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Structural elucidation of rabeprazole sodium photodegradation products

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Abstract

Rabeprazole sodium is a proton pump inhibitor, used in acid-related disorders, like peptic ulcers and gastroesophageal reflux. It is known to be an acid-labile drug, however, few data about its stability under other factors are available. The aim of this work was to study the photodegradation of rabeprazole, to determine its kinetics and to elucidate the structures of the main degradation products. UVC-254 nm and metal-halide lamps were used. The analysis of the samples was carried out by HPLC. When the drug was in methanol solution, one main degradation product was formed; the degradation rate followed zero-order kinetics. The ^{1}H and ^{13}C NMR spectroscopic determinations revealed the product was the benzimidazolone. Another isolated product was identified as benzimidazole. The latter was confirmed against an authentic sample. A third photodegradation product was identified as the [4-(3-methoxy-propoxy)-3-methyl-pyridin-2-yl]methanol, by ^{1}H and ^{13}C NMR of the reaction mixture in chloroform-*d*. When powdered commercial tablets were exposed to UVC irradiation, they showed the same degradation products along with other unidentified, which appeared as traces; the degradation rate was slower than in solution. The intact tablets were stable after 50 days of exposition to the same light source.

Keywords: Rabeprazole; Proton pump inhibitor; Photostability; Photodegradation products; Kinetics; Benzimidazole

1. Introduction

Rabeprazole (±)sodium-2-[4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methylsulfinyl]-1H-benzimidazole is a proton pump inhibitor that covalently binds and inactivates the gastric parietal cell proton pump (H^+/K^+ ATPase). It is an important alternative to H_2 antagonists and an additional treatment option to other proton pump inhibitors in the management of acid-related disorders [1]. It has also demonstrated efficacy in healing and symptom relief of gastric and duodenal ulcers, as well as a high-eradication rate of the microorganism *Helicobacter pylori* when associated with antimicrobial therapy [2]. Its structure is shown in Fig. 1.

An increasing number of publications are appearing describing the development of methods for rabeprazole determination, e.g. in plasma samples [3–10], in pharmaceutical dosage form [11–16] and others applying recent techniques like solid phase extraction, supercritical fluids and chiral chromatographic columns for the separation of rabeprazole enantiomers [17–20]. Like other proton pump inhibitors, rabeprazole has an asymmetric sulfoxide function resulting in a pair of enantiomers. However, in therapeutic applications, a racemic mixture of *R* and *S* isomers is administered. The dissolution test of rabeprazole tablets was also published [21], but descriptions on the drug have not appeared in any pharmacopeia up to now. The identification of six impurities in bulk substance was performed by LC–MS and spectral data (IR, NMR) [22].

The instability of rabeprazole under acidic conditions is known, and that is a reason for being commercialized as enteric-coated tablets [23]. However, very few data about its stability under other degrading factors, such as light, are available and there is only one work related to this topic. El-Gindy et al. [12] published the validation of analytical methods for determination of the drug in the presence of degradation products, which were

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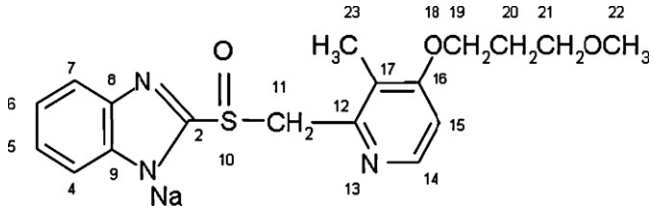

Fig. 1. Structure of rabeprazole sodium.

formed under oxidative, acidic and photolytic conditions. Some kinetic data were reported: it was found as a pseudo first-order kinetic law, but the structures of the two degradation products found were not elucidated. The exposition times used for the kinetics determination were not provided. Stability studies of other proton pump inhibitors, like omeprazole and lansoprazole, under acidic and thermal degradation conditions have been reported; only one main degradation product, the sulfenamide form, was described for acidic degradation [24–26].

Many factors can affect the stability of a pharmaceutical product; some of them includes the stability of the active ingredient, the manufacturing process, the environmental conditions, (such as heat, light and moisture during storage), as well as some chemical reactions like oxidation, reduction, hydrolysis and racemization that might occur [27,28]. Photochemical degradation can be an important factor in the stability of pharmaceuticals. Since ultraviolet radiation has a high-energy level, it can be the cause of many degradation reactions [29].

