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Photodegradation of Nabumetone in *n*-butanol solutions

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Abstract

The photolability of the anti-inflammatory drug Nabumetone was studied in *n*-butanol. The photoproducts were followed by UV-Vis absorption, fluorescence and FTIR spectroscopies as well as gas chromatography–mass spectrometry (GC/MS).

The photodegradation process in this organic medium followed first-order kinetics. In contrast with what was expected on the basis of the changes in the electronic spectra observed, the process seems to be more efficient than in water, with a $\Phi = 0.47$ and a half-life, $t_{1/2} = 3.0$ min, leading to different products.

In this medium, the side chain is photo-oxidised to 6-methoxy-2-naphthaldehyde, as a major product. In addition the (4-(6-methoxy-2-naphthyl)-3-buten-2-one) was detected.

The kinetic behaviour suggests that the photoproducts are formed from the singlet excited state (^{1}NB*) of the drug. Therefore the increase in the rate constant of the degradation of the Nabumetone, may be thought to be due to an increase in the concentration of this excited species via hydrogen bond formation with the solvent.

Keywords: Nabumetone; Photodegradation; UV-Vis absorption spectroscopy; Fluorescence; FTIR spectroscopy; Gas chromatography–mass spectrometry

1. Introduction

The photosensitivity disorders elicited by several drugs of the NSAID constitute a common type of the side effect associated with the widespread clinical use of this agents [1,2].

Nabumetone (4-(6-methoxy-2-naphthyl)butan-2-one) (Scheme 1), is a non-steroidal anti-inflammatory drug (NSAID) which also has analgesic properties. Nabumetone is a "prodrug" which in vivo is transformed into the acetic acid derivative, 6-methoxy-2-naphthylacetic acid, that is the pharmacological active form. Irradiation studies show that the metabolite is photolabile, giving in phosphate buffered saline aerated solutions two major compounds the 2-(1-hydroxyethyl)-6-methoxynaphthalene and the 6-methoxy-2-naphthaldehyde, this last compound through an oxidative photodegradation. This process has been described for related molecules, via a photodecarboxylation which has a higher quantum yield in aerated solutions. However, the methyl ester derivative which cannot undergo direct photodecarboxylation is reported to give upon irradiation in aerated acetonitrile the aldehyde as the only product of photodegradation [3].

There is little research about this relatively new drug, although there is some information about the photochemical and photobiological properties of the Nabumetone [4–6]. In this sense, it has been reported that Nabumetone is photodegraded in aqueous medium to give the 6-methoxy-2-naphthaldehyde as major photoproduct [4], as described for its active metabolite [7] and the (4-(6-methoxy-2-naphthyl)-3-buten-2-one) [4]. The presence of the major product produces important spectral changes in both absorption and emission spectra. The appearance of this compound, in aqueous medium, was initially observed when the solution was obtained by sonication of the sample, but not in other solvents even in concentrated solutions of the drug. These observations seem to indicate that the photodegradation process occurs only in aqueous media or that the photoproducts formed depend on the media in which the drug is irradiated. Therefore and taking into account that these drugs are often used as topic dosages it is important to know their behaviour in organic media. A satisfactory knowledge of drug's photoreactivity is necessary to understand their photobiological properties and to explain, or predict, the appearance of photosensitising side effects in new drugs. On this basis, in this paper, we report our investigation of the photoreactivity of Nabumetone in *n*-butanol solution. The photodegradative process was followed in typical laboratory conditions by light irradiation. The photoproducts (Scheme 2) formed were

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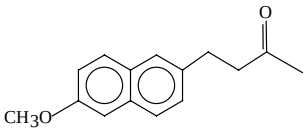
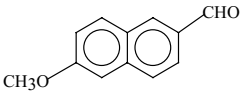
NABUMETONE

(4-(6-methoxy-2-naphthyl)butan-2-one)

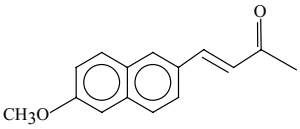


Scheme 1. The chemical structure of Nabumetone.

