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Photostability studies on the furosemide–triamterene drug association

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Abstract

The photostability of the diuretic drugs triamterene and furosemide, individually and combined, was evaluated. Spectrophotometric, spectrofluorimetric and chromatographic (HPLC) methods were applied to monitor the drug photodegradation. Furosemide was confirmed to be highly photolable in both pH 7.4 solution and methanol. Differently triamterene proved to be highly fluorescent (emission quantum yield: 0.9 in methanol and 0.8 in pH 7.4 solution), but essentially photostable (photochemical reaction quantum yield: $\cong 5 \times 10^{-4}$) under exposure at 365 and 313 nm radiations. When the combined drugs in pH 7.4 solutions were exposed to 365 nm radiations a significant photoprotective effect of triamterene on furosemide was observed. The photoreactivity of the drugs was exploited to develop an HPLC method involving a post-column on-line photochemical derivatization useful to confirm the analyte identity in a commercial dosage form (tablets). The commercial product, containing the combined drugs, proved to be photostable also after long (65 h) light exposure.

Keywords: Photostability; Triamterene; Furosemide; Drug photodegradation

1. Introduction

Drugs that facilitate diuresis are widely used for the treatment of edematous conditions and in the management of hypertension and other conditions for which the increase in urinary flow can relieve syntoms [1]. Several of these drugs have been reported to give rise to adverse photosensitivity responses in vivo and many have been the subject of photodegradation and other photochemical studies in vitro [2–5]. The more important photoreactive diuretic agents are characterized by an absorption spectrum in the sunlight region above 280 nm; among these hydrochlorothiazide ($\lambda_{MAX} = 318$ nm) and furosemide ($\lambda_{MAX} = 330$ nm) are the most studied [3–5]. Photochemical studies individually performed on furosemide and hydrochlorothiazide, under a variety of irradiation conditions (wavelength range, solvent, pH, presence or absence of oxygen), allowed to propose a similar photodegradation mechanism for the drugs [4].

Triamterene ($\lambda_{MAX} = 366$ nm), a potassium-sparing agent, mostly co-formulated with hydrochlorothiazide or furosemide, has been found to degradate slowly under UV radiation to give low yields of products which were only in part identified [4,6].

Triamterene, in the presence of oxygen, was found able to induce photohemolysis of human erythrocytes and this effect was ascribed to its ability of producing singlet oxygen [6]. Photochemical studies on the combination triamterene–hydrochlorothiazide were also carried out [6,7]; only a minor interaction in cross-sensitization between the drugs was observed [7].

As a part of a research program on the photochemical and phototoxic properties of drugs [8–10], the present investigation was focused on the photochemical stability of the combination triamterene–furosemide (Fig. 1), a formulation used to offer a more balanced diuretic effect.

The aim was to achieve further information on the photophysical and photochemical properties of triam-

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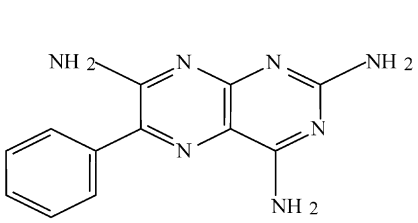
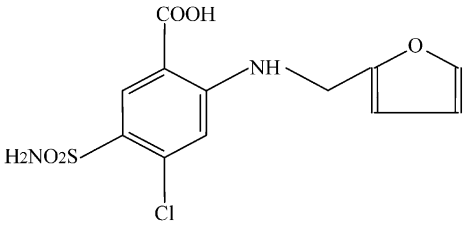


Triamterene



Furosemide

Fig. 1. Chemical structures of furosemide (I) and triamterene (II).

terene and to ascertain possible interaction between triamterene and furosemide detrimental for their photostability. To this end, spectrofluorimetric, spectrophotometric and chromatographic (HPLC) analyses were carried out on individual and combined drug solutions under various solvent and pH conditions.

A stability indicating HPLC method was developed and applied to the quality control of a commercial triamterene–furosemide formulation (tablets).

2. Experimental

2.1. Materials

Furosemide and triamterene were from Sigma–Aldrich, 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). The buffer solutions were prepared according to standard method. Phosphate buffer saline (PBS) solutions consisted of a phosphate buffer (0.02 M; pH 7.4) containing sodium chloride at 0.135 M concentration.

