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Photodegradation of *Nabumetone* in aqueous solutions

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Abstract

The photolability of the anti-inflammatory drug *Nabumetone* (4-(6-methoxy-2-naphthyl)-butan-2-one) was studied in water. 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 water followed first-order kinetics, with an half-life, $t_{1/2} = 9.7$ min whereas leading to different products.

In this medium, the side chain is photoxidised to 6-methoxy-2-naphthalene aldehyde, as major product, probably via a *Nabumetone* radical cation formation and the addition of singlet oxygen generated in the drug photolysis. In addition the (4-(6-methoxy-2-naphthyl)-3-buten-2-one) was detected. The most likely origin of the unsaturated compound is the dehydratation of an alcoholic derivative in alpha position of the naphthalene ring, produced via the same radical cation.

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

1. Introduction

Most drugs are subjected to some type of chemical decomposition, particularly when formulated as liquid dosage. Some of the consequences of degradation are that aged medicinal preparations no longer have the desired pharmacological potency. They may also exhibit physical manifestations of decomposition such as the bleaching that often follows photodegradation; or more seriously (but fortunately, more seldom), they may contain harmful decomposition products. The two most common causes of drug decomposition are hydrolysis or oxidation but their activity may also be lost due to photochemical degradation.

A number of drugs are capable of inducing photosensitizing skin side effects in patients treated with them. The photosensity 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. The most important advantage of *Nabumetone* is that it has an efficacy comparable with other NSAIDs but the incidence of side effects has been reported to be lower for *Nabumetone* than for acidic NSAIDs [3–5]. Furthermore, if necessary, the dose of *Nabumetone* can be increased without a simultaneous increase of adverse effects [6]. Several studies were carried out following complexation with cyclodextrins [7,8], determination of the active metabolites in biological samples [9,10] and the photochemical and photobiological properties of the drug [11,12]. *Nabumetone* is a "prodrug" which in vivo is transformed into the acetic acid derivative, 6-methoxy-2-naphthyl acetic acid, that it is the pharmacological active form. Irradiation studies show that the metabolite is photolabile, giving in phosphate buffered saline aerated solutions two major compounds the alcohol derivative and the 6-methoxynaphthaldehyde, 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 [13].

In recent reports *Nabumetone* has been associated with photosensitivity and skin lesions arising over photoexposed areas in a patient treated with the drug [14,15]. A satisfactory knowledge of drug's photoreactivity is necessary to understand their photobiological properties and to explain, or

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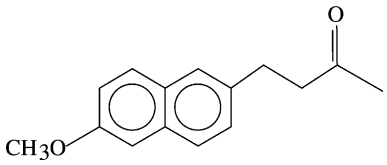
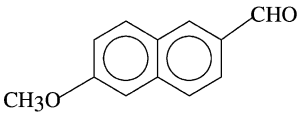
NABUMETONE

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

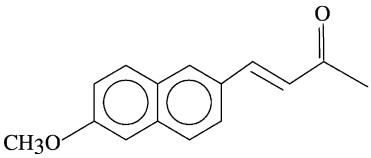


Scheme 1. The chemical structure of *Nabumetone*.

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.

predict, the appearance of photosensitizing side effects in new drugs. However, neither the structure of the products nor the kinetics of the degradative processes of *Nabumetone* have been studied.

In this paper, we report our investigation of the photoreactivity of *Nabumetone* in aqueous solution. The photodegradative process was followed in typical laboratory conditions by light irradiation. The photoproducts formed were characterised by UV-Vis absorption and fluorescence emission spectroscopies as well as by FTIR spectroscopy and Gas chromatography–mass spectrometry (GC–MS). The 6-methoxy-2-naphthaldehyde and the (4-(6-methoxy-2-naphthyl)-3-buten-2-one) were obtained as photodegradative products (Scheme 2). On the basis of spectroscopic and conductimetric data, the formation of the same products was also observed when the aqueous solutions were immersed in an ultrasonic bath.

2. Experimental

2.1. Materials

Nabumetone was purchased from Sigma. Bidistilled water was used for the preparation of all aqueous solutions.

The solubilisation of *Nabumetone* in aqueous solution 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 water solution was added to the evaporated residue and the resulting solution was mechanical stirring until the drug was solubilised. The final *Nabumetone* concentration was 0.05 mM.