6-methoxy-2-naphthaldehyde



(4-(6-methoxy-2-naphthyl)3-buten-2-one)



Scheme 2. The chemical structure of the photoproducts formed by Nabumetone irradiation.

characterised (Scheme 2) by UV-Vis absorption and fluorescence emission spectroscopies as well as by FTIR spectroscopy and gas chromatography–mass spectrometry. The same compounds—6-methoxy-2-naphthaldehyde and the (4-(6-methoxy-2-naphthyl)-3-buten-2-one)—as those obtained in water were detected as photodegradation products.

2. Experimental

2.1. Materials

Nabumetone and *n*-butanol were purchased from Sigma.

The solubilisation of Nabumetone in *n*-butanol was carried out as follows: appropriate volumes of a given concentration of the drug in methanol were placed into a volumetric flask and the solvent was evaporated by slow passage of N_2. The *n*-butanol solution was added to the evaporated residue and the resulting solution was mechanical stirring until the drug was solubilised. The final Nabumetone concentration was 5×10^{-5} M.

2.2. Apparatus

UV-Vis absorption spectra were recorded on a Hitachi UV-Vis spectrophotometer, model 150-20. Fluorescence emission spectra were achieved on a Perkin-Elmer LS 50B Spectrofluorimeter. The instrumental response at each wavelength was corrected by means of a curve provided by the apparatus. For each sample, emission spectra were achieved immediately after the measurement of the absorption spectra, using excitation at 317 nm or variable and the emission range was 325–600 nm. The spectral slits used were 2.5 and 2.5 nm.

Irradiation of Nabumetone was carried out using a radiation source constructed with a screen with aluminium reflector installed in a plate which position can be modified. In this screen six fluorescence lamps (40 W per unit) are installed.

The emission lamp had a maximum peak emission at 365 nm. The incident light intensity (I_0) was detected by a potassium ferroxilate actinometer solution (0.006 M) at 365 nm and was 3.784×10^{-6} einstein l^{-1} s^{-1}.

A fixed volume of the *n*-butanol solution of the Nabumetone was placed in a ceramic plate in a fixed position into the plate and irradiated during different intervals of time. The resulting solution was evaporated and the corresponding residue was redissolved in CCl_4 to obtain the infrared spectra. Infrared absorption spectra were recorded with a Perkin Elmer 1730 FTIR spectrophotometer with He–Ne laser of 2 cm^{-1} resolution. We used a cell of CaF_2 windows of variable pathlength.

Gas chromatography–mass spectrometry (GC/MS) analysis were achieve with a Shimadzu QP 5000 Spectrometer with a GC17 gas chromatograph equipped with an J&V DB5 column. Electronic impact (70 eV) was used as ionisation technique.

For the gas chromatography–mass spectrometry determinations, a higher amount of solid Nabumetone was dissolved in *n*-butanol and was irradiated until the change of the absorption and emission spectra occurred. After irradiation, the sample was concentrated.

3. Results and discussion

3.1. Electronic spectra

Nabumetone had recently been shown to be associated with photodegradative processes in water [4]. During the degradative process, the appearance of a new band at 445 nm in the emission spectra was observed in aqueous solution. This band was not observed in other solvents, even in concentrated solutions of the drug. However, spectral modifications occurred, indicating that photodegradation also takes place in this medium.

For this reason, irradiation of Nabumetone was performed in aerobic conditions using *n*-butanol as solvent. Irradiation of *n*-butanol solution of the drug results in appreciable spectral changes.

The absorption spectra of Nabumetone (Fig. 1) in *n*-butanol presents two band systems centred, respectively, at 240–280 and 310–330 nm. As far as the absorption spectra are concerned, not change in the spectra structure or intensity are observed when the organic solution of the drug is irradiated. The emission spectrum of the drug

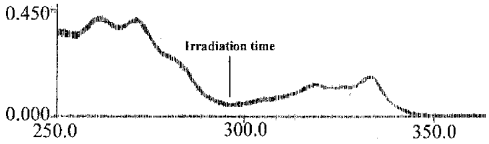


Fig. 1. Absorption spectra of Nabumetone (5.00×10^{-5} M) in *n*-butanol at different irradiation times.

presents a large non-structured band centred around 355 nm (Fig. 2a).

