

The improved photostability of naproxen in the inclusion complex with 2-hydroxypropyl- β -cyclodextrin

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Abstract

The aim of this work was the preparation of the inclusion complex of naproxen with 2-hydroxypropyl- β -cyclodextrin (HP- β -CD) in order to improve the physical and chemical properties of naproxen. The molecular inclusion complexes of naproxen with HP- β -CD were prepared by using the co-precipitation method in the solid state with the molar ratio of 1:1. The structure of the obtained complex was characterized by using FTIR, ¹H NMR, UV-Vis and XRD methods. The testing of naproxen photostability by the UV-Vis method indicated the degradation to aromatic ketone, 2-acetyl-6-methoxynaphthalene. FTIR analysis showed that the degradation has started 15 days after the exposure of naproxen to daylight while the inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin was photostable for a period of 30 days.

Keywords: naproxen, photodegradation, 2-hydroxypropyl- β -cyclodextrin, inclusion complex.

Available online at the Journal website: <http://www.ache.org.rs/HI/>

Naproxen, (+)-(S)-2-(6-methoxynaphthalen-2-yl)propanoic acid, is a derivative of 2-arylpropionic acids (profen drugs) which, in therapeutic doses, reduces the biosynthesis of prostaglandin and fever [1]. It exhibits anti-inflammatory and analgesic effects, relieves the symptoms of rheumatic diseases and other conditions accompanied by inflammation and the acute pain of moderate severity. Of two enantiomers of naproxen only the S-form is active.

Naproxen is a photosensitive and low soluble molecule which can be degraded under the influence of light by giving pharmacologically inactive products. A great number of published works were presented in the ways to improve the solubility of naproxen. For the improved solubility Mura and colleagues developed solid naproxen and chitosan systems [2,3] and triple systems of naproxen, amino acids and hydroxypropyl- β -cyclodextrin [4]. Various synthetic polymers were used as drug carriers in order to achieve the efficient and targeted delivery systems for a satisfactory therapeutic application. Agglomerated crystals of naproxen with hydroxypropyl cellulose improved the compactness [5]. A diblock copolymer of poly(ethylene- β -methacrylic acid) (PEO- β -PMAA) was synthesized by the atom transfer

radical polymerization and applied to the pH-dependent release of naproxen embedded into the core of the micelle [6]. The obtained results provided the potential use of the PEO- β -PMAA micelle system for a targeted delivery of various hydrophobic drugs in the small intestine. The interactions of poly(vinylpyrrolidone) (PVP) with ibuprofen and naproxen were also studied [7]. The influence of the drug on the glass transition, solubility and specific types of hydrogen bonding interactions were analyzed [8].

Cyclodextrins and their derivatives are suitable drug carriers because their molecule can host another substance in its cavity. The inclusion complex of naproxen with β -cyclodextrin increased the solubility and the drug release rate [9,10]. The interactions in inclusion complexes of α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin and dimethyl- β -cyclodextrin with naproxen, ibuprofen and panadol were examined [11]. The inclusion complexes of cyclodextrin and its derivatives were used to improve the physical and chemical properties of the drugs (solubility, vapor, odor, stability, etc.). A great number of researches proved that the solubility and stability of the drugs are increased, e.g., atenolol [12–14], nifedipine, nicardipine [15–17], amlodipine [18,19] and allicin [20]. The solubility of the usnic acid was improved by complexation with β -cyclodextrin (β -CD:UA) which is incorporated in liposomes [21].

It was observed that naproxen absorbed UV irradiation up to 360 nm and, in the presence of oxygen, lead

SCIENTIFIC PAPER

UDC 615:547:543.5

Hem. Ind. 69 (4) 361–370 (2015)

doi: 10.2298/HEMIND131128050I

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Paper received: 28 November, 2013

Paper accepted: 17 June, 2014

to its direct degradation. As a result of photodegradation, the obtained molecules were more hydrophobic with the increased toxicity which, compared to naproxen [22], reduced the pharmacological activity and safety of the drug administration. Photodegradation products of naproxen include 4-isobutylacetophenone, 1-(6-methoxy-2-naphthyl)ethanol and 2-acetyl-6-methoxynaphthalene. Both keto analogues of naproxen belonged to the group of aromatic ketones, that presence increases the rate of photodegradation during the light exposure. Aromatic ketones moved the molar absorptivity towards higher wavelengths and consequently acted as more photosensitive agents [23]. A recent research showed the improved photostability of the usnic acid and piroxicam in the inclusion complexes with 2-hydroxypropyl- β -cyclodextrin (HP- β -CD) [24,25].

The aim of this work was the preparation of the inclusion complex of naproxen with HP- β -CD, its structural characterization and the naproxen photosensitivity enhancement. The molecular inclusion complex based on naproxen and HP- β -CD, as a complexing agent, was prepared by the chemical co-precipitation method in the solid state and in the molar ratio of 1:1. For the structural characterization of the complex, a complexing agent, naproxen, the corresponding physical mixture of naproxen and HP- β -CD, the methods of nuclear magnetic resonance ($^1\text{H-NMR}$), X-Ray diffraction (XRD) and Fourier transform infrared spectrometry (FTIR) were used. For the investigation of the impact in the photostability of naproxen, the FTIR method and ultraviolet and visible spectroscopy (UV-Vis) were used for the analysis of photosensitive groups of naproxen in a pure and complexed form.

