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Photodegradation studies on lacidipine in solution: basic experiments with a *cis–trans* reversible photoequilibrium under UV-A radiation exposure☆

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Abstract

The photostability of Lacidipine, a dihydropyridine drug used in the treatment of mild and moderate hypertension, was studied in solutions exposed to UV-A radiations. The effects of the solvent (ethanol, acetone, dichloromethane), drug concentration and radiation wavelength on the drug photostability were evaluated. Lacidipine and its photoproducts were separated by a selective liquid chromatographic (HPLC) method, under normal phase conditions (CN-column), using *n*-hexane:ethanol 97:3 (v/v) as mobile phase, at a flow rate of 2.0 ml/min. The main photodegradation products were isolated and characterised and a photodegradation pathway was proposed for Lacidipine in solution. The *cis*-isomer and a photocyclic isomer proved to be the main photodegradation products.

Keywords: Lacidipine; Photostability; Liquid chromatography; *cis–trans* photoequilibrium

1. Introduction

Lacipidine (**I**) (*E*-4-[2-[3-(1,1-Dimethylethoxy)-3- oxo - 1 - propenyl]phenyl] - 1,4 - dihydro - 2,6 - dimethyl-3,5-pyridine-dicarboxylic acid diethyl ester) is a calcium channel blocker developed for an oral administration, for use in mild to moderate hypertension, and is widely used in therapy since early 90s [1,2].

A review on lacidipine [3] has been published concerning the main properties of the drug.

Lacidipine belongs to dihydropyridine class and its structure is characterised by the presence of a cinnamate moiety; the active *trans* form is used in therapy. From a physico–chemical point of view, lacidipine is very slightly soluble in water, while it is more soluble in some widely used solvents as ethanol, methanol and acetone. The redox behaviour of the drug has been studied and an electrochemical method for its determination in solution was proposed [4].

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The drug is sensitive to light, in line with the well known photosensitivity of dihydropyridine compounds class [5,6]. Most of these drugs are structurally characterised by a nitrophenyl substituent at C-4 of the dihydropyridine ring, such as nifedipine and furnidipine (2-nitrophenyl), or nicardipine and nitrendipine (3-nitrophenyl). When these nitrophenyl dihydropyridines are exposed to daylight, the nitrogroup is reduced to give the nitroso derivative while the dihydropyridine ring is oxidised to a pyridine derivative, with an overall loss of a molecule of water.

The esterified cinnamate moiety present in lacidipine structure, instead of the above mentioned nitrophenyl substituent, results in different, specific photochemical properties of the compound.

In view of the current increased importance of well conducted photostability studies, also in consequence of the issue of the ICH Q1B photostability guideline [7], it was considered worthwhile to perform some basic studies to investigate the photodegradation pathway of lacidipine in solution according to the current status of art.

2. Experimental

2.1. Materials and apparatus

Lacidipine and its *cis*-isomer reference standards were supplied by Glaxo Wellcome S.p.A. (Verona, Italy), potassium ferrioxalate was prepared according to the Hatchard-Parker method [8,9]. Solvents for chromatography were of HPLC grade from Lab-Scan (Ireland) and all other chemicals were of reagent grade from Carlo Erba Reagents (Italy).

Spectrophotometric measurements were performed on a UV–Vis spectrophotometer V530 Jasco (Japan).

An HPLC system equipped with a Photo Diodes Array detector (PDA, Hewlett Packard HP Ti series 1050) was employed. Chromatographic analyses were performed on a Water Spherisorb S5-CN, 5 μm (250 × 4.6 I.D.) column, using a mobile phase of *n*-hexane/ethanol 97:3 (v/v), at a flow rate of 2.0 ml/min; the injection volume was 20 μl.

Semi-preparative chromatography was performed on a Phenomenex Hypersil CN (10 μm; 250 × 10 mm I.D.) column, using the same chromatographic condition described above; the injection volume was 500 μl. The eluates were collected by a fraction collector Gilson FC 2038, dried and subjected to MS and H-NMR analyses.

GC-MS analyses were performed on a HP 5890 series II gas-chromatograph with a mass selective detector HP 5971.

The NMR spectra were recorded on a Varian 200 MHz NMR spectrometer, using TMS as internal standard. The chemical shift is expressed in δ (ppm) and J in Hz.