In this case, exposure to light does not induce the appearance of new bands, Fig. 2a, but the fluorescence intensity of the 355 nm band decreases with the time exposure of the sample, indicating that the new species are not or are less-fluorescent than the undegraded drug.

On this basis, Nabumetone photolability was followed by monitoring the changes of the emission band intensity with exposure time. Taking into account that the photodegradative process are not simple and several types of compounds are involved, the spectra were subjected to a deconvolution.

The deconvolution process is extremely sensitive to detect overlapped bands under the spectral contour, and it has been used successfully in the resolution of species in complex

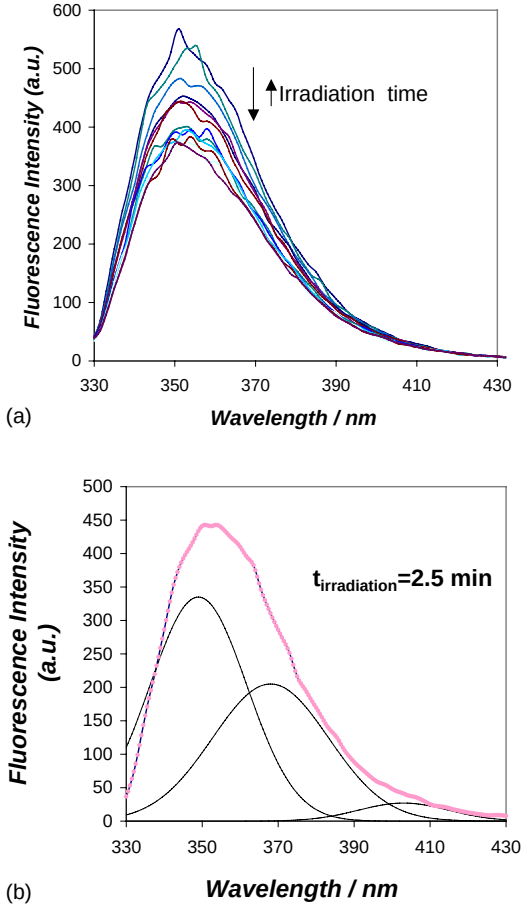


Fig. 2. (a) Emission spectra of Nabumetone (5.00×10^{-5} M) in *n*-butanol at different irradiation times; (b) curve fitting of the fluorescence spectra of Nabumetone irradiated in *n*-butanol medium.

Table 1
Fitting parameters of deconvolution of Nabumetone/*n*-butanol emission spectra at different irradiation times into Gaussian bands (λ and δ are in nm)

t (min)	A_1	λ_1	δ_1	A_2	λ_2	δ_2	A_3	λ_3	δ_3
0	500	352	16	135	375	20	14	410	16
0.5	470	352	15	155	374	18	18	410	14
1.0	415	350	16	165	372	18	21	406	13
1.5	372	350	16	165	371	18	21	404	13
2.0	335	350	16	220	366	19	23	403	13
3.0	235	349	15	220	366	19	23	403	13
3.5	225	349	13	235	364	20	20	405	16
4.0	205	349	13	240	363	20	22	404	16
4.5	180	348	13	245	362	20	23	402	16
6.0	135	348	10	290	359	20	28	400	16
6.5	120	347	9	300	359	20	28	400	17

mixtures. The spectral envelope was assumed to be the sum of a number "*N*" of Gaussian bands, whose emission intensities $F(\nu)$ are related to the frequency (ν) by the equation

$$F(\nu) = F_i(\nu_i) \exp\left(-\ln 2 \left[\left(\frac{\nu - \nu_i}{\delta_i}\right)^2\right]\right) \quad (1)$$

where $F_i(\nu_i)$ is the maximum emission intensity at a given frequency, and δ_i the width at half height.

Indeed, the fluorescence emission spectra can be fitted to several Gaussians (Fig. 2b), Table 1. The spectral contour, is reproduced by the sum of three Gaussian bands centred around 350 nm (A_1), 370 nm (A_2) and 400 nm (A_3), respectively. A_1 corresponds to the emission of the undegraded drug. The positions of the maxima of A_2 and A_3 are lower than the wavelengths at which the species formed through the effect of light in aqueous solutions emit. This suggests that the photoproducts formed are different in both media, or simply that the change in the nature of the environment shifts the position of their maxima. On comparing the position of the maximum of the emission band of the undegraded drug in water (355 nm) [4] and in *n*-butanol (350 nm), it is possible to observe that in the latter medium the position of the emission maximum is clearly blue-shifted, therefore the second option cannot be ruled out.