EXPERIMENTAL

Material and methods

Naproxen was supplied from Megafine Pharma Ltd. (99.67% purity), while 2-hydroxypropyl- β -cyclodextrin (97%) and potassium bromide (spectroscopic grade) were supplied from Merck, Darmstadt. Other solvents and reagents used were of p.a. purity.

Preparation of inclusion complex

The inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin was obtained by the co-precipitation method with the molar ratio of the reactants 1:1. The measured amounts of naproxen (230.259 mg) and 2-hydroxypropyl- β -cyclodextrin (1541.54 mg) were suspended in distilled water (150 cm³). The solution was mixed at room temperature for 48 h, protected from the light. In order to carry out the dissolution and due to the poor solubility of naproxen, the prepared solution was then subjected to ultrasound for 1 h. The ultrasound device Sonic (Niš, Serbia), and an ultrasonic

bath with the dimensions A:B:H = 300 mm×151 mm×200 mm, with 8 dm³ volume, were used under the following conditions: the temperature 30 °C, the ultrasound wave frequency 40 kHz and the power of 150 W, the total nominal power of 3×50 W. After the treatment by ultrasound, this solution was evaporated in a vacuum evaporator at 50 °C protected from the light, to the volume of approximately 20 cm³, and then dried in a desiccator above the concentrated sulfuric acid at 25 °C. After drying, a white crystalline complex was obtained and as such it was used for further investigations in this work.

Preparation of physical mixture

Physical mixtures were prepared by simple mixing of naproxen with 2-hydroxypropyl- β -cyclodextrin as complex agents in the mole ratio of 1:1.

Fourier transform infrared spectrometry (FTIR)

FTIR spectra of the samples were recorded by using the technique of thin transparent pills with potassium bromide, spectroscopic purity, under vacuum at the pressure of 200 MPa. Using this method, the following was analyzed: naproxen, 2-hydroxypropyl- β -cyclodextrin, the inclusion complex naproxen:2-hydroxypropyl- β -cyclodextrin and a physical mixture of naproxen and 2-hydroxypropyl- β -cyclodextrin with the measured 150 mg KBr and 0.2 mg samples. KBr tablets, with naproxen and the complex naproxen:2-hydroxypropyl- β -cyclodextrin, were exposed to daylight and, in certain time intervals, FTIR spectra were recorded.

For all the samples, the recording was carried out in the area of wave numbers from 4000 to 400 cm⁻¹ on the FTIR spectrophotometer Bomem Hartmann & Braun MB-series. The spectra were processed by using the Win-Bomem Easy software.

Nuclear magnetic resonance spectrometry ($^1\text{H-NMR}$)

$^1\text{H-NMR}$ spectra of the samples of the inclusion complex naproxen:hydroxypropyl- β -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin and naproxen were made on the Bruker AC 250 E NMR spectrometer with operating frequencies of 250 MHz, in a 5 mm diameter glass cuvette at room temperature. D₂O was used as a solvent.

X-ray diffraction (XRD)

X-ray diffraction was performed on the Phillips PW 1030 powder diffractometer by exposing the samples to monochrome CuK α radiation, $\lambda = 1.54178 \text{ \AA}$, and analyzed under the angle 2θ between 5 and 45° with 0.05° increments and recording time, $\tau = 5 \text{ s}$. The voltage and the strength of the electric current were 40 kV and 20 mA, respectively.

Ultraviolet and visible spectrophotometry (UV–Vis)

The sample was prepared by dissolving 2.5 mg of naproxen in 10 cm³ of distilled water. The quartz glass cuvette of dimensions 1 cm×1 cm×4.5 cm was used. The recordings were performed in the wavelength range of 200–800 nm using the Varian Cary 100 spectrophotometer while distilled water was used as a blind test.

RESULTS AND DISCUSSION

The structural characterization of the obtained molecular inclusion complex naproxen:2-hydroxypropyl- β -cyclodextrin, a complexing agent, naproxen and the corresponding physical mixtures were carried out by FTIR, ¹H-NMR, XRD and UV–Vis methods. For monitoring the formed photodegradation products of naproxen, FTIR and UV–Vis methods were applied. XRD diffraction patterns of naproxen, 2-hydroxypropyl- β -cyclodextrin, the physical mixture and the inclusion complex naproxen:2-hydroxypropyl- β -cyclodextrin are shown in Figure 1.

The comparative analysis of XRD diffraction patterns (Fig. 1) was used to observe the difference at some peaks in the diffraction patterns of the complex naproxen:2-hydroxypropyl- β -cyclodextrin, naproxen, 2-hydroxypropyl- β -cyclodextrin and the physical mixture of naproxen and 2-hydroxypropyl- β -cyclodextrin. Diffractogram of 2-hydroxypropyl- β -cyclodextrin (Fig. 1, data d) had two wide peaks with the maxima at 11.7 and 18.5° which did not show clearly defined reflec-