2.2. Photophysical and photochemical studies

Absorption spectra were recorded with a Perkin–Elmer Lambda 6 spectrophotometer; uncorrected emission spectra were obtained with a Perkin–Elmer LS 50 spectrofluorimeter.

Quartz cells (10 mm) were used for the measurements. Luminescence quantum yields were determined using quinine sulfate as standard in methanol ($\Phi = 0.546$) [11].

Luminescence lifetime (τ) values were obtained using an Edimburg 199 Single-photon counting apparatus (UK) able to measure lifetime values over the range 0.5–30 ns.

Photochemical experiments were carried out in 3 ml of solution in spectrofluorimetric quartz cells, using a medium pressure Hg lamp (Hanau Q 400) equipped with an interference filter ($\lambda = 313$ and 365 nm). The photon intensity of the lamp was measured with the microversion of the ferrioxalate actinometer [12].

2.3. Chromatographic (HPLC) analysis

2.3.1. Chromatographic conditions

HPLC analyses were performed on a Hewlett Packard Ti series 1050 liquid chromatograph, equipped with a Rheodyne Model 7125 injector and connected to a photodiode array detector (DAD, HP Ti series 1050). Chromatographic analyses were performed on a Waters Xterra™ MS C_{18}, 3.5 μm (3.0 × 150 mm I.D.) column, using both isocratic and gradient elution. Isocratic: acetonitrile/ammonium acetate buffer (0.02 M; pH 9) 20:80 (v/v), at a flow rate of 0.3 ml/min. Gradient: acetonitrile/ammonium acetate buffer (0.02 M; pH 9) 10:90 (v/v) for 5 min and then to 60:40 (v/v) in 30 min, at a flow rate of 0.3 ml/min. The injection volume was 20 μl. UV detection at three wavelength (270, 340 and 370 nm) was used.

LC-MS analyses were performed on a Jasco PU-1585 liquid chromatograph (Jasco Corporation, Tokio, Japan) interfaced with a LCQ Duo (ThermoQuest, Finnigan, USA) mass detector equipped with an Electrospray ionization (ESI) source, with an Ion Trap analyzer. ESI system employed a −4.5 kV spray voltage (negative polarity) and a capillary temperature of 220 °C. Chromatographic analyses were performed on a Waters Xterra™ MS C_{18}, 3.5 μm (2.1 × 100 mm I.D.) column, using a mobile phase of acetonitrile/ammonium acetate buffer (0.02 M, pH 9) 20:80 (v/v), at a flow rate of 0.3 ml/min. The injection volume was 20 μl.

2.3.2. Photochemical derivatization

In order to enhance the intrinsic selectivity of the HPLC-DAD method, the photoreactivity of furosemide and triamterene in solution was positively exploited by introducing a post-column on-line photochemical derivatization. In fact, a photochemical reactor Beam Boost (BB model C6808, ICT, Frankfurt, Germany) was arranged on-line between the analytical column and the detector, and the column effluent was subjected to UV irradiation at 254 and 365 nm (8 W low-pressure

mercury lamps), alternatively, in a capillary PTFE tube (20 m × 0.3 mm I.D.), in a crocheted geometry. Light-induced structural modifications in the drug chromophore resulted in modified UV spectral properties of the analyte. Therefore, using a diode array detector two UV spectra (photoreactor switched on and off) were recorded for each analyte.

2.3.3. Calibration graphs

Working standard solutions (0.5–8.0 μg/ml) of furosemide and triamterene were prepared in the mixture acetonitrile/ammonium acetate buffer (0.02 M; pH 9) 20:80 (v/v), containing the internal standard metile-*p*-hydroxybenzoate (3.0 μg/ml). These solutions were analysed by HPLC under isocratic conditions, without photochemical derivatization using UV detection (DAD) at 270 nm. Calibration graphs for furosemide and triamterene were then constructed by plotting the ratio of the peak area of the drug to that of internal standard versus the corresponding drug concentration.

2.3.4. Assay procedure

Tablets containing furosemide (40 mg/tab) and triamterene (25 mg/tab) association were analysed by HPLC, in order to verify the identity and the content of the drugs in the tablets.