According to ICH [30], the intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that light exposure does not result in unacceptable changes. The aim of the present work was to study the stability of rabeprazole under different conditions, to elucidate the structures of the main photodegradation products by their spectroscopic features and to estimate the rate of the photodegradation process by kinetic determinations.

2. Experimental

2.1. Materials

Rabeprazole sodium reference standard (99.7%) was supplied by Janssen-Cilag (Buenos Aires/Argentina) and used as received. The Pariet® tablets containing 20 mg of drug (Janssen-Cilag, São Paulo, Brazil) were purchased from local distributors. HPLC-grade acetonitrile, analytical grade methylene chloride, chloroform and methanol were obtained from Sintorgan® (Buenos Aires/Argentina).

HPLC experiments were performed on a Hewlett-Packard 1100 chromatograph, consisting of an HP-G1311A quat pump, HP-61315A UV detector and a C_{18} HPLC semi-preparative column (250 mm × 10 mm; 5 μm, Thermo®, Winsford, UK). For kinetic determinations a C_8 column (250 mm × 4.6 mm; 5 μm, Thermo®, Winsford, UK) was used. Data acquisition and treatment were performed by using a HP ChemStation software. Nuclear magnetic resonance (NMR) spectra were recorded on two spectrometers: a Bruker Topspin 500 MHz and a Bruker 200 MHz (Karlsruhe, Germany). Samples for NMR were dissolved either in methanol-*d* or chloroform-*d* (Aldrich) and spectra were referenced using tetramethylsilane as internal reference.

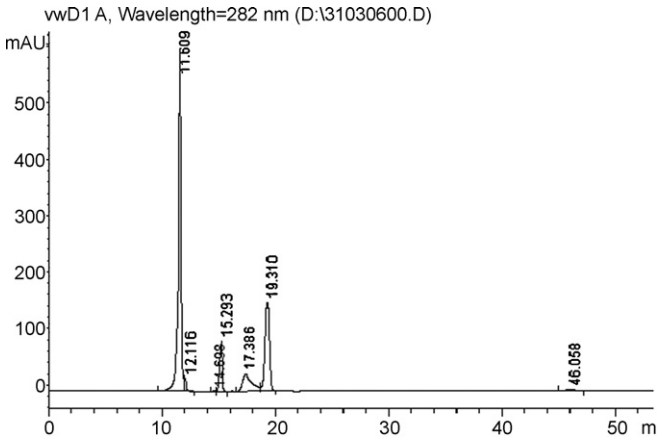

Fig. 2. HPLC chromatogram of rabeprazole sodium in HCl 0.1 M after 1 h. Chromatographic conditions: column Hypurity C18 (250 mm × 10 mm, 5 μm), mobile phase acetonitrile–water (35:65, v/v), flow rate 1.0 ml min^{-1}, UV detection at 282 nm, temperature 30 °C.

2.2. HPLC conditions

The analysis of the photodegraded samples were carried out by using the method previously validated by Garcia et al. [14]. The HPLC conditions used were: ambient temperature, acetonitrile–water (35:65, v/v) as mobile phase, flow rate of 1.0 ml min^{-1}. The wavelength of detection was 282 nm, and the injection volume was 20 μl. These conditions are valid for both columns.

2.3. Preliminary studies on the effects of acid solutions

In order to observe the effects of acid, rabeprazole tablet was powdered and transferred to a 100 ml volumetric flask and the volume was completed with hydrochloric acid 0.1 M. The

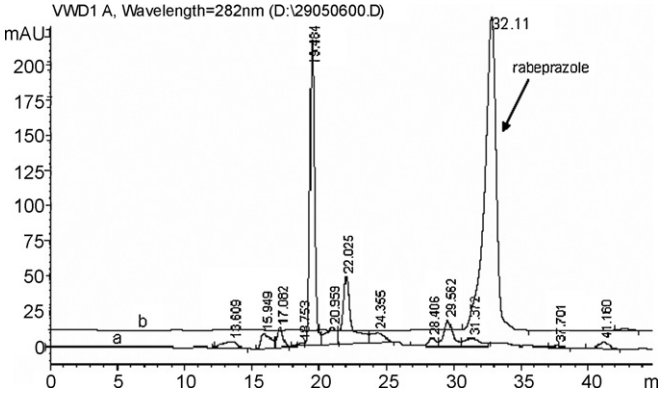

Fig. 3. HPLC chromatogram of rabeprazole sodium in methanol (800 μg ml^{-1}) exposed to UVC-254 nm lamp for 1 h (a); dark control (b). Chromatographic conditions: column Hypurity C18 (250 mm × 10 mm, 5 μm), mobile phase acetonitrile–water (35:65, v/v), flow rate 1.0 ml min^{-1}, UV detection at 282 nm, temperature 30 °C.