tions and the disordered crystal structure corresponded to the amorphous structure. The presence of well-structured sharp peaks with the maxima at 6.5, 12.6, 13.4, 16.6, 18.0, 18.8, 19.9, 20.6, 22.1, 22.5, 23.5, 23.9 and 28.2° with clearly defined reflections in the XRD diffractogram of naproxen (Fig. 1, data c) confirmed its crystalline structure. In the XRD diffractogram of the physical mixture of naproxen and 2-hydroxypropyl- β -cyclodextrin (Fig. 1, data a) characteristic peaks of naproxen with the maxima at 6.6, 12.6, 18.9, 20.6, 22.5 and 23.5° and wide peaks with the maximum at 11.7 and 18.5° derived from 2-hydroxypropyl- β -cyclodextrin were present. The results of the physical mixture indicated that there was no molecular interaction between the molecules of the guest and the host, *i.e.*, the diffraction of the physical mixture presented the sum of diffraction patterns of naproxen and 2-hydroxypropyl- β -cyclodextrin. The diffraction pattern of the inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin did not contain the peaks that are characteristic for diffractograms of naproxen and HP- β -CD. The loss of the peaks at 6.5, 13.4, 16.6, 18.0, 19.9, 21.1, 23.9 and 28.2°, and the peaks with the reduced intensity present at 12.6, 18.8, 20.6, 22.5 and 23.5°, which originated from naproxen in the diffraction pattern of the inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin (Fig. 1, data b), indicated that the drug molecules were protected from X-rays by the inclusion of the guest molecules in the hydrophobic cavities of the host molecule.

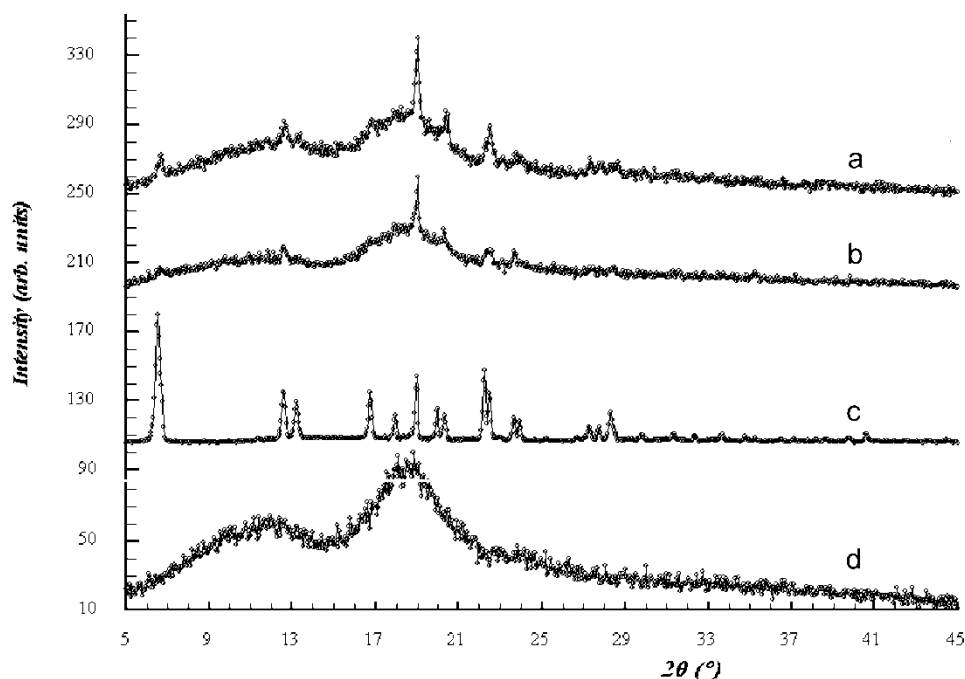


Figure 1. XRD diffraction: physical mixture of naproxen and 2-hydroxypropyl- β -cyclodextrin (a), inclusion complex naproxen:2-hydroxypropyl- β -cyclodextrin (b), naproxen (c) and 2-hydroxypropyl- β -cyclodextrin (d).

The numbering of C atoms at naproxen and glucopyranose units of 2-hydroxypropyl- β -cyclodextrin was shown in Fig. 2, while the results of $^1\text{H-NMR}$ analysis are given in Table 1.

The $^1\text{H-NMR}$ analysis of the complex of naproxen:2-hydroxypropyl- β -cyclodextrin (Table 1) showed the presence of a multiplet at δ 7.0 to 7.85 ppm which originated from the proton of naphthalene in the naproxen structure, but of a significantly lower intensity. The signal at δ 1.52 ppm assigned to protons in the position 3 of the CH_3 groups of naproxen is also present in the $^1\text{H-NMR}$ spectrum of the complex, but of lower intensity and shifted for +0.08 towards higher values of δ units. On the other hand, all of the signals originating from the protons of 2-hydroxypropyl- β -cyclodextrin glucopyranose units are present in the spectrum complex. The triplet at δ 3.975 ppm assigned to H_3 protons and the doublet at δ 1.125 assigned to H_9 protons from 2-hydroxypropyl- β -cyclodextrin complex, are moved to higher values of δ units (Table 1), to +0.045 and +0.065, respectively. The greatest displacement ($\Delta\delta = -0.1$ ppm) in the spectrum of the complex showed the signals at δ 3.9 ppm, which corresponds to H_6 protons of 2-hydroxypropyl- β -cyclodextrin glucopyranose units. Compared to naproxen and 2-hydroxypropyl- β -cyclodextrin, these movements in the $^1\text{H-NMR}$ spectrum of the naproxen:2-hydroxypropyl- β -cyclodextrin complex indicated that there were non-covalent interactions between H_3 protons of the guest molecules and H_3 , H_6

and H_9 protons of the host molecules, *i.e.*, there was a formation of a supramolecular structure by the type of the inclusion.