For comparative purposes, the emission spectrum of the 6-methoxy-2-acetyl naphthalene (a structural analogue of the carbonilic photoproduct formed in water) was obtained. The emission spectrum of this compound in *n*-butanol displays a maximum centred around 407 nm, which is strongly blue-shifted from the water where the band is centred around 440 nm. Therefore, A_3 may be structurally related with this compound and most likely corresponds with the 6-methoxy-2-naphthaldehyde, the major photoproduct formed in water from the active metabolite [3] and from the drug [4]. On this basis, it may be thought that A_2 corresponds to the other photoproduct formed in aqueous medium; that is (4-(6-methoxy-2-naphthyl)-3-buten-2-one).

As described in the previous paper, the evolution of the different species over time, in the photodegradative process,

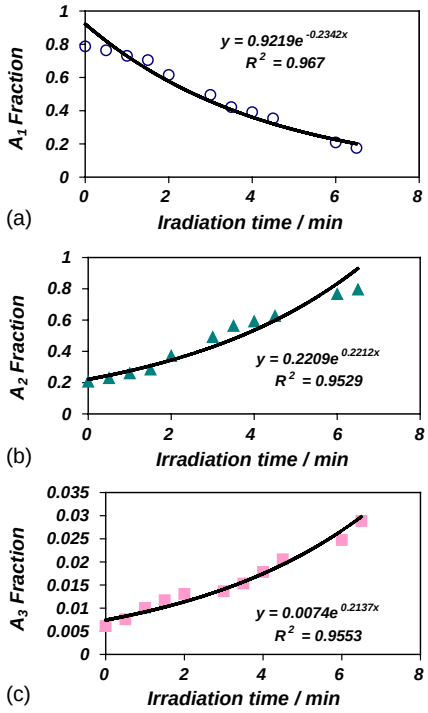


Fig. 3. Evolution of the different photoproducts formed by irradiation of Nabumetone in aqueous solution: (A) species that emits around 350 nm; (B) species that emits around 370 nm; (C) species that emits around 400 nm.

was followed through the change in the contribution of each emitting species to the total emission band. The proportion of each species, at the different irradiation time, was calculated as a ratio of the area of the corresponding Gaussian and the total area of the spectra.

Sample irradiation led to a variation in the proportion of each species with the exposure time (Fig. 3). As can be seen, the photodegradation of Nabumetone (A_1) followed first-order kinetics (Fig. 3A) to give the species that emit at 370 nm (A_2), and 400 nm (A_3), respectively.

The trend of the proportion of each species, A_2 and A_3, as a function of the time of irradiation (Fig. 3B and C, respectively) show that the proportion of both bands increase following first-order kinetics. The rate of the photodegradation of the drug and the appearance of the photoproducts were obtained from the fitting of the data. When the concentration of the light absorbing substance is sufficiently low, specially in aqueous solutions, and the light is weakly absorbed by the system, the quantum yield for the photodegradation, Φ, can be determined by the relation reported by Mill et al. [8]

$$\Phi = \frac{K_r}{2.3\varepsilon I_0 r} \quad (2)$$

where K_r is the apparent rate constant determined from deconvolution data, I_0 the incident light intensity, ε the molar extinction coefficient of the drug and r is a reactor constant. Experimentally determined value for r was 1.005 cm, and ε was 937 M^{-1} cm^{-1}.

Table 2
Rate constant, half-life and quantum yields of Nabumetone photodegradation and photoproducts formation in *n*-butanol

Compound	k (min^{-1})	$t_{1/2}$ (min)	Φ
Nabumetone (A_1)	0.234	3.0	0.47
Photoproduct 1 (A_2)	0.221	3.1	0.45
Photoproduct 2 (A_3)	0.214	3.2	0.44
Nabumetone (A_1)/in H_2O	0.0714 [4]	9.7 [4]	0.19

Table 2 lists the rate constant obtained as well as the quantum yield and half-life of the Nabumetone photodegradation and photoproducts formation. For comparative purposes, the quantum yield of degradation of the drug in aqueous medium was determined, using the rate constant value reported in the previous works [4] and $\varepsilon = 731\ M^{-1}\ cm^{-1}$ determined experimentally for the drug in water. The value obtained is also included in Table 2. As can be observed, the process of degradation of the drug (A_1) in the organic medium was much faster than in aqueous medium [4] and more efficient, with a $\Phi = 0.47$ and a half-life of $t_{1/2} = 3.0$ min.