2.2. Photostability instruments

For UV radiation exposure a 150 W Xenon-arc lamp (Solar Simulator, model 68805, Oriel Co, USA) was used, fitted with a dicroic mirror to block both visible and IR radiation so minimising the sample heating. An air-mass filter (Mod. 81090) to simulate solar conditions and a UV-B/C blocking filter were also employed. The output beam was directed downward by a 'beam turning assembly', which held the dicroic mirror. In these conditions, lacidipine solutions in 3 ml-quartz cells were exposed only to radiation in the UV-A range (320–400 nm).

For single wavelength studies, a 150 W medium pressure Mercury lamp Hanau Q400 was used, characterised by a line output, equipped with interference filters to isolate 313 and 365 nm wavelengths.

The UV-A dose (J/cm^2) from the Xenon arc lamp was measured by a radiometer (Goldilux, mod. 70127, from Oriel Co, USA), fitted with an external interchangeable probe for UV-A.

The 'microversion' of potassium ferrioxalate actinometer [9] was used to measure the photons emitted per min (*Nhv*/min) from the fixed wavelength light source.

2.3. Photodegradation studies in solution

Photostability studies were carried out on lacidipine solutions exposed to UVA range radiations; in particular, the effect of drug concentra-

tion, solvent nature and radiation wavelength were evaluated. All experiments were performed in triplicate.

2.3.1. Concentration effect

In order to observe possible concentration effects on lacidipine photodegradation rate and pathway, solutions in ethanol were prepared at different concentrations (0.02, 0.20, 0.50, 1.00, 8.00 and 20.00 mg/ml).

Three millilitre aliquots of these solutions were placed into quartz cells (1 cm path length) closed with teflon caps. Quartz cells were positioned horizontally and exposed to Xe-arc lamp for increasing irradiation times (0–4 h), corresponding to increasing UV-A doses (0–20 J/cm^2). After irradiation all samples were immediately protected from light with aluminium foil. The photoexposed solutions were then subjected to both UV–Vis spectrophotometric analysis, to detect any spectral absorption changes, and to HPLC analysis, to follow lacidipine photodegradation rate and pathway.

These analyses were also carried out on dark control samples, i.e. 3 ml lacidipine solution in a 1 cm quartz cells wrapped in aluminium foil during irradiation.

2.3.2. Solvent effect

In order to evaluate any solvent effect on the photodegradation rate and pathway, lacidipine solutions in acetone and dichloromethane at different concentrations (0.50, 1.00, 20.00 mg/ml) were exposed to UV-A radiation (0–4 h) and then subjected to spectrophotometric and HPLC analyses.

2.3.3. Wavelength effect

Photoexposure tests were performed with monochromatic radiations ($\lambda = 313$) using 3.0 ml of a lacidipine ethanolic solution (0.50 mg/ml), continuously stirred during irradiation.

Similar experiments were carried out on ethanolic solutions (0.50 mg/ml) containing lacidipine and/or its *cis*-isomer. In particular the following compositions were examined:

- lacidipine/*cis*-isomer 50:50 (w/w), irradiated by UV-A and at $\lambda = 313$ nm;
- lacidipine/*cis*-isomer 30:70 (w/w), irradiated by UV-A and at $\lambda = 313$ nm;
- *cis* isomer (0.50 mg/ml), irradiated by UV-A.

2.3.4. Kinetic model

Data from lacidipine photodegradation were fitted using a three-compartment model with linear first order kinetics.

The software SAAM II (Vers. 1.1.2), SAAM Institute, University of Washington, was used for data fitting.

2.3.5. Photodegradation product isolation

Lacidipine solution (5 mg/ml) in ethanol was exposed to UV-A radiation (Xenon-arc lamp) up to obtain severe photodegradation of the drug. The solution was diluted with *n*-hexane (1:2) and then subjected to semipreparative chromatographic separation on a CN-column (250 × 10 mm I.D.) under the above described conditions. The eluate fraction, containing the photoproduct P2, was collected and evaporated to dryness. The residue was used for subsequent NMR, Mass Spectrometry and UV analyses. The obtained data are reported below.

^{1}H-NMR ($CDCl_3$), δ: 1.35 (s, 3H, CH_3 *p*); 1.48 (s, 9H, CH_3 *n*); 2.20 (s, 3H, CH_3 *m*); 3.48 (d, J = 9.9 Hz, 1H, CH *h*); 4.40 (d, J = 9.9 Hz, 1H, CH *g*); 4.65 (s, 1H, NH exchanges with D_2O, *f*); 4.71 (s, 1H, CH, *e*); 7.35–7.19 (m, 4H, H Arom., a + b + c + d).