In the FTIR spectrum of naproxen (Fig. 3, curve a) there was a wide absorption band of the medium intensity with the maximum at 3215 cm^{-1} attributed to the valence vibrations of OH groups from carboxylic acids, $\nu(\text{OH})$.

The weak absorption band at 3002 cm^{-1} originated from CH valence vibrations of the aromatic part of the structure. In the FTIR spectrum of naproxen (Fig. 3, curve a), the characteristic band with a very high intensity and the maximum at 1727 cm^{-1} was the result of the valence vibration of C=O group from carboxylic acids, $\nu(\text{C=O})$, which is consistent with the investigations of other authors [8,26]. The weak band at 1416 cm^{-1} and the medium intensity band with the maximum at 1267 cm^{-1} in the spectrum were caused by coupling between C–O valence vibrations and the OH deformation vibration in the plane. The existence of the condensed polycyclic aromatic structure (naphthalene) confirmed the bands of C=C valence vibrations, $\nu(\text{C=C})$, which occurred in the range of $1600\text{--}1450\text{ cm}^{-1}$ and were present in the spectrum with the maximal peaks at 1605 , 1505 , 1484 and 1458 cm^{-1} . OH deformation vibrations in the plane, $\delta(\text{OH})$, and out of the plane, $\gamma(\text{OH})$, in the spectrum of naproxen (Fig. 3), provide the bands with the maximum at 1393 and 672 cm^{-1} , respectively [7]. The medium strength band at

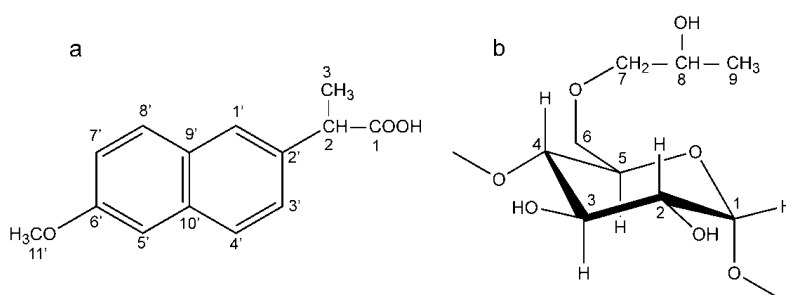


Figure 2. The numbering of C atoms with naproxen (a) and glucopyranosyl unit 2-hydroxypropyl- β -cyclodextrin (b).

Table 1. Chemical shifts (δ / ppm) of protons in the $^1\text{H-NMR}$ spectrum of naproxen, 2-hydroxypropyl- β -cyclodextrin and inclusion complex naproxen:2-hydroxypropyl- β -cyclodextrin and changes in chemical shift ($\Delta\delta$ / ppm); s – singlet, d – doublet, dd – doublet of doublets, t – triplet, q – quartet, m – multiplet, HP- β -CD – 2-hydroxypropyl- β -cyclodextrin

| C-atom | Naproxen | Complex | $\Delta\delta$ | C-atom | HP- β -CD | complex | $\Delta\delta$ |
|--------|---------------|--------------|----------------|--------|-------------------|--------------|----------------|
| 1' | 7.25 (s, 1H) | 7.25 (s, 1H) | – | 1 | 5.15 (d, 1H) | 5.15 (d, 1H) | – |
| 2 | 3.84 (q, 1H) | – | – | 2 | 3.62 (t, 1H) | 3.62 (t, 1H) | – |
| 3 | 1.52 (d, 3H) | 1.6 (d, 3H) | +0.08 | 3 | 3.975 (t, 1H) | 4.02 (t, 1H) | +0.045 |
| 3' | 7.13 (dd, 1H) | – | – | 4 | 3.46–3.53 (m, 1H) | – | – |
| 4' | 7.71 (d, 1H) | 7.71 (d, 1H) | – | 5 | – | – | – |
| 5' | 7.68 (s, 1H) | 7.68 (s, 1H) | – | 6 | 3.9 (s, 2H) | 3.8 (s, 2H) | –0.1 |
| 7' | 7.4 (dd, 1H) | 7.4 (dd, 1H) | – | 7 | – | – | – |
| 8' | 7.76 (d, 1H) | 7.76 (d, 1H) | – | 8 | – | – | – |
| 11' | 3.92 (s, 3H) | – | – | 9 | 1.125 (d, 3H) | 1.19 (d, 3H) | +0.065 |