Five tablets of Fluss® 40 (Scharper, Milan, Italy) were powdered and an accurately weighted amount (200 mg) was treated with 200 ml of a mixture of acetonitrile/ammonium acetate (0.02 M; pH 9) 50:50 (v/v) and sonicated for 15 min. An aliquot (2 ml) of this solution was then centrifugated, filtrated and diluted with acetonitrile/ammonium acetate (0.02 M; pH 9) 20:80 (v/v), containing the internal standard methyl-*p*-hydroxybenzoate (3.0 μg/ml), to give a final concentration of furosemide and triamterene of approximately 2 and 1.2 μg/ml, respectively. The sample solution was then analysed by HPLC.

2.4. Photodegradation studies

In photodegradation studies, a 150 W Xenon-arc lamp (Solar Simulator, model 68805, Oriel Co. USA) was used, fitted with a dichroic mirror to block both visible and IR radiation so minimizing the sample heating. An air-mass filter (mod. 81090) to simulate solar conditions was also employed. The UVA and UVB dose (J/cm^2) from the Xenon-arc lamp was measured by a radiometer (Goldilux, mod.70127, from Oriel Co. USA), fitted with external interchangeable probes for UVA and UVB.

2.4.1. Photostability in solution

Standard solutions of the furosemide–triamterene association were prepared dissolving 2 mg of furosemide and 1 mg of triamterene in 10 ml of the mixture acetonitrile/phosphate buffer (0.02 M; pH 7.4) 20:80 (v/v) and diluting these solutions with phosphate buffer to the final concentration of 2 and 1 μg/ml (w/v) respectively. Standard solutions of furosemide (2 μg/ml) and triamterene (1 μg/ml) were separately prepared as described above.

Three milliliters aliquots of these solutions were placed into quartz cells (1 cm path length) closed with screw caps. The quartz cells were placed horizontally and exposed to the Xe-arc lamp for increasing irradiation time (0–7 h), corresponding to increasing UV dose (UVA = 0–52.4 J/cm^2, UVB = 0–8.67 J/cm^2). The photoexposed solutions were then subjected to HPLC analysis to follow furosemide and triamterene photodegradation pathway.

In order to evaluate the possible effect of one drug on the photodegradation kinetic of the other one, these solutions were also exposed to fixed wavelength radiations: 365 nm and 254+365 nm, simultaneously (8W low pressure mercury lamp). The photoexposed solutions were then subjected to HPLC analyses.

These analyses were also carried out on dark control samples, i.e. 3 ml of furosemide and triamterene solutions in 1 cm quartz cells wrapped in aluminium foil during irradiation.

2.4.2. Photostability of a solid formulation

Tablets of the commercial preparation Fluss® 40 (Scharper, Milan, Italy), containing the furosemide triamterene association, were exposed to different light sources simultaneously (neon, 40 W tungsten lamp, solar light), to simulate environment light, for increasing time (8, 16, 24, 32, 40, 48, 57, 65 h). Each tablet was turned upside down every 4 h to have the tablets surface exposed homogeneously. The tablets were then analysed by HPLC as described in Section 2.3.4.

3. Results and discussion

3.1. Photophysical and photochemical properties of triamterene

The absorption spectra of triamterene in methanol and PBS solution (pH 7.4) are shown in Fig. 2, while the corresponding emission spectra are in Fig. 3. The relative photophysical data are summarized in Table 1. As it can be seen, the absorption maximum in PBS, compared with the spectrum in methanol, is shifted to shorter wavelength, whereas the emission spectra in PBS is shifted toward the visible region. The greater Stoke's shift in PBS solution indicates that in this solvent the excited state in the drug is more distorted than in methanol. The drug was found to be highly fluorescent with an emission quantum yield of 0.9 (methanol) and 0.8 (PBS).

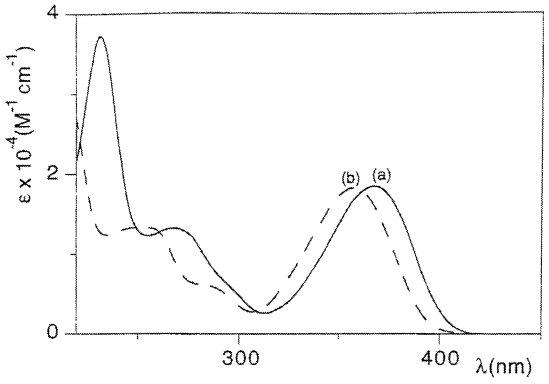


Fig. 2. Absorption spectra of triamterene in methanol (a) and in PBS solution (pH 7.4) (b).