MS spectrum: 455 (M^+; 12); 398 (M^+-$C(CH_3)$; 17); 382 (M^+-$OC(CH_3)_3$; 12); 354 (M^+-$COOC(CH_3)_3$; 17); 326 (17.5); 280 (15); 252 (100); 208 (25); 196 (25); 165 (25).

UV (Ethanol): λ_{max} 288 nm ($\varepsilon = 16500$).

For reference, the Lacidipine MS spectrum is characterised by: 455 (M^+; 10.2), 398 (20.5), 382 (50), 354 (12.6), 326 (93.4), 298 (20.5), 280 (8.4), 252 (100), 224 (25.3), 196 (20).

3. Results and discussion

3.1. Photodegradation studies

Photochemical studies were undertaken in order to achieve information on the photostability

of lacidipine solution, the nature of its photodegradation products and the photodegradative pathway. Spectrophotometric and chromatographic (HPLC) methods were applied to this purpose.

After UV-A exposure, a 0.50 mg/ml lacidipine ethanolic solution exhibited significant changes in its absorption spectrum (Fig. 1); in particular a decrease of the absorption bands at $\lambda = 240$ and 368 nm were observed. The decrease of the absorption band at 368 nm, due to the dihydropyridinic system, suggested a significant modification of this chromophore. HPLC chromatograms of the photoexposed solution showed the formation of two new chromatographic peaks, at retention times lower than that of lacidipine (photoproducts P1 and P2 in Fig. 2), while no temperature dependent degradation products were detected in the dark control samples. Lacidipine and its photoproducts P_1 and P_2 exhibit different UV spectra (Fig. 3), obtained by on-line Photo Diode Array detector, which are in agreement with the overall spectral modifications shown in Fig. 1.

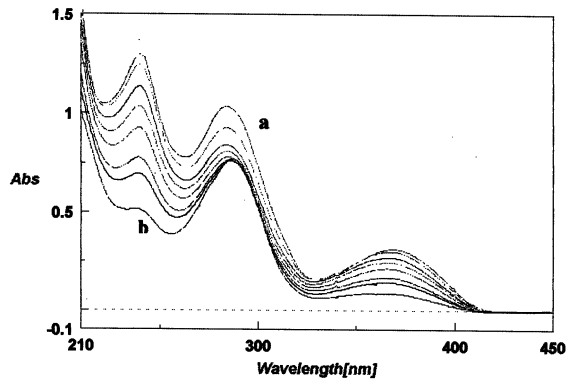

Fig. 1. Change of lacidipine UV spectrum after UV-A exposure: (a) Not exposed; (b) UV-A dose = 42.4 J/cm^2.

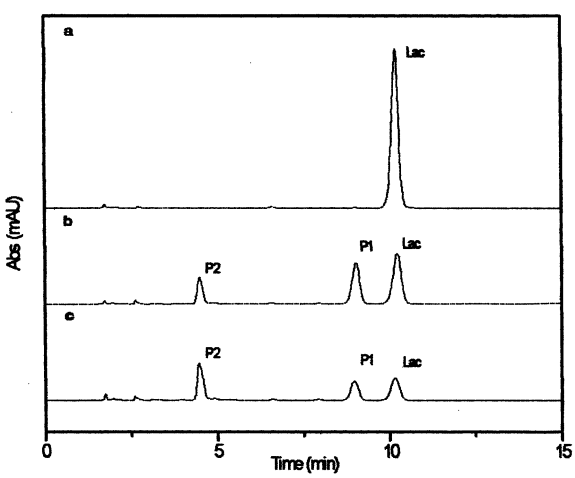

Fig. 2. HPLC chromatograms of lacidipine ethanolic solution (0.50 mg/ml) exposed to different UV-A levels: (a) 0.0 J/cm^2, (b) 9.8 J/cm^2, (c) 30.7 J/cm^2. Stationary phase: S5 CN, 5 μm (250 × 4.4 mm I.D.); mobile phase: *n*-hexane/EtOH 97/3 (v/v); flow rate 2.0 ml/min; UV detection at 240 nm (LAC, lacidipine, P1 and P2, photoproducts 1 and 2).