2.2. Apparatus

Absorption spectra were recorded with a JASCO V-560 UV-Vis spectrophotometer. Steady-state emission measurements were recorded with a Perkin-Elmer LS 50B spectrofluorimeter with the sample holder thermostated. All data was stored in a computer. The instrumental response at each wavelength was corrected by means of a curve obtained using appropriate fluorescence standards (up to 400 nm) together with the one provided with the apparatus. For each sample, emission spectra were recorded immediately after the measurement of the absorption spectra, using excitation at 317 nm or variable and the emission range was 330–600 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. A fixed volume of the mechanically stirred aqueous 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 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, an excess of solid *Nabumetone* and a small amount of CCl_4, were added to the aqueous solution of the drug; the resulting mixture was irradiated until the change of the absorption and emission spectra occurred. CCl_4 promotes the degradative process in the case of the analogue Naproxen [13] and solubilizes the photoproducts formed, enabling higher amounts of them to be collected. After irradiation, both phases were separated and the aqueous mixture was extracted with *n*-hexane:ethyl acetate (1:1).

3. Results and discussion

3.1. Electronic spectra

NSAIDs are frequently associated with photodegradative processes [16,17] in which free radicals are involved. For

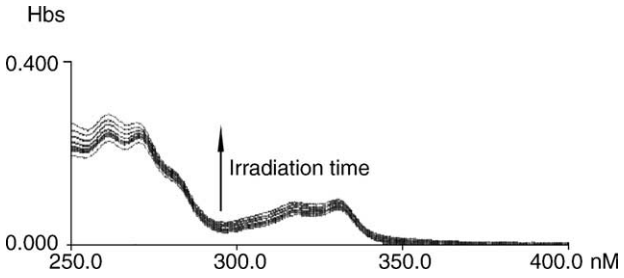


Fig. 1. Absorption spectra of aqueous *Nabumetone* (5.00×10^{-5} M).

this reason, irradiation of *Nabumetone* was performed in aerobic conditions using distilled water as solvent.

The absorption spectra of *Nabumetone* (Fig. 1) in water present three band systems centred, respectively, at 220 nm ($^1A_{1_g} \rightarrow {}^1B_b$), 240–280 nm ($^1A_{1_g} \rightarrow {}^1L_a$) and 310–330 nm ($^1A_{1_g} \rightarrow {}^1L_b$), as the 2-substituted naphthalene compounds [18–20]. The fine vibrational structure is clearly observed in the *Nabumetone* absorption spectra [7]. Irradiation of aqueous solution of the drug results in appreciable spectral changes.

As far as the absorption spectra are concerned, an increase of the absorbance is detected when the aqueous solution of the drug is irradiated (Fig. 1) but not change in the spectra structure is observed. At the four maxima, absorbance increases linearly with the time exposure. On comparing the rate of increase in the absorbance of the bands of each system, it is possible to observe that in the first band system, A_{260} increases faster than A_{270}; in the second one A_{317} increases faster than A_{330}. This observation suggests the appearance of a new species with absorption maxima close to 260 and 317 nm.

The emission spectra of the drug presents a large non-structured band centred around 355 nm (Fig. 2a).

In this case, light exposure, induces the appearance of a new band centred around 440 nm, Fig. 2a. The fluorescence intensity of the new band increases with the time exposure of the sample, with the concomitant decreases of the 355 nm band intensity appearing an isoemissive point around 410 nm.

The excitation spectra (Fig. 2b), of the irradiated samples, obtained by recording emission at 350, 370 and 440 nm change, clearly indicating that different emitting species are present in the ground state. A closer examination of the excitation spectra shows that at higher energies, there is a shift to the red but the spectra keep their shape. At the emission wavelength of 440 nm, the excitation spectra change their shape; two bands centred around 260 and 319 nm appear, in good agreement with the absorption results obtained.

Therefore, the spectral data obtained show that in the ground state, three species may coexist after excitation as a result of irradiating the sample with light.

Similar spectral changes had been previously observed in our laboratory when the drug was dissolved in aqueous solution but not in other solvents. *Nabumetone* aqueous solutions was initially prepared with a small sonication, since the drug is only sparingly soluble in this media. In these conditions (aqueous solution of *Nabumetone*, obtained by ultrasonication), the same changes in the emission and excitation spectra, were observed.

