure powder and the solid pharmaceutical formulation (tablets) were exposed to UV-A radiations (solar simulator, Xe-arc lamp) at ambient temperature. Reference lercanidipine solutions at the same concentration, kept in the dark, were undergone to parallel irradiation experiments. The drug photodegradation was monitored by UV spectrophotometry and LC–UV–MS techniques.

As shown in Fig. 1, the radiation exposure resulted in photoinduced modifications of the drug chromophore, as indicated by the significant changes of the UV spectral absorption of the solutions (irradiation time 0–210 min). In particular a decrease of the absorption bands at $\lambda = 240$ and 360 nm were observed, according to a previous study [3]. The decrease of the absorption band at 360 nm, due to the 1,4-dihydropyridine system, suggest a significant modification of this chromophore (aromatisation), according to the literature data [4]. Moreover, increased absorption at 265 and 310 nm (ethanol/PBS solution) can be observed. Almost the same modifications were found for both ethanolic and ethanol/PBS solutions, but the modification rate is higher in ethanol.

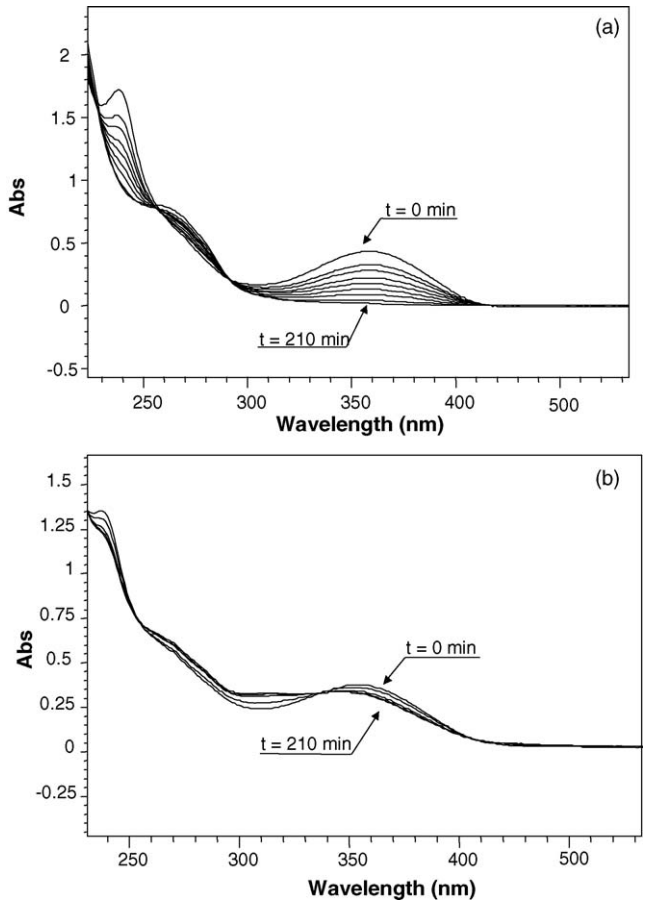


Fig. 1. Changes in the absorption spectrum of lercanidipine solutions (0.2 mg/ml) in ethanol (a) and in ethanol/PBS 50:50 (v/v) (b), after UV-A irradiation (0–210 min).

HPLC–UV chromatograms, acquired at 265 nm, of the photoexposed solutions (Fig. 2) showed the formation of several photoproducts, some of which were more hydrophilic and others more hydrophobic than the parent drug, while no degradation products were detected in the dark control samples. In ethanol/PBS (Fig. 2b; exposure time 360 min) the degradation appeared more complex, with the formation of several products, than in pure ethanol (Fig. 2a; exposure time 120 min), where the photodegradation process leads to PE5 as the prevailing photoproduct. Most of these compounds were simultaneously obtained upon light exposure, suggesting a complex pathway of photodegradation.

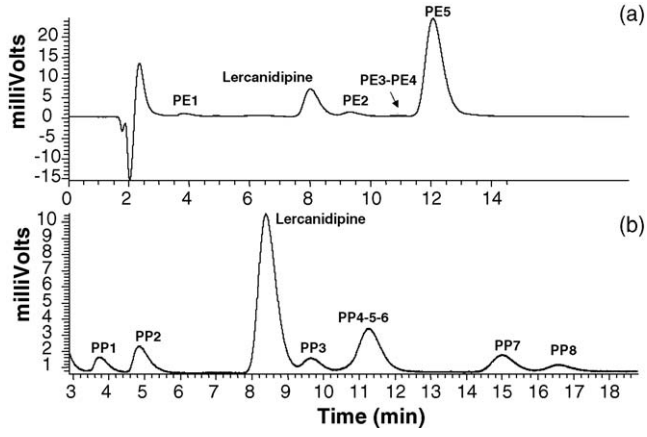


Fig. 2. HPLC–UV chromatograms of photoexposed lercanidipine solutions (0.2 mg/ml) in: (a) ethanol (irradiation time 120 min) and (b) ethanol/PBS 50:50 (irradiation time 360 min). Chromatographic conditions: Phenomenex Luna C_{18}, 3.5 μm (2.0 × 150 mm i.d.) column; mobile phase consisting of methanol/TEA buffer (0.01 M) 60:40 (v/v), adjusted to pH 4 with acetic acid; 250 μl/min flow rate; UV detection at 265 nm.