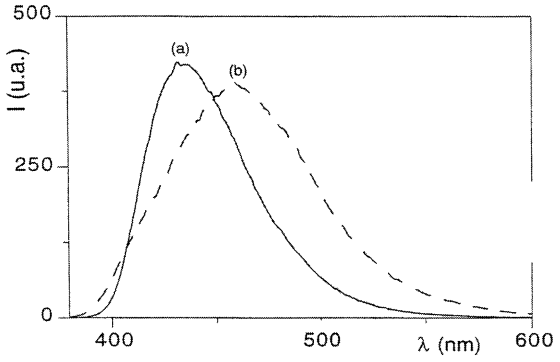


Fig. 3. Emission spectra of triamterene in methanol (a) and in PBS (b).

In both the solvents the luminescence lifetime (τ) was about 5 ns. This suggest that the short-lived excited singlet state cannot interact with oxygen via energy transfer or electron transfer; therefore, the reported [6] formation of oxygen singlet should be ascribed to interaction of oxygen with the excited triplet state of triamterene.

When methanolic solutions of the drug were exposed to 365 and 313 nm radiations, only a minor decrease of the absorption maximum was observed; exposure to 254 nm radiations resulted in a slight increase of the absorption bands at 268 and 367 nm with decrease of the absorption band at 232 nm. The quantum yields (Φ) of the photochemical reaction in methanol, under exposure to different wavelength radiations, were as follow: $\leq 10^{-4}$ (365 and 313 nm), 5×10^{-4} (254 nm).

When triamterene solutions in PBS were exposed to 313 and 365 nm radiations, a progressive decrease of the bands in both absorption and emission spectra were observed (Fig. 4). The reaction quantum yield (Φ), derived from the measurement of the absorption band at 357 nm, was found to be 5×10^{-4} (365 nm; with and without oxygen) and 4×10^{-4} (313 nm).

These data confirm a substantial photostability of triamterene [4], which undergoes photodegradation only in very low extent, with higher yield in PBS solution. As the photoproducts identity is concerned, the observed very low absorption over the 240–400 nm range (Fig. 4) suggests the degradation of the heterocycle structure, and not the formation of a dimer [6]. Differently, in methanolic solution, after exposure to 254 nm radiations, photoproducts were obtained having absorption spectra similar to that of the drug, but slightly shifted to lower wavelength.

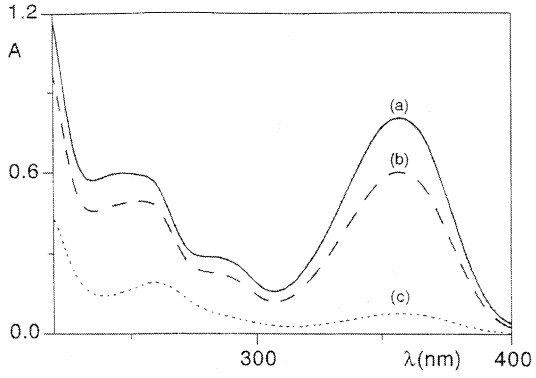


Fig. 4. Changes in the absorption spectrum of triamterene in PBS solution under esposure to 365 nm radiations: (a) $t = 0$; (b) $t = 3$ h; (c) $t = 20$ h.

Table 1
Photophysical data of triamterene

Solvent	Absorbance		Emission [a]		
	λ_{MAX} (nm)	ε (M^{-1} cm^{-1})	λ_{MAX} (nm)	Φ	τ (ns)
Methanol	367	18 400	435	0.9	5
	268	13 300			
	232	37 400			
PBS	357	18 200	460	0.8	5 [b]
	283	6100			
	250	13 300			

Φ, emission quantum yield; τ, luminescence lifetime.
[a] 298 K, solutions with oxygen.
[b] Same value obtained in oxygen-free solution

3.2. Photodegradation studies

Both triamterene and furosemide absorb light in the UV region (Fig. 5), making them potential sensitizers. Photochemical studies on their combination have not been performed previously; this led us to investigate the possibility of an interaction between the two drugs, ensuing from the UV light absorption.

3.2.1. Photodegradation studies in solution

Information on the photostability of the furosemide–triamterene association in solution was achieved using reverse-phase HPLC methods, under isocratic and gradient conditions. Preliminary investigations in flow, using the on-line photochemical reactor, confirmed the photolability of furosemide which was found to undergo photoinduced structural modifications as evidenced by comparing the UV spectra obtained on-line with photoreactor off and on, respectively (Fig. 6a). Only a slight spectral modification was observed for triamterene (Fig. 6b), in agreement with the photochemical data.