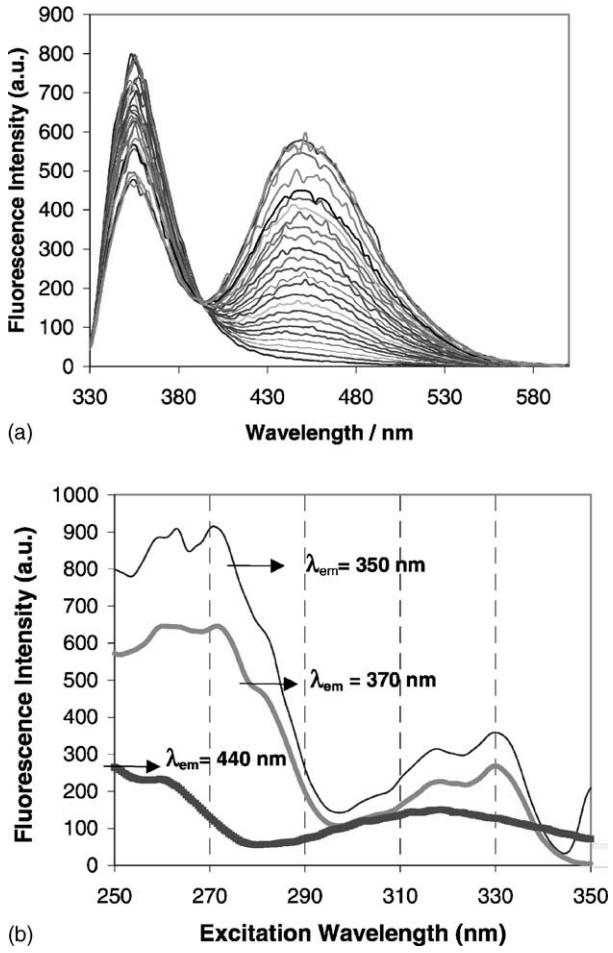


Fig. 2. (a) Emission spectra, (b) excitation spectra at different emission wavelengths of aqueous *Nabumetone* (5.00×10^{-5} M).

Experimental results showed that the band, centred around 440 nm in the emission spectra, is no longer present if the dissolution is achieved with mechanical stirring. In addition, the excitation spectra obtained by collecting at different emission wavelengths does not show any wavelength dependence. Therefore, it was quite conclusive that the preparation of the aqueous solutions with ultrasound triggers the effects observed.

The conductivity of aqueous solutions of *Nabumetone* (obtained by ultrasonication) was studied showing a dependence with the concentration characteristic to the dissociation of weak electrolytes.

From the dependence of the absorption and emission spectra to the pH, a pK_a value of 10.7 were determined for the weak electrolyte (data not shown).

The pK_a of 6-methoxy-2-naphthyl acetic acid, that is the pharmacological active form should be similar to that of

Naproxen (6-methoxy-(α-methyl-2-naphthyl acetic acid)) which has a $pK_a \cong 3.9$ [21] or 4.15 [22]. Thus, it is not likely that the electrolyte formed can be an acetic acid derivative, but most probably an alcohol derivative.

The spectral changes observed when the aqueous solution is irradiated, are the same as those observed in sonicated aqueous solution indicating that the same products must be involved.

It is known that ultrasonication of aqueous solutions has been shown to produces both OH radicals, and hydrogen atoms [23], that reacts with ketones. The fact that ultrasound and light produce the same products, seems to indicate that the reaction occurs in both cases via free radicals.

On this basis, *Nabumetone* photolability was followed by monitoring the changes of the emission bands 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 mixtures. The spectral envelope was assumed to be the sum of a number "*N*" of Gaussian bands, whose emission intensity $F(\nu)$ are related to the frequency (ν) by equation

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

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

Indeed, the fluorescence emission spectra can be fitted to several Gaussians (Fig. 3), Table 1. The spectral contour, is reproduced by the sum of four Gaussian bands centred around 355 nm (A_1), 390 nm (A_2) and 440 nm (A_3) and 450 nm (A_3). A_1 corresponds to the emission of the undegraded drug. The positions of the maxima of A_2 and A_3 are close to the wavelengths at which the changes in the excitation spectra occur, due to the species formed in the ground state through the effect of light and ultrasound. Therefore the excitation spectrum obtained at $\lambda_{em} = 370$ nm could be assigned to the absorption spectra of A_2 with the same form of the *Nabumetone* but slightly red-shifted. The corresponding one at $\lambda_{em} = 440$ nm, could be assigned to the absorption spectra of A_3 with two maxima centred around 260 and 319 nm, respectively.