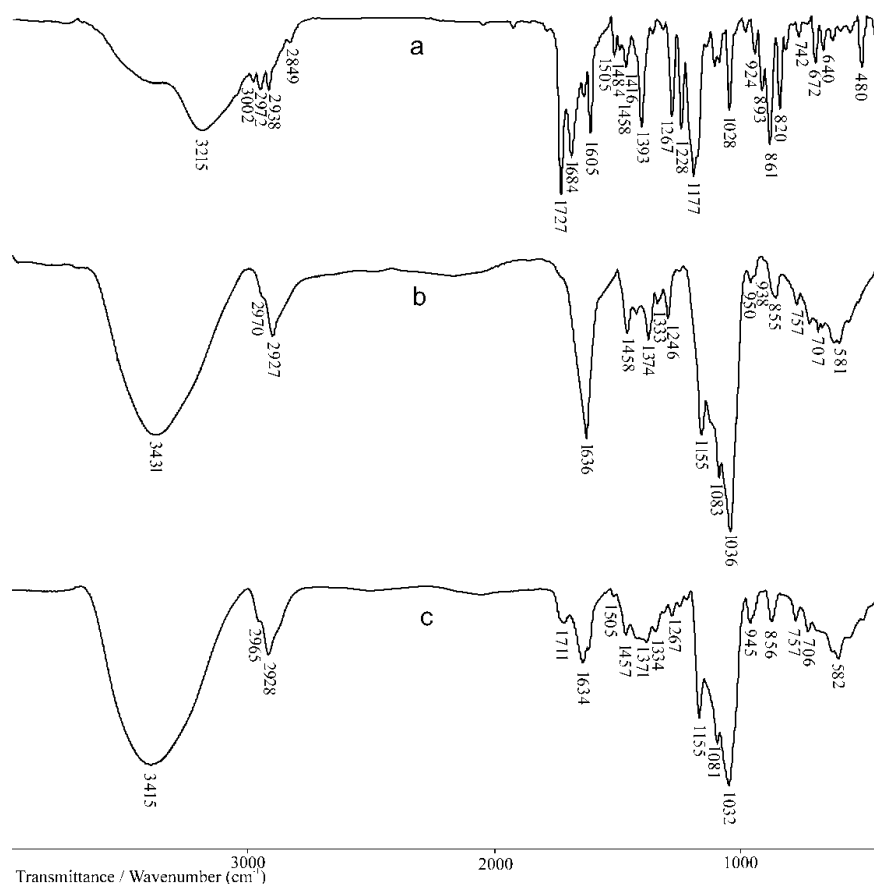


Figure 3. FTIR spectrum of naproxen (a), 2-hydroxypropyl- β -cyclodextrin (b) and inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin (c).

924 cm^{-1} , which also originating from the OH group out-of-plane deformation vibration, indicates the possibility of dimeric forms of naproxen.

The FTIR analysis of the spectrum of 2-hydroxypropyl- β -cyclodextrin (Fig. 3, curve b) showed the characteristic wide band of high intensity with the maximum at 3431 cm^{-1} , which originated from the valence vibration of OH groups, $\nu(\text{OH})$. The bands of valence vibrations of CH groups, $\nu(\text{CH})$, in the of 2-hydroxypropyl- β -cyclodextrin were present at 2970 and 2927 cm^{-1} , while the bands of deformation vibrations in the plane, $\delta(\text{CH})$, appeared at 1458 and 1374 cm^{-1} . The intensive band with the maximum at 1155 cm^{-1} was the result of valence vibrations of C–O–C bond, and this is the characteristic of saturated cyclic ethers. In the range of $1200\text{--}1000\text{ cm}^{-1}$ there was a complex band with the maxima at 1155 , 1083 and 1036 cm^{-1} resulting from the coupling of asymmetric valence vibrations C–O, C–O–C, C–C–O and C–C–C bonds. In the FTIR spectrum of the host (Fig. 3, curve b) the existence of glucopyranose units was confirmed by the bands in the area of $700\text{--}1000\text{ cm}^{-1}$, whereas the C1 of chairs conformation indicated the bands appearing in the spectrum at 950 and 855 cm^{-1} .

The analysis of the FTIR spectrum of the inclusion complex naproxen:2-hydroxypropyl- β -cyclodextrin (Fig. 3, curve c) showed that there was a difference in comparison to the FTIR spectra of naproxen (Fig. 3, curve a) and 2-hydroxypropyl- β -cyclodextrin (Fig. 3, curve b). The band of OH group valence vibrations, $\nu(\text{OH})$, from 2-hydroxypropyl- β -cyclodextrin in the spectrum of the complex (Fig. 3, curve c) at 3415 cm^{-1} was shifted to lower wave numbers by 16 units, compared to the position of the same band in the spectrum of the host. This band covers the band of OH group valence vibrations from carboxyl groups of naproxen. In the spectrum of the complex, the valence vibrations of C=O group of naproxen provided a low intensity band with the maximum at 1711 cm^{-1} , the centroid of which was shifted towards smaller wave numbers by 16 units, compared to naproxen. This shift may indicate a non-covalent interaction of the host molecule with the guest molecule. In the spectrum of the complex, there was a characteristic band from the condensed polycyclic aromatic structure of naproxen, as a single band of low intensity which occurred at 1505 cm^{-1} . In the spectrum of the complex there was also a low intensity band with the maximum at 1267 cm^{-1} , which was the result of coupling between the valence vibration of C–O

groups and the deformation vibrations of OH groups from naproxen. Compared to the same bands in 2-hydroxypropyl- β -cyclodextrin spectrum (2970 and 2927 cm^{-1}), the medium intensity band with the maxima at 2965 and 2928 cm^{-1} , which were attributed to CH valence vibrations, showed a movement of the centroid towards smaller wave numbers for 5 and 1 units, respectively. This shift may be the result of establishing a hydrogen bond between the CH groups of complexing agents which are proton donors and the guest molecules.

The differences in the FTIR spectra indicated the formation of supramolecular structures by the type of inclusions and they were in compliance with the investigations of $^1\text{H-NMR}$ and XRD analysis.