Subsequently, solutions of furosemide (2 μg/ml) and triamterene (1 μg/ml) in phosphate buffer solution (0.02 M; pH 7.4) were exposed to UVA–UVB and fixed wavelength radiations and then analysed by HPLC and LC-ESI-MS. As shown in Fig. 7, furosemide was found to undergo a marked photodegradation, yielding two main photoproducts (**1** and **2**) at short retention time; conversely, triamterene proved to be more stable.

Temperature dependent degradation products were not detected in the dark control samples. The same photodegradation profile was found when the solutions were exposed to UV-A-B and to fixed wavelength (365 and 254+365 nm) radiations; moreover the same photoproducts were found when furosemide and triamterene were irradiated separately or in association.

LC-MS analysis confirmed the presence of the dechlorined derivative (peak 1), at *m/z* 294 $(M-H)^-$

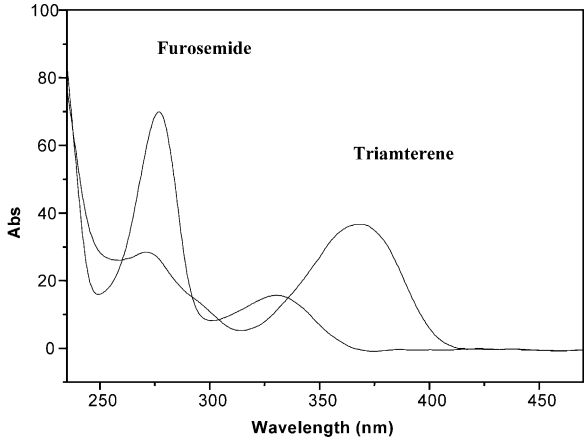


Fig. 5. Absorption spectra of triamterene and furosemide in phosphate buffer solution (0.02 M; pH 7.4), obtained on-line with photodiode array detector.

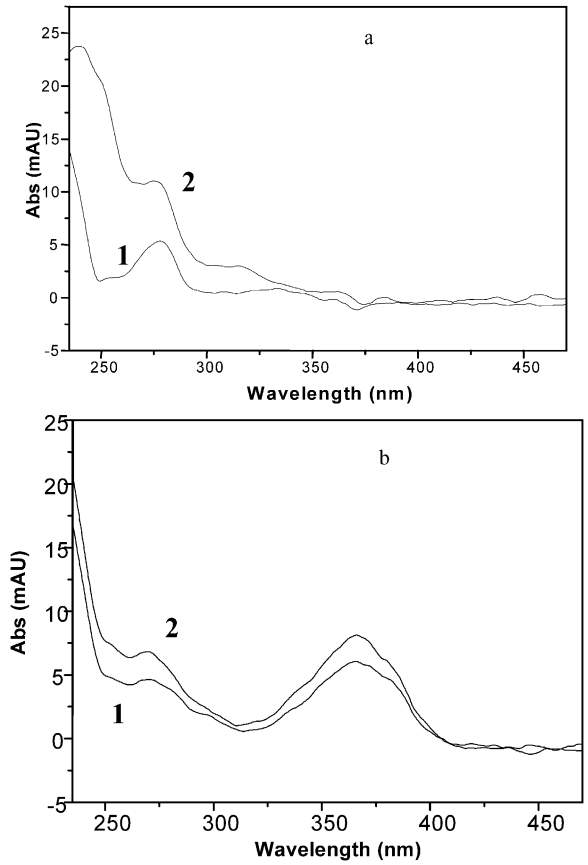


Fig. 6. Absorption spectra of furosemide (a) and triamterene (b), obtained on-line with photoreactor off (1) and on (2).

in the furosemide photoproducts [4], while the very low levels of the triamterene photoproducts did not allow their identification. Further investigations on the photoproduct structure were not performed, being not the aim of the present study.