The kinetic behaviour suggests that the photoproducts are formed directly from the singlet excited state of the drug, in good agreement with the data existing in the literature concerning the degradative pathways of its structural analogue Naproxen [7]. Thus a possible scheme for the formation of these photoproducts could be

$$NB \rightarrow {}^1NB^* \quad (v = I_{abs})$$

$${}^1NB^* \xrightarrow{K_1} NB$$

$${}^1NB^* \xrightarrow{K_2} A_2 + A_3$$

where I_{abs} is the absorbed light intensity, K_1 the sum of the rate constants of fluorescence and non-radiative decays, and K_2 the rate constant of the photodegradation reaction.

It is known that the presence of a butanone substituent leads to β-aryl-quenching of the excited ketone-like singlet

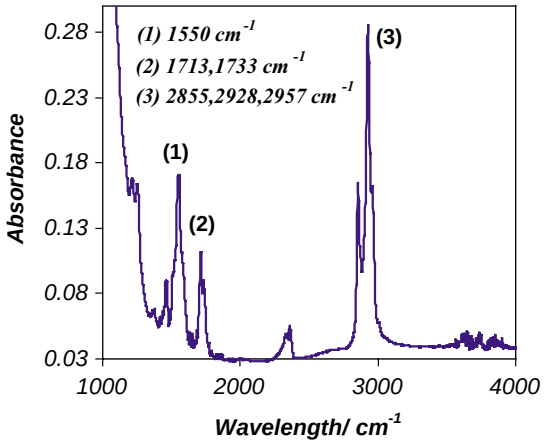


Fig. 4. IR spectra of the Nabumetone in CCl_4 of the residue of the drug irradiated in *n*-butanol.

[6]. In addition, recent reports have shown that Nabumetone has two preferred conformations with different lifetimes. In presence of protic solvents there is a high proportion of long lifetime species due to the hydrogen bond formation between the drug and solvent [9]. On this basis, and taking into account the kinetic scheme and the mechanisms of photoproducts formation of the Naproxen [7], the most likely cause of the increase in the photodegradation rate constant of the drug, in this medium, would be the increase in the concentration of $^{1}NB^{*}$ by means of the decrease in the deactivating routes via the butanone side chain.

3.2. Infrared study

FTIR spectra of the residue obtained after solvent evaporation of irradiated Nabumetone in *n*-butanol was obtained in carbon tetrachloride (Fig. 4).

The non-irradiated drug spectrum exhibited characteristic bands of the aromatic systems, the C–H aliphatic stretching vibration of the side chain, the carbonyl stretching band and the stretching vibration of the C–O group, corresponding to the ether [4].

When the *n*-butanol solution was irradiated, the spectrum was clearly modified as a consequence of photodegradation