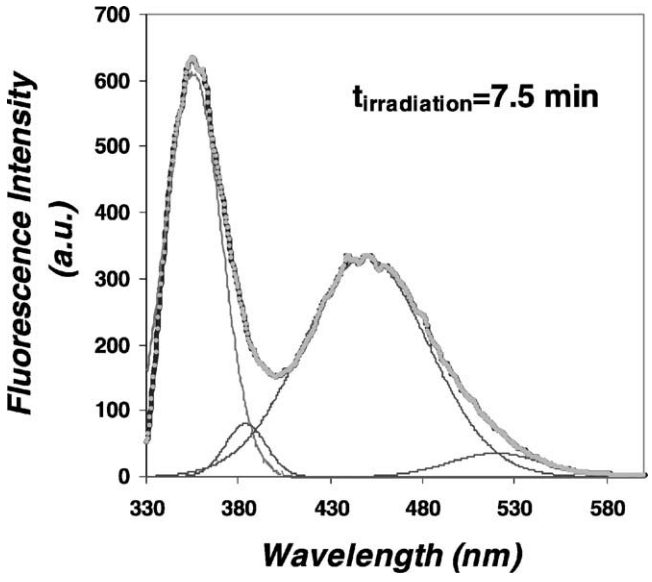


Fig. 3. Curve fitting of the fluorescence spectra of *Nabumetone* irradiated in aqueous medium.

On comparing these spectra with those existing in the literature corresponding to the photoproducts formed 6-methoxy-2-naphthyl acetic acid [13], it is possible to observe that considerable similarity exists, pointing to a structural analogy with the photoproducts formed from the prodrug *Nabumetone* and its active metabolite. The absorption spectrum of A_2 is very similar to that of the 6-methoxy-2-naphthyl acetic acid and the alcoholic photoproduct formed from it [13]. Taking into account the pK_a value obtained previously, A_2 cannot correspond to the active form 6-methoxy-naphthyl acetic acid or any other acidic compound therefore this compound must correspond with an alcoholic derivative of the drug.

The absorption spectra of the species that emits at 440 nm, A_3, are very close to the corresponding one of the carbonilic photoproduct formed from de active metabolite [13], which means that A_3 must be structurally related with this compound.

For comparative purposes, the absorption and emission spectra of the 6-methoxy-2-acetyl naphthalene (carbonilic photoproduct of the structural analogue AINE Naproxen) were obtained. The absorption spectrum presents a maximum centred around 310 nm, as described previously for this compound [24]. As expected, the fluorescence spectrum of this compound shows a broad band centred around 440 nm.

It may therefore be assumed that, in aqueous media, *Nabumetone* is degraded, to give 6-methoxy-2-naphthalene derivatives that are structurally related to the photoproducts formed from its analogues 6-methoxy-2-naphthyl acetic acid and Naproxen [17,24].

In order to obtain more information about the species formed in the photodegradative process, the evolution of the different species over time, was followed through the change in the contribution of each emitting species to the total emission band. The proportion of each specie, at the different irradiation time, was calculate 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. 4). As can be seen, the photodegradation of *Nabumetone* (A_1) followed first-order kinetics (Fig. 4A), to give the species that emit at 390 nm (A_2), 440 nm (A_3) and 510 nm (A_4), respectively.

Table 1
Fitting parameters of deconvolution of *Nabumetone*/H_2O emission spectra at different irradiation times into Gaussian bands

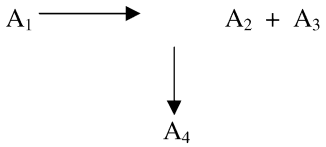
t (min)	A_1	λ_1	δ_1	A_2	λ_2	δ_2	A_3	λ_3	δ_3	A_4	λ_4	δ_4
0	790	355	20	80	395	14	25	428	45	–	–	–
0.5	780	356	20	77	395	15	42	430	45	–	–	–
1.0	770	356	19	85	395	14	55	441	45	–	–	–
1.5	750	356	19	80	394	16	67	445	45	–	–	–
2.0	720	356	19	80	393	16	88	445	45	–	–	–
2.5	760	355	18	90	389	16	120	445	47	–	–	–
3.0	760	355	18	95	388	16	120	444	47	–	–	–
3.5	680	355	18	90	386	16	140	446	47	–	–	–
4.0	660	355	18	90	385	15	162	448	47	–	–	–
4.5	660	355	18	90	386	15	182	450	47	–	–	–
5.0	650	355	18	80	386	15	209	450	45	–	–	–
5.5	640	355	18	70	384	15	229	450	45	–	–	–
6.0	630	355	17	85	384	13	248	451	46	–	–	–
6.5	630	355	17	82	382	12	272	450	46	–	–	–
7.0	610	355	18	75	387	12	300	449	40	32	515	27
7.5	610	355	18	80	384	13	332	449	40	35	520	30
8.0	590	355	18	60	384	15	355	450	40	35	520	30
8.5	590	355	18	65	384	14	380	451	40	35	520	30
9.0	550	355	18	60	384	13	400	451	40	35	520	30
9.5	540	355	18	60	384	13	425	451	40	40	520	30
10.0	550	355	18	65	384	13	445	451	39.5	44	520	30
11.0	560	355	18	55	384	11	490	451	39	52	516	33
12.0	480	355	18	55	384	11	540	451	38	70	515	29
13.0	475	356	21	–	–	–	560	451	37	80	515	29
14.0	465	355	21	–	–	–	570	450	37	92	510	30
15.0	460	355	21	–	–	–	570	450	37	92	505	35

λ and δ are in nm.