3.2.2. Kinetic of photodegradation

In order to achieve information on the kinetic of the process, solutions of individual furosemide (2 μg/ml) and triamterene (1 μg/ml) as well as their association, in phosphate buffer (0.02 M; pH 7.4), were exposed to radiations at 365 and 254+365 nm for increasing time (0–6 h) and the disappearance of the two drugs was evaluated by HPLC. Linear relationships were observed for furosemide, according to the equation: $\ln A = \ln A_0 - kt$ (apparent first-order kinetic), where A is the remaining peak area, A_0 is the 100%, k is the slope and t is time (min). Differently, triamterene was found to be stable under this photoexposure conditions.

When the mixture of the drugs was exposed to radiations at 254+365 nm, for furosemide the following kinetic data were obtained: $\ln A = -0.0051\ (\pm 0.0004)\ t + 4.53\ (\pm 0.04)$, $r^2 = 0.979$, $n = 8$ (furosemide+triamterene); $\ln A = -0.00497\ (\pm 0.0004)\ t + 4.54\ (\pm 0.03)$, $r^2 = 0.980$, $n = 8$ (furosemide only).

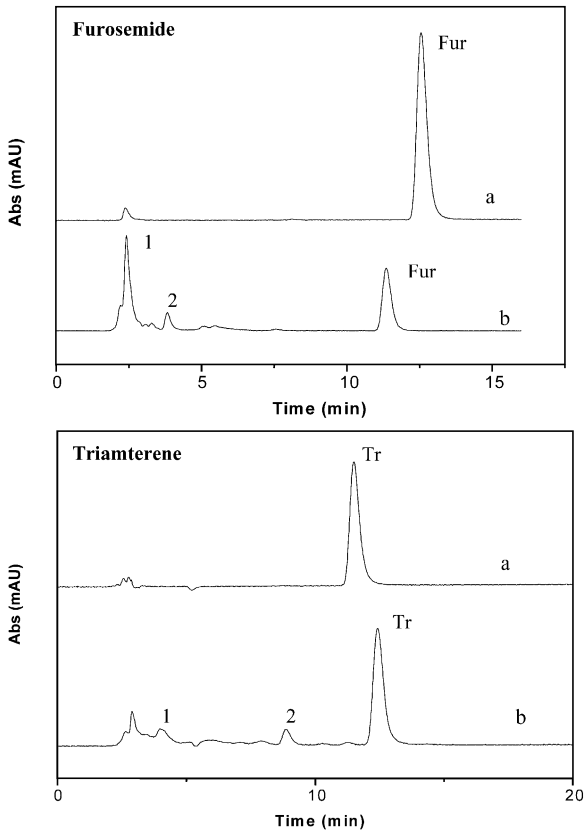


Fig. 7. HPLC chromatograms of furosemide and triamterene phosphate buffer solutions not exposed (a) and exposed (b) to UVA–UVB radiations (UVA = 13.5, UVB = 2.3 J/cm^2 for furosemide and UVA = 40.5, UVB = 6.7 J/cm^2 for triamterene). Chromatographic conditions: C18 column (5 μm, 2.1 × 100 mm I.D.), mobile phase acetonitrile/ammonium acetate buffer (0.02 M; pH 9) 20:80 (v/v), flow rate 0.3 ml/min, $\lambda = 270$ nm.

On the contrary, for exposure to 365 nm radiations, the photodegradation rate of furosemide was lower in the mixture than in individual solution, reveling a photoprotective effect of triamterene, as shown by the following data: $\ln A = -0.00026\ (\pm 0.00003)\ t + 4.59\ (\pm 0.05)$, $r^2 = 0.978$, $n = 8$ (furosemide + triamterene); $\ln A = -0.00043\ (\pm 0.00004)\ t + 4.54\ (\pm 0.04)$, $r^2 = 0.965$, $n = 8$ (furosemide only). As a result, from the regression data the following half-time $t_{0.5}$ for furosemide were estimated: 24 h (furosemide alone), 44 h (furosemide + triamterene).

The observed photoprotective effect of triamterene on furosemide is in agreement with the strong absorption of triamterene at 357 nm (UVA) and its high fluorescent emission at higher wavelength (460 nm in PBS), where furosemide does not absorb. On the other hand, on account of the short life-time of the excited state (5 ns), at the low concentrations used, triamterene cannot give detrimental interactions of electron transfer with furosemide. This protective effect was not observed after irradiation at 254 nm, where furosemide is highly absorbing; the UVC radiations (220–280 nm), however, are not in the solar light and, therefore, the UVA photoprotective effect by triamterene is important for the photostability of furosemide.