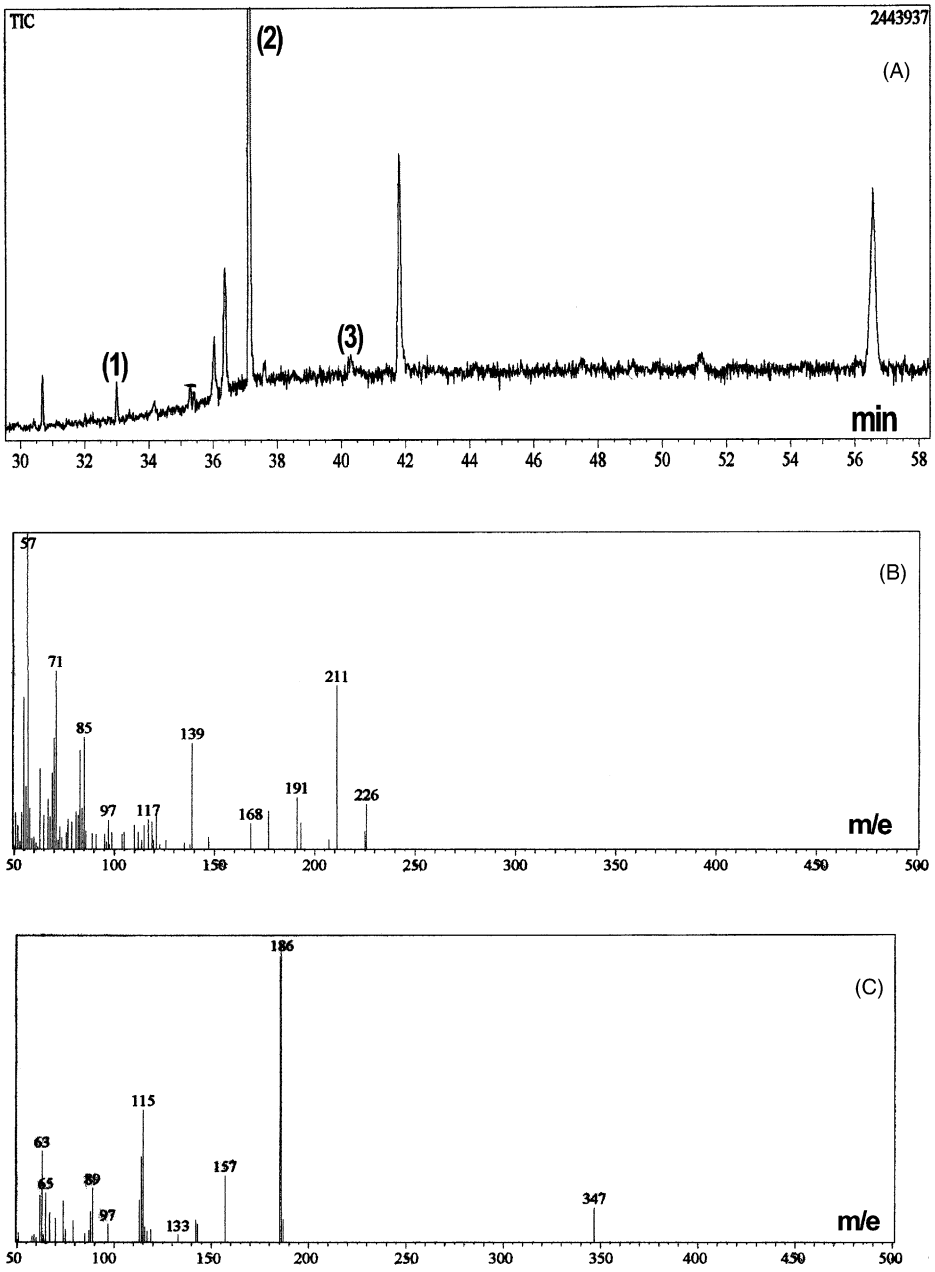


Fig. 5. GC/MS spectra of the Nabumetone irradiated in *n*-butanol: (A) chromatogram of the irradiated sample; (B) mass spectrum of (1) corresponding to the 6-methoxy-2-naphthaldehyde; (C) mass spectrum of (3) corresponding to the 4-(6-methoxy-2-naphthyl)-3-buten-2-one.

(Fig. 4). In this case, the same spectral changes in the bands corresponding to the C–C vibrations of the naphthalene ring (1550 cm^{-1}) and the carbonyl stretching band (around 1720 cm^{-1}) as in aqueous irradiated samples [4] were observed. Therefore, the same photoproducts must be formed in this organic medium, as shown by the spectroscopic results. In addition, an important change was observed in the bands centred around 2900 cm^{-1}, whose intensity underwent a strong increase. The band centred at around 2957 cm^{-1} and the shoulder appearing at around 2872 cm^{-1} are the two characteristic bands arising from the CH_2 group, corresponding to the in-phase and out-phase vibrations of the hydrogen atoms. The intensity of these bands is directly related to the proportion of this group and changes with the unit increase in chain length [10].