The degradation of the drug occurred with a half-life of $t_{1/2} = 9.7$ min.

The trend of A_2 as a function of the time of irradiation (Fig. 4B) shows that the proportion of the band increased initially, but after 4 min the compound was degraded following first-order kinetics, with $t_{1/2} = 5.2$ min. This type of behaviour indicates that the species emitting at 390 nm (A_2) is initially formed from the drug but also undergoes a degradation process to give A_3 or/and A_4.

The variation of the band centred at 440 nm with time, did not follow first-order kinetics (Fig. 4C). The kinetic behaviour of A_3 suggests that this form would be involved in the disappearance and formation of several of the species present. A_4 appeared after 6 min of irradiation, following first-order kinetics (Fig. 4D) with $t_{1/2} = 4.4$ min. The time delay appearing in the kinetics of A_4 seems to indicate that it is a secondary product formed. Comparing the kinetic behaviour of A_2 and A_4 and the respective rate constants of disappearance and appearance, respectively, it is most likely that A_4 would be formed from A_3. Thus, a possible scheme of the formation of these photoproducts could be:



3.2. Infrared study

FTIR spectra of solid *Nabumetone* as well as of the residue obtained after solvent evaporation of the irradiated samples were obtained in carbon tetrachloride (Fig. 5).

The non-irradiated drug spectrum (Fig. 5a) had characteristic bands of the aromatic systems: the C–H stretching vibrations, which absorb at 3000 cm^{-1}, and the C–C skeletal ring breathing mode absorptions, at around 1600–1500 cm^{-1}.

The C–H aliphatic stretching vibration of the side chain appears at around 2900 cm^{-1}. The band centred at 1721 cm^{-1} can be assigned to the carbonyl stretching band. Below 1200 cm^{-1}, the stretching vibration of the C–O group, corresponding to the ether, and the skeletal spectrum of the drug appear [25].

When aqueous solution was irradiated the spectrum was clearly modified as a consequence of photodegradation (Fig. 5b).

First, in the spectrum of the aqueous residue a strong increase in the absorption intensity of the band corresponding to the C–C vibrations of the naphthalene ring (1550 cm^{-1}) was observed indicating the existence of the interaction between a π cloud and the ring or an atom attached directly to the ring with a lone pair of electrons [25]. Also, the carbonyl band showed noticeable changes. This band appeared as a doublet centred around 1733 and 1713 cm^{-1}. This situation has been reported for many benzaldehydes showing