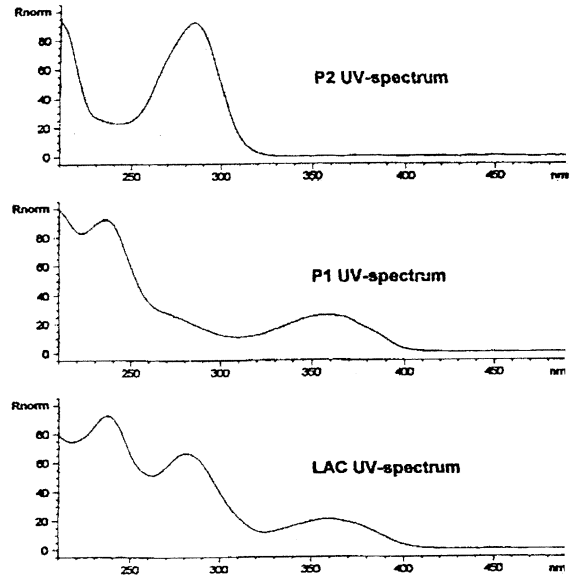

Fig. 3. Absorption spectra of lacidipine and photoproducts P1 and P2, recorded on-line by PDA detector (chromatographic conditions as in Fig. 2).

Photoproduct P_1 has been identified as the lacidipine *cis* isomer (Fig. 4), by comparison of HPLC retention time and UV data with a reference standard supplied by Glaxo Wellcome S.p.A.

Photoproduct P_2, isolated by semi-preparative chromatography on CN-column, was identified by UV (Fig. 3), MS and H-NMR spectra as the lacidipine photocyclization product (Fig. 4). The UV absorption spectrum of P_2 exhibits a simple benzenoid profile, showing that the dihydropyridinic moiety is not present in its molecular structure. The mass spectrum (M^+ 455) appears to be

analogous (with different relative abundance of the fragments) to that of lacidipine and suggests it was a photoisomerization product. H-NMR data showed clearly the pattern of the aliphatic part of the molecule; the two singlets of the two protons f and e confirmed there was no aromatization of the heterocyclic ring.

The photodegradation profile obtained on a 0.5 mg/ml ethanolic solution exposed to the Xe-arc (UV-A) lamp is shown in Fig. 5a, while the overall photodegradation pathway of lacidipine is illustrated in Fig. 4, where the photodegradation of the drug and the formation of the photoproducts P_1 and P_2 are shown. According to the data obtained the lacidipine photodecomposition in solution appears to follow a consecutive reaction model, the photoproduct P_1 (*cis*-isomer) being converted in P_2 (cyclic derivative).

3.2. Effects of the photoexposure conditions

3.2.1. Drug concentration

The same above mentioned photoproducts were obtained after UV-A irradiation of lacidipine ethanolic solutions of different concentrations, from 0.02 to 20.0 mg/ml. As anticipated from literature [10], it was observed that lacidipine photodegradation rate decreased as the concentration increased. It was possible to find a linear correlation between the UV-A dose necessary to reach a 50% lacidipine degradation ($UV\text{-}A_{50\%}$) and the solution concentration C (mg/ml), i.e.: $UV\text{-}A_{50\%} = 17.9\ (\pm 0.3)\ C + 5.0\ (\pm 0.9)$ [$r^2 = 0.999$; $n = 6$].

3.2.2. Solvent

The same photoproducts P1 and P2 were found after irradiation of lacidipine solutions in acetone and dichloromethane. However, it was observed that lacidipine photodegradation rate significantly increased moving from ethanol to dichloromethane to acetone; moreover the *cis*-isomer levels reached higher values in these two solvents than in ethanol.

3.2.3. Radiation wavelength

Photoexposure tests (up to 20 h) were performed with monochromatic photon sources at