Thus, taking into account the increase in band intensity (relative to the 1550 cm^{-1} band), the most likely situation is that with the sample irradiation a compound other than those detected previously appears, increasing the signal of the CH_2.

Accordingly, the IR data are in good agreement with the formation of the same photoproducts as those formed in water together with a third compound that was not detected by the electronic spectroscopy.

3.3. GC/MS study

In this part of the work, the structures of the photoproducts formed, were determined by means of gas chromatography–mass spectrometry determinations. In order to obtain sufficient amounts of photoproducts, a higher amount of solid Nabumetone than that used for the spectroscopic studies was dissolved in *n*-butanol, and then irradiated until the change in the absorption and emission spectra occurred. After irradiation, the sample was concentrated and analysed.

As can be seen, the chromatogram has several peaks. The most intensive peaks, with retention times of around 36, 42 and 56 min, corresponds to different amounts of different ethers formed from *n*-butanol, such as dibutyl ether, butyl–propyl ether or most probably to oligomers of these compounds and butyl–pentyl ether. The formation of these compounds with a long hydrocarbon chain accounts for the strong increase in the intensity of the CH_2 band in the IR spectra.

In addition, the chromatogram (Fig. 5A) displayed three peaks, with retention times of 32.945 (1), 37.125 (2) and 40.225 min (3), respectively. These part of the chromatogram clearly resembled that obtained when the drug is irradiated in aqueous solution [4]. Indeed, the spectrum of the compound with a retention time 37.125 min (2), corresponded to the undegraded Nabumetone.

The mass spectra of the other two peaks are shown in Fig. 5B and C. As can be seen, the mass spectra of these compounds clearly correspond to the 6-methoxy-2-naphthaldehyde (Fig. 5B) and the (4-(6-methoxy-2-naphthyl)-3-buten-2-one) (Fig. 5C). Thus, the formation of the same photoproducts as those detected in water [4] is confirmed.

4. Conclusions

In the organic medium, *n*-butanol, Nabumetone undergoes a photodegradation process under laboratory conditions when it is irradiated with near UV light (365 nm). Small changes in the absorption and emission spectra occur as a result of the light irradiation, suggesting that the photodegradation process does not take place. Nevertheless, this process does occur; it follows a first-order kinetics and—in addition—it seems to be faster than in water, with a $\Phi = 0.47$ and $t_{1/2} = 3.0$ min. The photoproducts formed in this medium are the same as those observed in water, i.e., 6-methoxy-2-naphthaldehyde, as major product, and the (4-(6-methoxy-2-naphthyl)-3-buten-2-one).

The most likely origin of the increase in the photodegradation rate constant is the formation of hydrogen bonds between the drug and the solvent. This type of interaction reduces the deactivating routes of the Nabumetone singlet state via butanone side chain, which in turn increases the $^1NB^*$ concentration, from where the degradation process begins.

References

[1] I.E. Kochevar, Arch. Dermatol. 125 (1989) 824–826.
[2] M.A. Miranda, Phototoxicity of drugs, in: J.V. Castell, M.J. Gómez Lechón (Eds.), In Vitro Alternative Models to Animal Pharmaco-toxicology, Farmaindustria, Madrid, 1992, p. 239.
[3] F. Boscá, N. Canudas, M.L. Marín, M.A. Miranda, Photochem. Photobiol. 71 (2000) 173–177.
[4] M. Valero, S.M.B. Costa, J. Photochem. Photobiol. A: Chem. 157 (2003) 93–101.
[5] N. Canudas, J. Moulinier, D. Zamora, A. Sánchez, Pharmazie 55 (2000) 282–285.
[6] L.J. Martínez, J.C. Scaiano, Photochem. Photobiol. 68 (1998) 646–651.
[7] F. Boscá, M.L. Marín, M.A. Miranda, Photochem. Photobiol. 74 (2001) 637–655.
[8] T. Mill, W.R. Mabey, B.Y. Lan, A. Baraze, Chemosphere 10 (1981) 1281–1288.
[9] M. Valero, S.M.B. Costa, M.A. Santos, J. Photochem. Photobiol. A: Chem. 132 (2000) 67–74.
[10] L.J. Bellamy, The Infrared Spectra of Complex Molecules, Chapman & Hall, London, 1975.