Marrota *et al.* studied the photosensitivity of naproxen and kinetics of photodegradation. In the aqueous medium, 2-acetyl-6-methoxynaphthalen and 1-(6-methoxy-2-naphthyl)ethanol were determined as the main photodegradation products [27]. The scheme of photolytic degradation of naproxen is given in Fig. 4 [23].

Naproxen is a photosensitive molecule that, in the

presence of oxygen, gives two degradation products, aromatic alcohol and ketone (Fig. 4). By decarboxylation of naproxen (I) a product is formed (II), *i.e.*, 1-(6-methoxy-2-naphthyl) ethanol. By further oxidation of the resulting alcohol the photodegradation product (III), 2-acetyl-6-methoxynaphthalen was obtained, which may be derived directly from naproxen. By photodegradation of naproxen, the molecules with higher toxicity of naproxen which reduce the pharmacological activity and the safety of the drug application were obtained [23].

In these investigations the photostability of naproxen in the pure state and in the complex was monitored by FTIR spectroscopy during 30 days of exposure to daylight. The structure change of naproxen under the influence of daylight was monitored using UV–Vis spectrophotometry. The results of this testing are given in Fig. 5.

In the UV–Vis spectrum of naproxen, which was not exposed to daylight (Fig. 5, curve a), three absorption maxima at 208, 256 and 328 nm originating from the $\pi \rightarrow \pi^*$ transitions of naphthalene were found. The

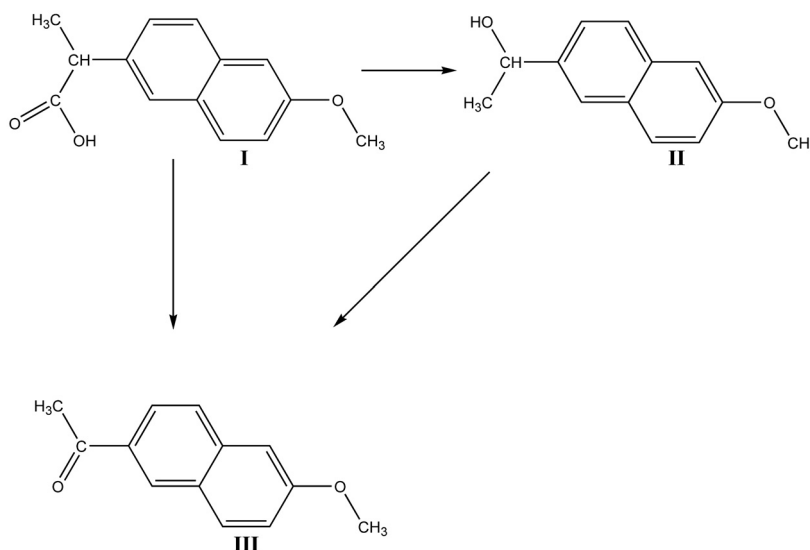


Figure 4. Photodegradation route of naproxen.

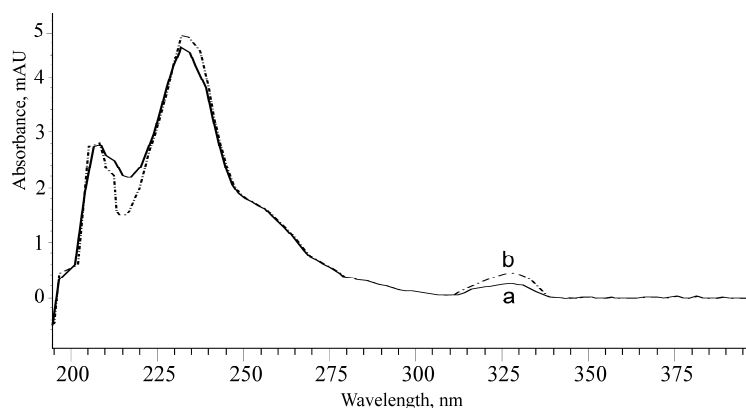


Figure 5. UV–Vis spectrum of naproxen not exposed to daylight (a) and after exposure to 30 days (b).

presence of C=O of carboxyl group in naproxen which originated from the $n \rightarrow \pi^*$ transitions was confirmed by the maximum absorbance at 232 nm. In the UV–Vis spectrum of naproxen which was exposed to daylight for 30 days (Fig. 5, curve b) the absorption maxima at the same wavelengths as naproxen were observed but of a bit greater intensity. These maxima corresponded to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of naphthalene and keto groups, respectively, which means that these functional groups were retained in the photodegradation product of naproxen. Based on the UV–Vis analysis it can be concluded that under the influence of daylight naproxen most probably formed aromatic ketone, 2-acetyl-6-methoxynaphthalen (**III**), which is in accordance with the studies of other authors [23].

FTIR spectra naproxen and naproxen which was exposed to daylight for a period of 30 days are given in Fig. 6.

The comparative analysis of the FTIR spectra of naproxen (Fig. 6, curve a) and naproxen exposed to daylight (Fig. 6, curve b) showed that in the spectrum of naproxen exposed to daylight for 15 days (Fig. 6, curve b) bands at 3213, 1393 and 924 cm^{-1} from the OH valence and deformation vibration were observed, which were less intensive than in the spectrum of naproxen (Fig. 6, curve a). The centroid of the band attributed to valence vibrations of OH group (3213 cm^{-1}) in the spectrum of naproxen which was exposed to daylight for 15 days was shifted to lower wave numbers by 2 units. These changes in the spectrum might indicate

that a certain extent of naproxen was succumbed to photodegradation.