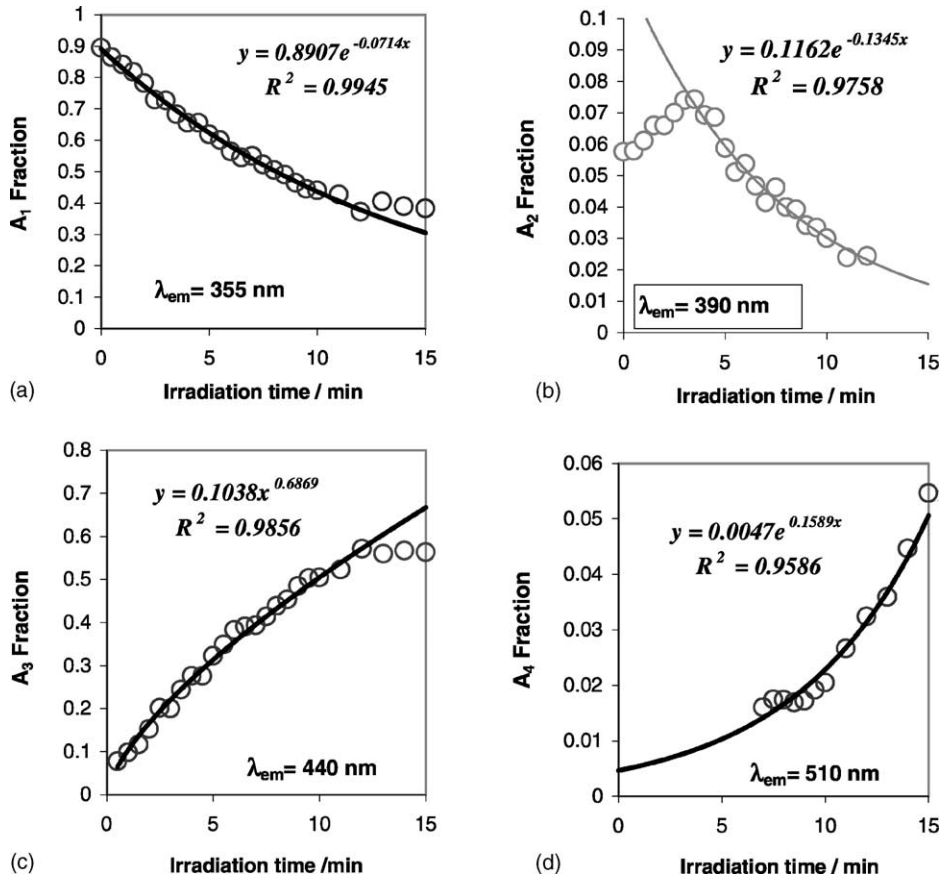


Fig. 4. Evolution of the different photoproducts formed by irradiation of *Nabumetone* in aqueous solution.

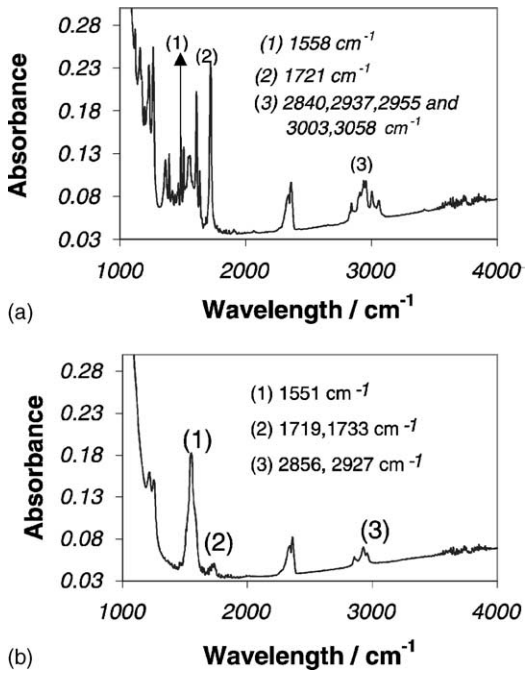


Fig. 5. IR spectra of the *Nabumetone* in CCl_4: (a) *Nabumetone* solid non-irradiated, (b) residue of the drug irradiated in water.

two bands in the carbonyl region due to Fermi resonance [25].

These results suggest that the side chain is oxidised to give an aldehyde or/and conjugated insaturation directly bound to the naphthalene ring, as described, in the case of the aldehyde, for its active form [13].

It was not possible to detect the presence of the alcoholic derivative, but on the basis of the conductivity data, and taking into account that this photoproduct must correspond with A_2 specie which is disappearing with the time (and therefore it is in a very low concentration) its presence cannot be ruled out.

The IR data shown that A_4 must have an structure similar to A_3, its signal overlapping with that of this compound.

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. With the aim to obtain an enough amount of photoproducts an excess of solid *Nabumetone* and a small amount of CCl_4, were added to the aqueous solution of the drug; the resulting mixture was irradiated until the change of the absorption and