3.3. HPLC analysis of furosemide–triamterene association in solid formulation (tablets)

3.3.1. Qualitative analyses

The photoreactivity of furosemide and triamterene was positively exploited to achieve unambiguous identification of the drugs in tablets; in fact the HPLC method selectivity can be enhanced through a post column on-line photochemical derivatization. When a photoreactor was arranged between the analytical C_{18} column and the diode array detector (DAD) each separated analyte was subjected to UV (254 and 365 nm) radiation as it moved to the detector. Triamterene and, in particular, furosemide were found to undergo photoinduced structural modifications resulting in modified UV spectra (Fig. 6). The same modifications in UV spectra occur in standard and sample drugs, confirming the identity of compounds. Therefore, this device can offer a simple and practical method to achieve additional information useful to support the retention data for the analytes identification.

3.3.2. Analysis and photostability of a commercial formulation

Quantitative applications were carried out using HPLC-DAD method with UV detection at 270 nm (Fig. 8). A linear relationship between the ratio (y) of the peak area of the drugs to that of internal standard (fixed concentration 3.0 μg/ml) and the corresponding compounds concentration (x) (0.5–8.0 μg/ml) was found. The following data for furosemide and triamterene calibration graphs were obtained: $y = 0.373\ (\pm 0.001)\ x + 0.00904\ (\pm 0.007)$, $r^2 = 0.9999$, $n = 5$ (furosemide); $y = 0.272\ (\pm 0.003)\ x - 0.0202\ (\pm 0.011)$, $r^2 =$

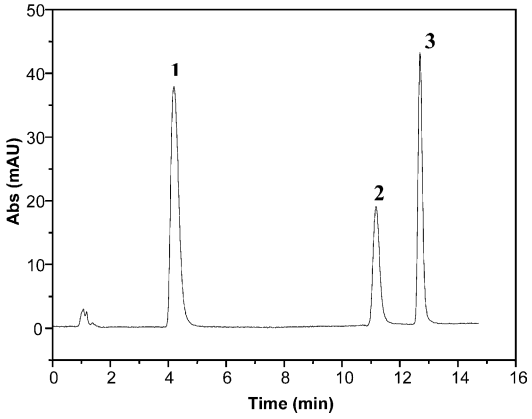


Fig. 8. HPLC chromatogram of furosemide–triamterne association in pharmaceutical formulation (tablets); 1 = methyl-p-hydroxybenzoate (IS), 2 = triamterene, 3 = furosemide. Chromatographic conditions as described in Fig. 7.

0.9997, $n = 5$ (triamterene). The limit of detection (LOD), derived from the regression equation, was 0.06 and 0.1 μg/ml for furosemide and triamterene, respectively, and the limit of quantification (LOQ, expressed as $3 \times$ LOD) was about 0.18 and 0.3 μg/ml.

The results of quantitative analyses are reported in Table 2. As it can be seen, the found content of the drugs in the examined commercial formulation was in agreement with the declared value.

Photoexposure tests were performed with different light source (neon, tungsten lamp and solar light simultaneously) for increasing time (0–65 h) to verify the photostability of furosemide and triamterene combined in a solid formulation. After irradiation, tablets were analyzed by HPLC-DAD; no significant drugs content variation was observed and no photodegradation products were detected. Therefore, furosemide and triamterene in the examined commercial dosage form were found to be photostable under various photoexposure conditions.

Table 2
Assay results for furosemide and triamterene in commercial tablets

	Claimed mg/tab	Found mg/tab (RSD %)	
		Intraday	Interday
Furosemide	40	39.6 (1.261)	39.2 (2.106)
Triamterene	25	25.3 (0.993)	25.4 (1.124)

4. Conclusion

The drug association furosemide–triamterene, commercially available to offer a balanced diuretic effect, was examined for its photostability in both solution and solid phase.

Furosemide was confirmed to be highly photolable in solution (pH 7.4 buffer and methanol), but photostable in a commercial dosage form (tablets) containing also triamterene. In particular, photochemical studies in solution showed a significant photoprotective effect by triamterene on furosemide, which can be ascribed to a filter effect by triamterene strongly absorbing at 357 nm and emitting at higher wavelength where furosemide does not absorb.

Commercial tablets, containing combined furosemide and triamterene, were photoexposed under a variety conditions and then analyzed by a stability indicating HPLC method; the drugs were found to be stable also after long photoexposure (65 h).

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