It is evident that there is no loss of the band from C=O valence vibrations in the spectrum of naproxen which is exposed to daylight for 15 days, which leads to the conclusion that in the structure of photodegradation products a keto group, C=O is still present. According to the studies of other researchers this corresponds to the photodegradation products **III** [23] (Fig. 4). The spectrum of naproxen which is continuously exposed to daylight for 30 days (Fig. 6, curve c) showed the additional reduction of the band intensity with the maxima at 3216, 1393, 924 and 672 cm^{-1} , while the band of the C=O group at 1727 cm^{-1} remained unchanged, compared to the same band in the spectrum of naproxen and naproxen exposed to daylight for 15 days. Based on the obtained results it can be suggested that photodegradation is heading towards the product **III**, *i.e.*, 2-acetyl-6-methoxynaphthalen, which is consistent with the UV–Vis analysis in this paper.

In order to determine the stability of naproxen in the inclusion complex with 2-hydroxypropyl- β -cyclodextrin, the change of the bands using the FTIR spectra was monitored for 30 days. Periodical recording was carried out and the results are shown in Fig. 7.

Comparing the FTIR spectra of the inclusion complex which was not exposed to daylight (Fig. 7, curve a) and the inclusion complex which was exposed to daylight for 30 days (Fig. 7, curve b), it is evident that there is no loss of the bands as well as their changes in

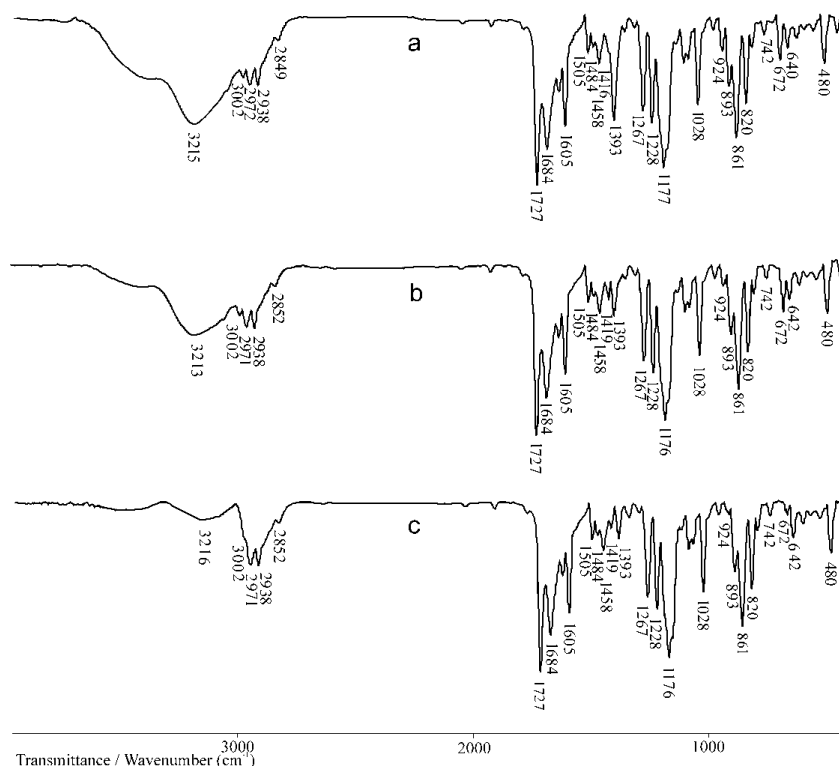


Figure 6. FTIR spectrum of naproxen not exposed to daylight (a) and after exposure to daylight for 15 (b) and 30 days (c).

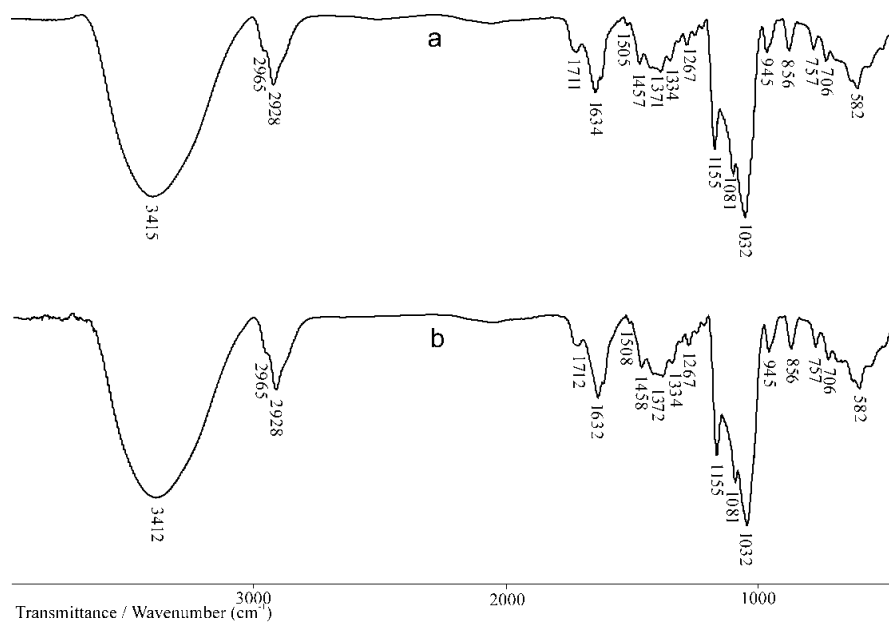


Figure 7. FTIR spectrum of the inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin not exposed to daylight (a) and after exposure to 30 days (b).