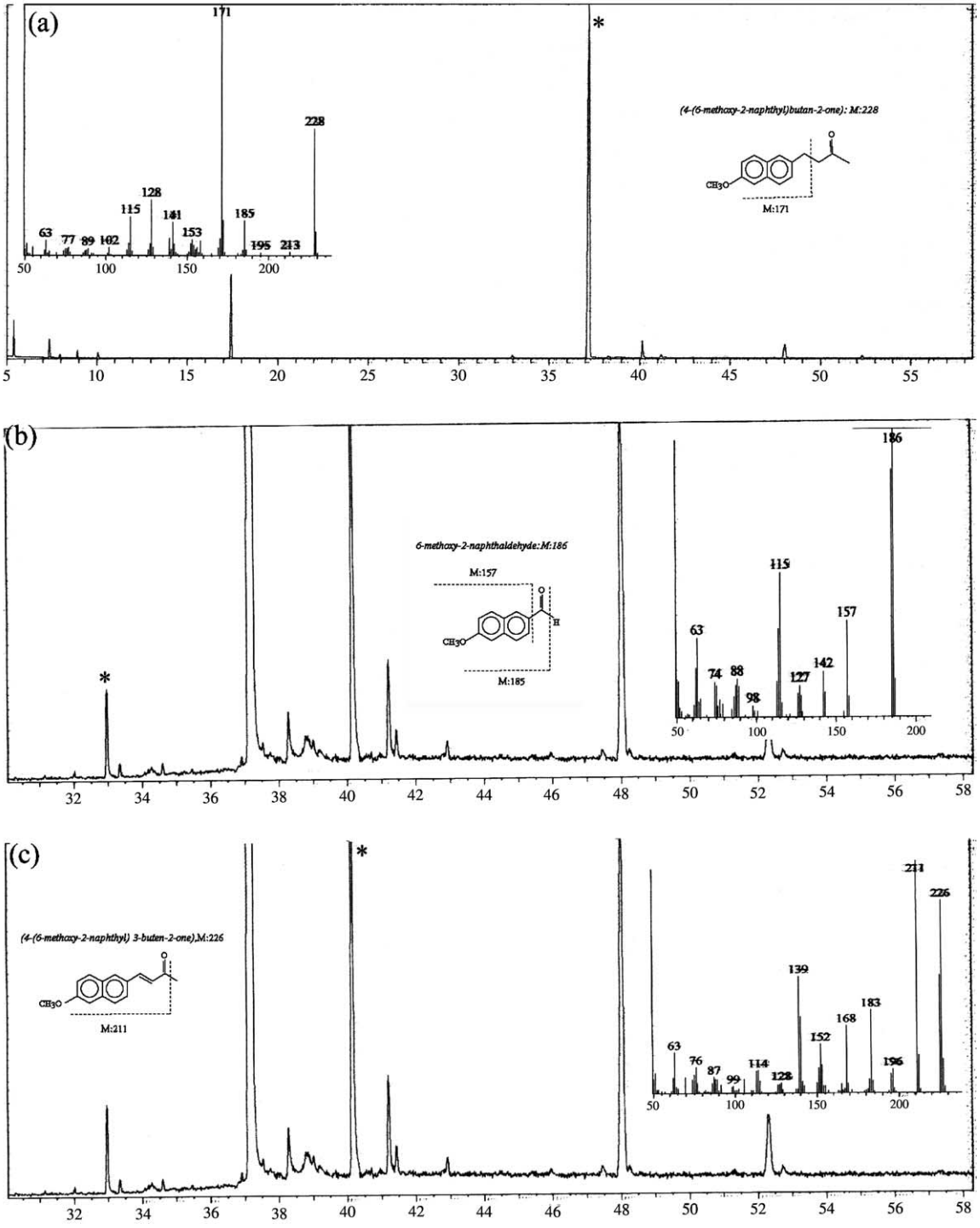


Fig. 6. GC–MS spectra of the *Nabumetone* irradiated in water, CCl_4 phase.

emission spectra occurred. After irradiation, both phases were separated and the aqueous phase was extracted with *n*-hexane:ethyl acetate (1:1) and concentrated. Both organic phases were analysed.

As expected, the most concentrated phase is that of CCl_4 and the peaks detected are therefore most clearly observed. For the above reasons, the results obtained on studying this phase will be discussed first. As can be seen the chromatogram of this phase (Fig. 6) presents three peaks, with retention times of 32.917, 37.125 and 40.075 min, respectively.

The mass spectrum of the most intensive peak (t = 37.125 min) is shown in the inset of Fig. 6a. Two peaks with M: 228 and 171 appear, corresponding to the structures