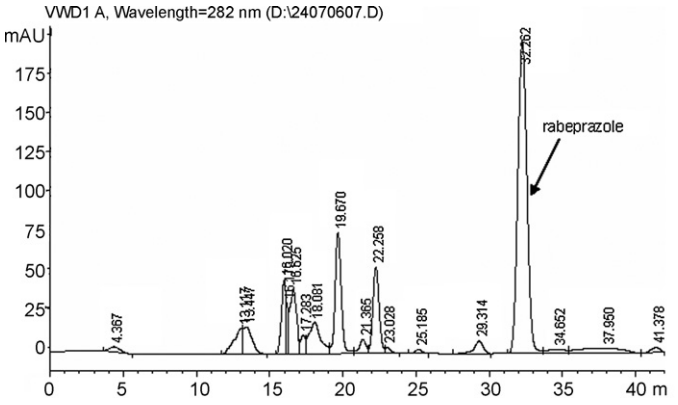

Fig. 4. HPLC chromatogram of rabeprazole in methanol exposed to metal-halide lamp for 10 min. Chromatographic conditions: column Hypurity C18 (250 mm × 10 mm, 5 μm), mobile phase acetonitrile–water (35:65, v/v), flow rate 1.0 ml min^{-1}, UV detection at 282 nm, temperature 30 °C.

solution was kept at ambient temperature for 1 h. Before the HPLC analysis, the pH of the solution was adjusted to about 8 and it was filtered using 0.45 μm nylon membrane.

2.4. Photodegradation studies

Rabeprazole methanolic solutions (800 μg ml^{-1}) were filtered using 0.45 μm nylon membranes and transferred to quartz cells of 1 cm. The cells were closed and exposed to a UVC-254 nm 15 W lamp (Philips, Holland) during 1 h in a chamber provided with mirrors. The distance between the lamp and the samples was 10 cm. The temperature into the chamber was controled and kept always around 25 °C. Another test was carried out by using a metal-halide lamp, which has a uniform emission across the 350–550 nm region (HPA 400 W—Philips, Belgium), in order to compare the degradation products formed under the two different radiation sources. In both cases, a dark control was carried out by exposing the rabeprazole solutions in quartz cells, wrapped in aluminium foil, for the same time period.

2.5. Kinetics determination

The kinetics of photodegradation of rabeprazole was evaluated in methanol, under the same conditions described above, but only the UVC lamp was used. The solutions of rabeprazole in quartz cells were exposed to the UVC irradiation for time intervals of 0, 5, 10, 15, 20, 25 and 30 min. Three samples were analysed for each time interval. After the required time, aliquots of 1 ml were transferred to a 20 ml volumetric flask and diluted with acetonitrile to 40 μg ml^{-1}, for the HPLC determinations. The concentrations of the remaining rabeprazole determined at the different time intervals were used in the plots. The plots were: (a) values of concentration against time (zero-order kinetics), (b) log of concentration versus time (first-order kinetics) and (c) reciprocal of concentration versus time (second-order kinetics). The regression coefficients (r) were obtained and the best fit observed, indicates a zero-order reaction rate law.

Table 1
Kinetics of photodegradation of methanolic solutions of rabeprazole exposed to UVC lamp

Time (min)	Concentration of rabeprazole (μg ml^{-1})	log concentration	1/Concentration
0	40.0	1.60	0.025
5	32.2	1.51	0.031
10	25.4	1.41	0.039
15	19.4	1.29	0.052
20	14.4	1.16	0.069
25	10.0	1.00	0.099
30	4.68	0.671	0.213
r	0.995	0.973	0.858

Values of correlation coefficients, r, for three reaction orders.