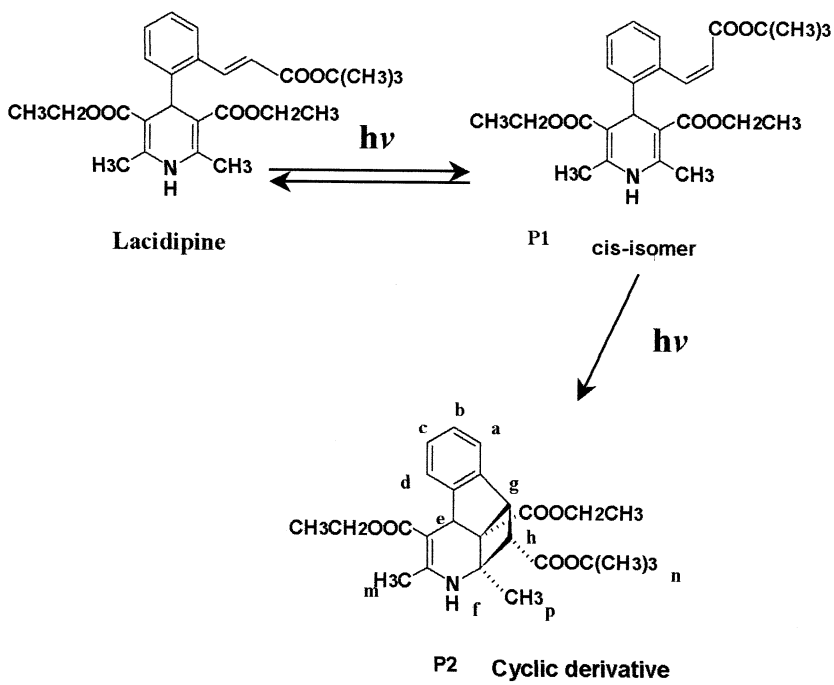

Fig. 4. Photodegradation pathway of lacidipine in ethanolic solution under UV-A radiation.

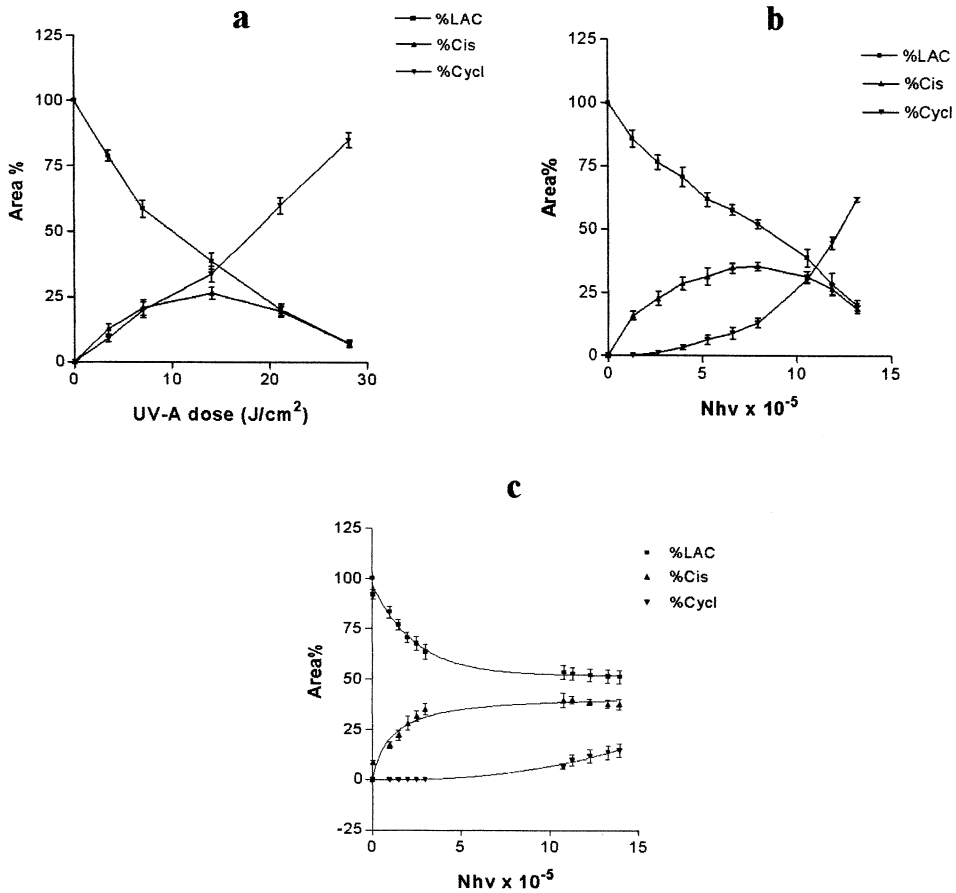

Fig. 5. Effect of the radiation wavelength on photostability of lacidipine in ethanol (0.5% w/v): (a) Xe-arc (UV-A); (b) $\lambda = 365$ nm; (c) $\lambda = 313$ nm.