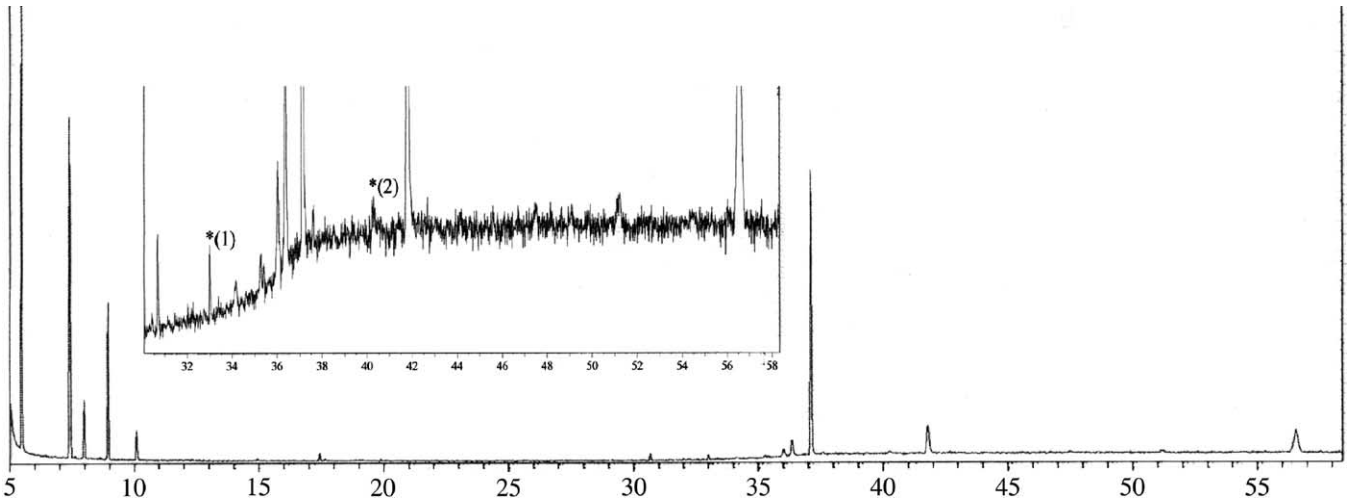


Fig. 7. GC–MS spectra of the *Nabumetone* irradiated in water, aqueous phase. Inset: peaks corresponding to the photoproducts formed (1) 6-methoxy-2-naphthaldehyde and (2) 4-(6-methoxy-2-naphthyl)-3-buten-2-one.

included into the spectrum, and therefore to the undegraded *Nabumetone*. The peak with retention time of 32.917 min (Fig. 6b) shows a mass spectrum with two major peaks, with *M*: 186 and 115, corresponding to the indicated structures. Therefore, the formation of the same photoproduct as that from the active metabolite of the drug, 6-methoxy-2-naphthaldehyde, is confirmed.

Additionally, the peak appearing at 40.075 min, (Fig. 6c) has a mass spectrum with two characteristics peaks at *M*: 226 and 211, corresponding to the second photoproduct formed an the ion resulting of its fragmentation (structures included in the spectrum). In this case, the major photoproduct formed is (4-(6-methoxy-2-naphthyl)-3-buten-2-one). The presence of this compound (with a π cloud cojugated with the ring) is in good agreement with the IR data.

In addition other chlorates-derivatives have been detected in different proportions, giving clear proof of the nucleophilic addition of the solvent.

The same products were detected in the aqueous phase (Fig. 7), but in lower concentration than in CCl_4 (in good agreement with the partition coefficient of the photoproducts).

Therefore using GC–MS the formation of the 6-methoxy-2-naphthaldehyde in aqueous media as major product was verified. In addition the (4-(6-methoxy-2-naphthyl)-3-buten-2-one) was also detected.

The rest of the peaks that appear in the chromatogram were assigned to traces of plastics coming from the laboratory material. Taking into account the results described in previous sections, the most probably origin of the latter compound is the dehydratation of an alcoholic derivative in alpha position of the naphthalene ring.

The formation of the same aldehyde derivative in the dark in aqueous solutions exposed to ultrasound radiation seems to indicate that in this case OH radicals, which are generated, may catalyse the formation of peroxide radicals in the presence of the dissolved oxygen and H abstraction from alkyl chains. It is known that *Nabumetone* is able to generate singlet oxygen through a triplet–triplet energy transfer (type II photodynamic mechanism) [11,12] that may react with itself to yield peroxide compounds [12].

Therefore the degradative process must occur via naphthalene-like radical cation formation from the singlet state of the drug, as demonstrated by other authors [11], followed by formation of the benzylic radical. Thus, the singlet oxygen can interact in the allylic position giving rise to a hydroperoxide intermediate in good analogy to what happens with the drug metabolite [13] and the structural analogue, Naproxen [17]. This compound can rearrange to give 6-methoxy-2-naphthaldehyde and eliminate acetone.

4. Conclusions

In aqueous medium, *Nabumetone* undergoes a photodegradation process in laboratory conditions when is irradiated with near UV light (365 nm). Noticeable changes in the absorption and emission spectra occurred as a result of the photodegradation, allowing to follow the degradative process with these techniques. The photodegradation process follows first-order kinetics, with $t_{1/2} = 9.7$ min. The photoproducts formed in this medium are the 6-methoxy-2-naphthaldehyde, as major product, and the (4-(6-methoxy-2-naphthyl)-3-buten-2-one).

Peroxidation of the side chain via benzyl radical addition followed by scission of the radical could be considered a possible mechanism to account for the formation of the aldehyde. The most probably origin of the unsaturated compound is the dehydratation of the alcoholic derivative in alpha position of the naphthalene ring, produced via the same radical cation.

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