Table 2
^{1}H and ^{13}C NMR assignments for rabeprazole sodium in methanol-d

Position[a]	^{1}H (ppm/J)	^{13}C (ppm)
1	–	–
2	–	159.06
3	–	–
4	7.6/2H, dd, 2.98/8.47 Hz	117.01
5	7.1/2H, dd, 2.75/5.5 Hz	120.21
6	7.1/2H, dd, 2.75/5.5 Hz	120.21
7	7.6/2H, dd, 2.98/8.47 Hz	117.01
8	–	145.35
9	–	145.35
10	–	–
11	4.8/2H, s	59.09
12	–	150.15
13	–	–
14	8.25/1H, d, 5.49 Hz	147.67
15	6.9/1H, d, 5.49 Hz	105.97
16	–	164.07
17	–	123.37
18	–	–
19	4.2/2H, t, 5.95/5.95 Hz	65.09
20	2.05/2H, m, 6.18/5.95 Hz	28.80
21	3.55/2H, t, 5.96/6.17 Hz	68.54
22	3.35/3H, s	57.55
23	2.11/3H, s	9.70

[a] According to Fig. 1: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet.

2.6. Isolation of the photodegradation products

In the present work, different procedures should be applied for the appropriate isolation of each photodegradation product. Two degradation products are named according to their retention times in the HPLC analysis of the irradiated samples. A third product, that could be identified from the dried reaction mixture of the photochemical degradation, extracted with chloroform, was called DPchloroform.

Isolation of DP-19. After irradiation for 1 h, the methanolic solutions in each cell were collected in a 50 ml round flask; silicagel for column chromatography (0.062–0.200 mm, Merck®, Dermstadt, Germany) was added to the vessel. The solvent in the suspension was distilled to dryness under reduced pressure and the solid was transferred to the preparative chromatographic glass column top. Methylene chloride was used as the first eluent. The separation was carried out by the addition of 30 ml portions

Table 3
^{1}H and ^{13}C NMR assignments for photodegradation product DP-16 in methanol-*d*

Position[a]	^{1}H (ppm/J)	^{13}C (ppm)
1	–	–
2	8.08/1H, s	140.11
3	–	–
4	7.55/2H, m, 2.97/2.75/3.20 Hz	107.92
5	7.17/2H, m, 2.98/2.97/3.21 Hz	121.00
6	7.17/2H, m, 2.98/2.97/3.21 Hz	121.00
7	7.55/2H, m, 2.97/2.75/3.20 Hz	107.92
8	–	126.28
9	–	126.28

[a] According to Fig. 5: s, singlet; m, multiplet.

of mixtures of methylene chloride and methanol (increasing 5% of methanol in each portion until reaching the composition 85:15, v/v). Each fraction was analysed by thin layer chromatography (TLC) applying methylene chloride–methanol (90:10, v/v), as mobile phase and visualization by 254 nm light. Those, which showed to have degradation products, were analysed also by HPLC. The fractions containing the main degradation product were mixed and purified by preparative TLC, using the same conditions described above. The spot corresponding to the product, named DP-19, was removed and extracted with methanol (3× 10 ml).

For the *isolation of the DP-16* degradation product, the irradiated samples were mixed, concentrated under reduced pressure and submitted to preparative TLC, using chloroform–methanol (85:15, v/v) as mobile phase and visualization by 254 nm light. The spot that has lower Rf, relative to DP-16, was removed and it was extracted from the silicagel with three portions of 10 ml of methanol. This product was named DP-16 and its purity was evaluated by HPLC.

Another set of methanolic solutions of rabeprazole, irradiated for 1 h at the UVC lamp, was distilled to dryness under reduced pressure and then diluted in chloroform-*d* to run the NMR spectra (200 MHz) of the reaction mixture. The degradation product thus obtained, was named *DPchloroform*.

2.7. Identification of the products

The identification of the isolated photodegradation products was carried out by ^{1}H and ^{13}C NMR spectroscopy, following the same methodology applied to the identification of the alprazolam photodegradation products [31]. The ^{1}H and ^{13}C NMR spectra of rabeprazole sodium reference standard were also determined under the same conditions.

2.8. Tablets evaluation

Tablets of rabeprazole were exposed to the UVC-254 lamp under two forms: intact and powdered tablets. The presence of degradation products was evaluated by HPLC after 3, 10, 35 and 50 days of exposition for powdered tablets, and 22, 35 and 50 days for the intact tablets. After irradiation, the tablets were powdered, dissolved in acetonitrile and filtered using 0.45 μm nylon membrane before the HPLC analysis. The final concentration was 800 μg ml^{-1}.