the intensity and position or the appearance of new bands. These results indicate that the inclusion complex of naproxen:2-hydroxypropyl- β -cyclodextrin is photostable and preserves naproxen for 30 days, while the uncomplexed naproxen is largely degraded for the same period.

CONCLUSION

The molecular inclusion complex was prepared by the co-precipitation method in the solid state at 1:1 molar ratio of the reactants. The loss of peaks in the complex naproxen:2-hydroxypropyl- β -cyclodextrin at 6.5, 13.4, 16.6, 18, 19.9, 22.1, 23.9 and 28.2°, which is a characteristic of naproxen in the XRD diffractogram, indicates that the drug is sheltered from the X-rays and shows that there was an inclusion of the drug in the hydrophobic cavity of 2-hydroxypropyl- β -cyclodextrin. Chemical shifts of the signals from H₃, H₆ and H₉ protons of glucopyranose units, as well as the signals of protons from CH₃ group of naproxen at position 3 in the ¹H-NMR spectrum of the complex, suggest the presence of non-covalent interactions of the host molecule with the guest molecule. The loss of characteristic bands in the FTIR spectrum of naproxen:2-hydroxypropyl- β -cyclodextrin also demonstrates the formation of supramolecular structures, which is consistent with the results of the previous analysis. The results of the investigation of photodegradation of naproxen by FTIR and UV-Vis methods show that naproxen is photounstable and that the main degradation product is the aromatic ketone, 2-acetyl-6-methoxynaphthalen (III). The inclusion complex of naproxen:2-hydroxypropyl- β -

-cyclodextrin showed the increased photostability of naproxen, compared to the uncomplexed naproxen.

Acknowledgement

This work is a part of the research done within the project TR 34012. The authors would like to thank to the Ministry of Education, Science and Technological Development, Republic of Serbia.

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IZVOD

POBOLJŠANA FOTOSTABILNOST NAPROKSENA U INKLUZIONOM KOMPLEKSU SA 2-HIDROKSIPROPIL- β -CIKLODEKSTRINOM

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(Naučni rad)

Naproxen, (+)-(S)-2-(6-metoksinaftalen-2-il)propionska kiselina, je derivat 2-arilpropionske kiseline (profena) iz grupe nesteroidnih antiinflamatornih lekova koji u terapijskim dozama smanjuje biosintezu prostaglandina i snižava povišenu telesnu temperaturu. Ovaj slabo rastvoran i fotoosetljiv molekul se transformiše pod uticajem svetlosti dajući farmakološki neaktivne proizvode. Cilj ovog rada je priprema inkluzionog kompleksa naproksena sa 2-hidroksipropil- β -ciklodekstrinom (HP- β -CD) u cilju poboljšanja fizičko-hemijskih svojstava naproksena. Molekulski inkluzioni kompleks naproksena i HP- β -CD pripremljen je metodom koprecipitacije u čvrstom stanju u molskom odnosu 1:1. Za strukturnu karakterizaciju kompleksa, kompleksirajućeg agensa, odgovarajuće fizičke smeše i naproksena, korišćene su metode protonske nuklearne magnetne rezonance (¹H-NMR), difrakcije rendgenskih zraka (XRD) i infracrvene spektrofotometrije sa Furijeovom transformacijom (FTIR). FTIR i UV-Vis metode korišćene su za analizu fotoosetljivih grupa naproksena u čistom i kompleksiranom obliku radi ispitivanja uticaja na fotostabilnost naproksena. Difraktogram inkluzionog kompleksa naproksen:2-hidroksipropil- β -ciklodekstrin ne sadrži pikove koji su karakteristični za difraktograme naproksena i HP- β -CD. Ovo ukazuje da je naproxen zaklonjen u šupljine domaćina prilikom molekularne inkapsulacije. Odsustvo karakterističnih pikova naproksena u FTIR spektru kompleksa ukazuje na formiranje supramolekularne strukture po tipu inkluzije. Hemijska pomeranja u ¹H-NMR spektru nakon inkluzije naproksena u šupljine HP- β -CD, posebno H₃, H₆ i H₉ protona i vodonika iz CH₃ u HP- β -CD takođe ukazuju na formiranje molekulskog inkluzionog kompleksa. Ispitivanje fotostabilnosti naproksena, pomoću UV-Vis metode, ukazuje na degradaciju do aromatičnog ketona, 2-acetil-6-metoksinaftalena. FTIR analiza je pokazala da degradacija naproksena počinje nakon 15 dana izlaganja dnevnoj svetlosti i da je molekularnom inkapsulacijom on zaštićen od fotodegradacije za vremenski period od 30 dana.

Ključne reči: Naproxen • Fotodegradacija • 2-hidroksipropil- β -ciklodekstrin • Inkluzioni kompleks