3.2. Photostability at the solid state

Photoexposure tests were performed with the Xe-arc lamp (irradiation time: 12–20 h), to verify the photostability of lercanidipine drug substance and incorporated in filmed tablets (entire and powdered tablets). After exposure, the solid forms were treated as described in Section 2.3 (dug substance) and Section 2.5 (tablets) and analysed by LC–ESI–MS/MS.

After 12 h irradiation, the drug substance was found to be slightly unstable, with the formation of two main photoproducts at retention time higher than that of lercanidipine (chromatogram in Fig. 3a). On the contrary the entire tablets did not show any drug content variation or photoproducts formation, even after 20 h of irradiation (Fig. 3b). The LC–MS chromatogram (TIC) of the powdered tablets (irradiation time 16 h; Fig. 3c) showed the formation of several photoproducts and a profile similar to that of exposed lercanidipine in ethanol/PBS solution. Photolysis of solid-state samples (drug substance, tablets) is a surface phenomenon and radiation does not penetrate beyond the surface layer of the material [10]. The different behaviour of lercanidipine in intact tablets and in powdered ones can be ascribed to the fact that, by powdering, the protective film on the pharmaceutical formulation was removed. The higher photoreactivity of the drug in powdered formulation than as drug substance could be ascribed to a self-photoprotective effect by the drug and its photoproducts, which prevent further penetration of radiation and photodegradation. The solid-state photolysis can be considered a self-limiting process.

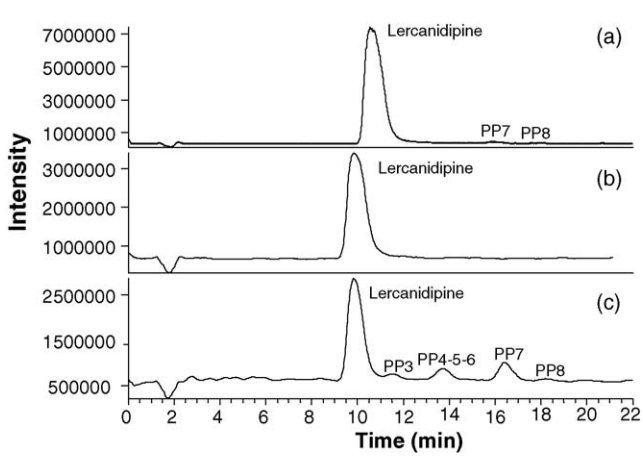


Fig. 3. LC–ESI–MS chromatograms (TIC, 100–900 *m/z* mass range, positive polarity) of lercanidipine solid forms exposed to UV radiations. (a) Drug substance (irradiation time: 12 h); (b) tablets (irradiation time: 20 h); (c) powdered tablets (irradiation time: 16 h). Chromatographic conditions as described in Fig. 2.

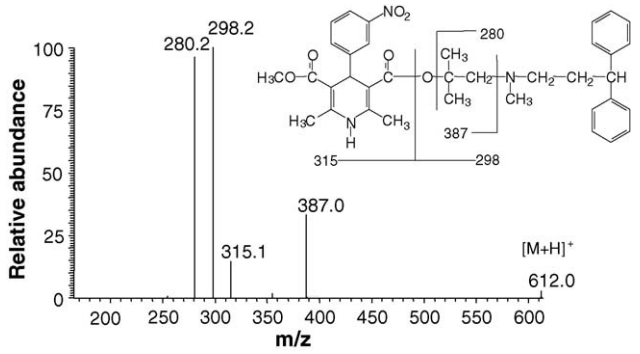


Fig. 4. Explicative LC–MS/MS spectrum of lercanidipine and a representative scheme of the fragmentation pattern.

3.3. Identification of the photoproducts

The analyses by HPLC coupled with mass spectrometry with electrospray ionization interface, a soft ionization technique, provided information on the analytes molecular weight and the tandem mass analyses furnished structural information. The lercanidipine MS/MS spectrum is shown in Fig. 4, along with a scheme of fragmentation, representative of the fragmentation pattern of all the main photoproducts.

Although several photoproducts showed the same retention time (i.e. PP4, PP5, PP6), the high selectivity and specificity of this technique allowed their structural elucidation.

The structures of the identified photoproducts are summarized in Table 1.

The photoreactive centres, on which all the modifications take place, were found to be the nitrogroup, the dihydropyridinic ring and the methylamino group on the side chain. In particular the nitro group was converted in nitroso (PP2, PP4, PP6-PE4, PP7), or substituted with an hydroxylic group (PP1–PE1); the dihydropyridinic moiety was oxidized to pyridinic (PP1–PE1, PP3–PE2, PP4, PP7–PE5, PP8), according to the absorption spectra modifications; the methylamine underwent to the loss of the methyl group (PP1–PE1, PP3–PE2, PP4, PP5–PE3, PP6–PE4).