$\lambda = 365$ and 313 nm on an ethanolic (0.5% w/v) lacidipine solution. Subsequent HPLC analysis of the photoexposed solutions showed that lacidipine photodegradation rate was higher when the drug was irradiated at $\lambda = 365$ nm than at $\lambda = 313$ nm, under the conditions of equivalent absorbed photon number. It was also observed that the overall photodegradation profile obtained with the UV radiations at 365 nm (Fig. 5b) was more similar to the one obtained with the Xe-arc (UV-A) lamp. Differently, under irradiation at $\lambda = 313$ nm, an higher *cis*-isomer formation rate was initially observed, up to a roughly constant value, with an apparent *trans–cis* photoequilibrium, while P_2 formation rate was lower (Fig. 5c).

It is suggested that irradiation at $\lambda = 365$ nm, corresponding to the dihydropyridinic nucleus absorption maximum, could induce lacidipine internal photocyclization, resulting in a rapid P_2 formation. Differently *trans–cis* photoisomerization to *cis* isomer of lacidipine could be selectively induced by UV radiation at 313 nm, which are preferentially absorbed by the *trans*-cinnamate moiety of lacidipine; the following P2 formation is accordingly not favourite.

3.2.4. Kinetic model

The photodegradation data were fitted using a three-compartment model with first order kinetics. The model structure is shown in Fig. 6, where lacidipine is referred to compartment q_1, the *cis*-

isomer to the compartment q_2 and the cyclic derivative to the compartment q_3.

Lacidipine data were used as the forcing function for the compartment q_1 and thus are reported as 'q_1FF' in the model set of equations (reported in Appendix A). SAAM features are such that the program linearly interpolates between data points whenever intermediate values are required. Model fitting was performed for compartments q_2 and q_3.

A delay between compartment q_2 and q_3 was included as an additional parameter to be estimated, to allow the use of the same model for the three lacidipine photodegradation data sets (i.e. under UV-A source and at $\lambda = 365$ and 313nm). Further details on the equations represented by the model are provided in Appendix A.

Photodegradation data obtained under the UV-A Xe-arc lamp fitted well to a simplified model, without the need to consider a delay (i.e. with a delay value estimated equal to zero). Parameter estimates are reported in the Table 1. The data obtained using the fitted model are also compared with experimental data in Fig. 7a.

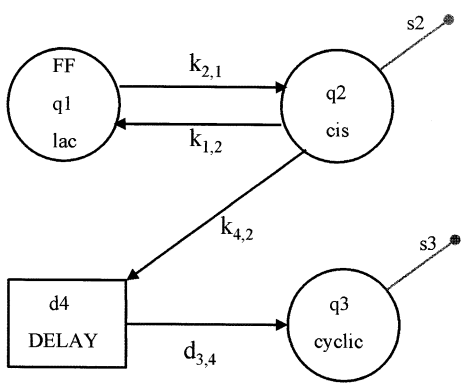

Fig. 6. The three compartment model structure.

Table 1
UV-A (Xe-arc lamp) Lacidipine photodegradation data kinetic fitting

Parameter	UV-A (Xe-arc lamp), photoexposure data estimates, (J/cm^2)	95% Confidence intervals
Delay	0	–
k (2,1)	0.0715	0.0645–0.0784
k (4,2)	0.1442	0.1175–0.1709
k (3,4)	0	–

When fitting the whole photodegradation data set obtained under the monochromatic photon source at $\lambda = 365$ nm to the model, no reliable parameter estimates could be obtained. However, when the data set was fitted limiting the independent variable (photon exposure level) up to 10 *Nhv* 10 e^{-5}, a good fitting and acceptable parameter estimates, including a delay different from zero, could be obtained. The final parameters estimates (with 95% Confidence Intervals) are reported in Table 2.

Parameter estimates were reasonably accurate, as shown by the confidence intervals. Residuals determined up to 10 *Nhv* 10 e^{-5} do not suggest systematic error.

The extrapolation of data up to 13.2 *Nhv* 10 e^{-5} obtained using the fitted model are also compared with experimental data in Fig. 7b. It is evident in this Figure an over-estimation of the *cis* form and an underestimation of the cyclic form from the 10 *Nhv* 10e^{-5} exposure level onwards.

This could be possibly due to the start of a more rapid process of the cyclic compound formation, after an initial induction phase. Further investigations would be needed to fully appreciate this phenomenon.