The same photoproducts as in ethanol/PBS solutions were found in the photoexposed powdered tablets, except for the absence of PP1 and PP2. Samples of lercanidipine drug substance, after light exposure, presented the formation of the photoproducts PP7 and PP8.

These results show that lercanidipine is subjected to the following major photodegradation reactions: aromatisation of the 1,4-dihydropyridine moiety, reduction to the nitrosoderivatives, *N*-demethylation on the basic side chain.

3.4. Kinetic of photodegradation

To achieve some information on the kinetics of the process, low concentration solutions of lercanidipine (0.1 mg/ml) were exposed to UV radiations and the disappearance of the drug was evaluated by HPLC–UV. Linear relationships were observed according to the equation: $\ln A = \ln A_0 - kt$ (apparent first-order kinetics), where A is the remaining peak area, A_0, the initial percentage of the drug (100%), k, the slope and t is time (min). The following data were obtained: ethanol: $\ln A = 4.627\ (\pm 0.01415) - 0.01717\ (\pm 0.0005938)t$ ($r^2 = 0.9905$, $n = 7$), half life $t_{1/2} = 40.36$ min; ethanol/PBS 50:50 (v/v): $\ln A = 4.596\ (\pm 0.01285) - 0.002532\ (\pm 0.00006298)t$ ($r^2 = 0.9963$, $n = 7$), half life $t_{1/2} = 273.7$ min. The lercanidipine photodegradation rate is significantly higher in ethanol than in the mixture ethanol/PBS.

3.5. Assay of lercanidipine in pharmaceutical formulation

Quantitative applications were carried out using HPLC–UV method with UV detection at 265 nm. A linear relationship between the peak area of the drugs (y) to and the corresponding compound concentration (x) (5.0–40.0 μg/ml) was found. The following data for calibration graphs were obtained: $y = 61{,}380\ (\pm 1660)\ x + 50.18\ (\pm 30.44)$, $r^2 = 0.9988$, $n = 5$. The limit of detection (LOD), derived from the regression equation, was 1.49 μg/ml, and the limit of quantitation (LOQ, expressed as $3 \times$ LOD) was about 4.96 μg/ml.

The content of the drug in the examined commercial formulation resulted 9.65 mg/tab (R.S.D.% = 0.58), with a mean recovery of 102.7%, in agreement with the declared value of 9.4 mg/tab.

4. Conclusion

Lercanidipine, a 1,4-dihydropyridine drug with a side chain containing a 3,3-diphenylpropyl-methylamine-2-methyl-2-propyl group, was confirmed to be photolabile in solution (ethanol and ethanol/PBS 1:1 v/v). Solid forms of the drug (powdered commercial tablets) were also found to undergo to a photodegradative process, but in minor extent than the drug solutions. Moreover, the photochemical studies on the drug solutions showed the influence of the solvent nature on the photodegradation process and reaction rate. These results suggest that a particular attention has to be put on the drug handling and storage.

Finally, this study allowed to develop a stability-indicating HPLC method useful for photostability studies of lecarnidipine and for the quality control of its commercial pharmaceutical formulations.

Acknowledgement

The work was supported by a grant by the Alma Mater Studiorum — Università di Bologna (fondi Ricerca Fondamentale Orientata).

References

[1] S.C. Sweetman (Ed.), Martindale — The Complete Drug Reference, 34th ed., Pharmaceutical Press, 2005, p. 946.
[2] L.M. Bang, Drugs 63 (2003) 2449–2472.
[3] A. Albini, E. Fasani, Drugs: Photochemistry and Photostability, The Royal Society of Chemistry, 1998, pp. 1–65.
[4] A. Alvarez-Lueje, S. Pujol, J.A. Squella, L.J. Nunez-Vergara, J. Pharm. Biomed. Anal. 31 (2003) 1–9.

[5] A.B. Baranda, R.M. Jimenez, R.M. Alonso, J. Chromatogr. A 1031 (2004) 275–280.
[6] N. Erk, Pharmazie 58 (2003) 801–803.
[7] A. Alvarez-Lueje, S. Pujol, L.J. Nunez-Vergara, J.A. Squella, J. AOAC Int. 85 (2002) 1247–1252.
[8] I.I. Salem, J. Idrees, J.I. Al Tamimi, P. Farina, J. Chromatogr. B 803 (2004) 201–207.
[9] J.T. Piechocki, in: A. Albini, E. Fasani (Eds.), Drugs: Photochemistry and Photostability, The Royal Society of Chemistry, London, 1998, pp. 247–271.
[10] H.D. Drew, in: A. Albini, E. Fasani (Eds.), Drugs: Photochemistry and Photostability, The Royal Society of Chemistry, London, 1998, pp. 227–242.