Photodegradation data set obtained under the monochromatic photon source at $\lambda = 313$ nm, was also well fitted using the same model. In this case the delay value was higher; also the transfer rate between compartment q_1 and q_2 (*cis* derivative formation from lacidipine) was higher than the one calculated with $\lambda = 365$ nm, while the opposite was true for the formation rate of the cyclic compound from the *cis* derivative. The final parameter estimates (with 95% Confidence Intervals) are reported in Table 2. The data obtained using the fitted model are also compared with experimental data in Fig. 7c.

In summary, the chosen model is able to fit the three data sets (i.e. under UV-A and under $\lambda =$ 365 and 313 nm), considering different delay values from compartment q_2 to compartment q_3 (i.e. formation of cyclic compound).

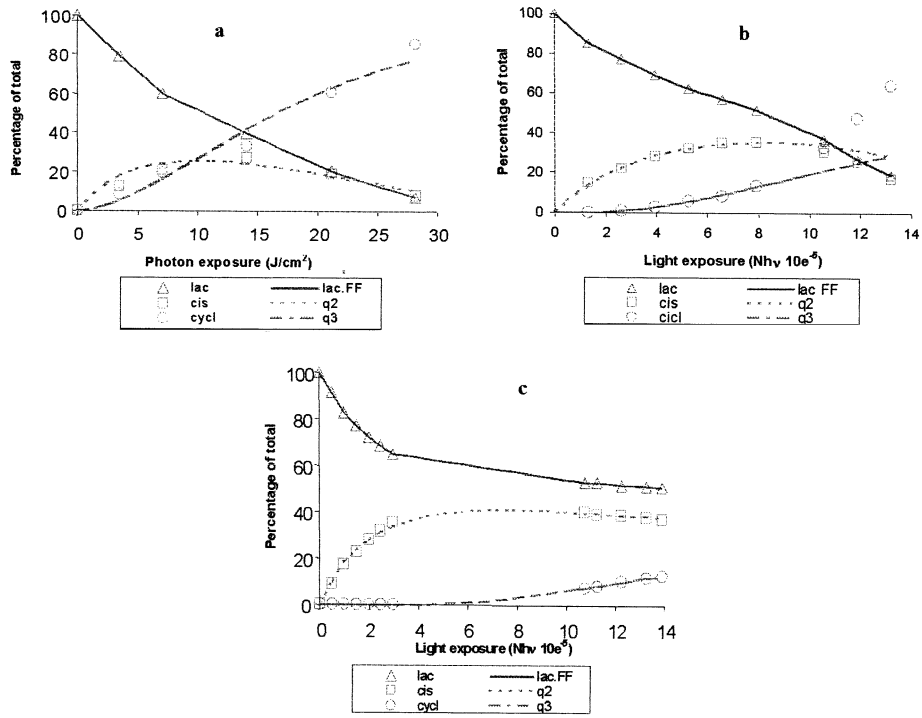

Fig. 7. Comparison between the whole set of experimental data and the extrapolations obtained using the fitted model; (a) Xe-arc (UV-A), (b) $\lambda = 365$ nm, (c) $\lambda = 313$ nm.

3.3. Trans–cis photoisomerization

In order to confirm the *cis–trans* photoequilibrium, ethanolic solutions containing lacidipine/*cis*-isomer mixture were exposed to UV-313 nm radiations and to UV-A radiations.

After UV-A exposure of a 50/50 (w/w) lacidipine/*cis*-isomer solution, a rapid photodegradation of both lacidipine and its *cis*-isomer with the rapid cyclic derivative formation was observed.

Significantly different results were obtained after irradiation of the same solution by the monochromatic radiation at $\lambda = 313$ nm; a very slow *cis*-isomer photodegradation and cyclic derivative formation were observed while a slight lacidipine (*trans*-isomer) concentration increase was noticed (Fig. 8a). Identical exposure tests, carried out on a lacidipine/*cis*-isomer 30:70 (w/w) solution, produced similar results, although a more significant lacidipine increase was found, after irradiation by $\lambda = 313$ nm. To confirm the conversion of *cis*-isomer to lacidipine, a *cis*-isomer (0.50 mg/ml) ethanolic solution was exposed to UV-A radiation; the formation of a small quantities of lacidipine was observed after irradiation confirming a *cis–trans* photoequilibrium (Fig. 8b).

Table 2
Monochromatic Lacidipine photodegradation data kinetic fitting

Parameter	$\lambda = 365$ nm, photoexposure data estimates *, (*Nhv* $10e^{-5}$)	$\lambda = 313$ nm, photoexposure data estimates *, (*Nhv* $10e^{-5}$)
Delay	1.53 (0.83–2.23)	4.89 (4.60–5.19)
k (2,1)	0.12 (0.11–0.13)	0.28 (0.27–0.30)
k (4,2)	0.088 (0.069–0.107)	0.041 (0.039–0.043)
k (3,4)	6.55 (3.54–9.56)	2.04 (1.92–2.17)

95% Confidence Intervals are reported into parenthesis.

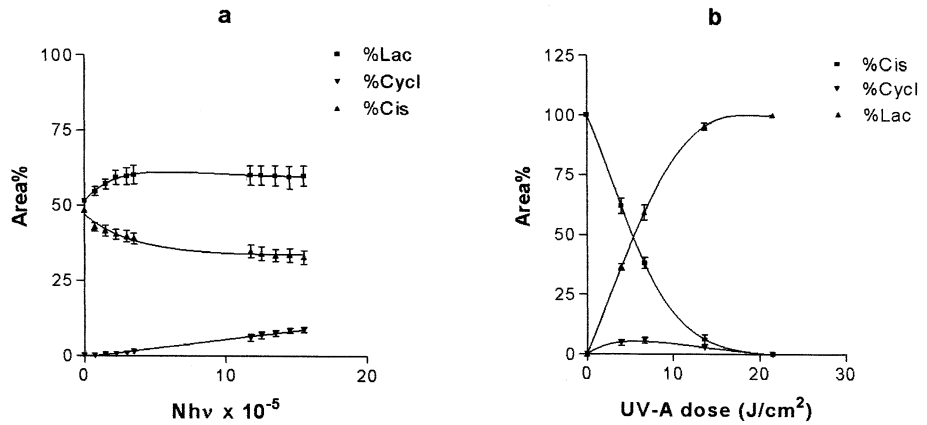

Fig. 8. *Trans–cis* photoisomerization of lacidipine in ethanolic solutions (0.50 mg/ml). (a) Effect of radiation at 313 nm on photostability of a 50/50 (w/w) lacidipine/*cis* isomer mixture. (b) Effect of UV-A radiation on the *cis*-isomer of lacidipine.

4. Conclusion

Lacidipine, a dihydropyridine drug bearing a *trans*-cynnamic moiety, was found to be photolabile in solution. The photodegradative pathway was elucidated; the *cis*-isomer and a photocyclic isomer proved to be the main photodegradation products.

The photochemical studies on the drug solutions showed the influence of the solvent nature and of the radiation wavelength on the photodegradation reaction. In particular, a *trans–cis* isomer photoequilibrium was observed under irradiation at 313 nm.

The studies performed allowed to develop a stability indicating HPLC method useful for photostability studies. Moreover, the achieved information on the lacidipine photoreactivity offer the basis for further investigations on the photostability of lacidipine in solid state and when formulated in solid dosage forms.

Appendix A. Equations represented by the three compartment model

The applied model corresponds to a set of simple linear differential equations with constant coefficients, linking mass fluxes between compartments (corresponding to lacidipine photodegradation products) as follows:

$$\dot{q}_1 = q_2 \cdot k_{1,2} - q_1 FF \cdot k_{2,1}$$

$$\dot{q}_2 = q_1 FF \cdot k_{2,1} - q_2(k_{1,2} + k_{4,2})$$

$$\dot{q}_3 = r(t) \otimes (q_2 k_{4,2})$$

$\dot{q}_t$ represents the derivative respect to the independent variable (photon exposure level, directly proportional to time) for the i-th compartment, $\otimes$ represents the convolution operator, $r(t)$ is the Erlang distribution, which is the transfer function of the delay

$$r(t) = \frac{k^n t^{n-1}}{(n-1)!} e^{-kt}$$

Including a 'delay' block in SAAM, corresponds to add a cascade of n compartments (we chose $n = 10$), each linked with the following one with a transfer coefficient 'k'. It can be shown that the transfer function of such a series of compartments is the Erlang distribution, and determines a delay; Delay $= n/k$.

The parameters to be estimated were $k_{1,2}$, $k_{2,1}$, $k_{4,2}$ and Delay.

The equations for the secondary parameters are as follows:

$$k_{3,4} = d_{3,4} k$$

$$d_{3,4} = 1$$

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