3. Results and discussion

Preliminary studies of rabeprazole stability under thermal, acidic, oxidative and photolytic stress conditions were performed; they indicated that the drug is unstable in solution. Tablets stored at 80 °C showed a small alteration in the chromatogram after 4 days. On the other hand, when rabeprazole was dissolved in hydrochloric acid 0.1 M it was completely degraded in 1 h (Fig. 2). The addition of hydrogen peroxide 30% (v/v) to an aqueous solution of rabeprazole, resulted in total degradation after 1 h, at room temperature. Methanolic solutions exposed to UVC light showed a fast degradation, one major degradation product was formed, as it is shown by the chromatogram in Fig. 3. The dark control did not show any degradation product in the chromatogram, under the same conditions. This indicates that the effect of heat or solvent were not responsible for the observed degradation, only the radiation causes the new products formation. In agreement with the work by El-Gindy et al. [12], acidic and oxidative factors are really damaging for rabeprazole, but the number of degradation products observed in our studies was different. The chromatograms exhibited much more peaks and the products formed were not the same for all the degradation factors. The chromatogram of rabeprazole methanolic solution exposed to metal-halide lamp for 10 min is in Fig. 4. The degradation of the drug is faster than that of the UVC lamp and it is possible to observe the presence of the same degradation products formed in that source.

In the present work, the main degradation factor investigated was light. In the kinetics determination of the photodegradation, it was found that around 88% of rabeprazole was degraded in 30 min. The solutions developed a yellow color. The values of concentration, log of concentration and reciprocal of concentration of the remaining drug versus time are shown in Table 1. Through the evaluation of the correlation coefficients, it can be concluded that the photodegradation of rabeprazole in methanolic solution shows a zero-order kinetics under the experimental conditions applied. The calculated zero-order degradation rate constant was $k = 1.343\ \text{min}^{-1}$.

As it is partly described in Section 2, several attempts should be carried out in order to find appropriate methods for the isolation and purification of the photodegradation products. For the case of the main degradation product, DP-19, TLC and column chromatography were first applied using different mixtures of chloroform–methanol as eluent, but these conditions did not afford satisfactory and reproducible results. The number of

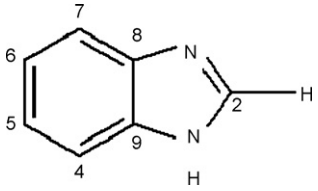

Fig. 5. Structure of the degradation product DP16 (benzimidazole).

Table 4
^{1}H and ^{13}C NMR assignments for photodegradation product DP-19 in methanol-*d*

Position[a]	^{1}H (ppm/J)	^{13}C (ppm)
1	–	–
2	–	167.78
3	–	–
4	7.24/2H, m, 3.84/2.88/3.12/3.12 Hz	109.51
5	7.19/2H, m, 3.12/3.12/2.87/3.84 Hz	122.56
6	7.19/2H, m, 3.12/3.12/2.87/3.84 Hz	122.56
7	7.24/2H, m, 3.84/2.88/3.12/3.12 Hz	109.51
8	–	132.43
9	–	132.43

[a] According to Fig. 6: m, multiplet.

products was different in each day, probably because of some decomposition of the substances inside the preparative column. On the other hand, methylene chloride–methanol demonstrated to be a better eluent, the elution of the product started in the first fractions and the amount of product obtained was relatively significant. For DP-16, the best technique was preparative TLC, which resulted in a separate spot with low Rf that could be easily removed from the plates.

The ^{1}H and ^{13}C NMR data for the spectra of rabeprazole sodium reference standard are shown in Table 2. The attributions were done according to the numbered structure present in Fig. 1.

From the ^{1}H and ^{13}C NMR spectra of the isolated photodegradation products it was possible to elucidate their structures. The ^{1}H and ^{13}C NMR data of product DP-16 are given in Table 3. The assignments correspond to the numbers in the structure shown in Fig. 5. Bidimensional spectra (COSY, HSQC and HMBC) were also carried out, those were very helpful for the identification. The analysis of the data provided by the NMR experiments allowed characterization of the DP-16 product as the benzimidazole ring, which was confirmed by comparison of NMR spectra available in literature. To further confirm this structure, the commercial sample of benzimidazole (Fluka®) was analyzed by HPLC and by TLC, under the same conditions described in Section 2. The retention time in HPLC and the Rf of the spot in TLC were the same of DP-16, what confirms that the DP-16 is the benzimidazole.

The ^{1}H and ^{13}C NMR spectra data for the main signals of DP-19 are given in Table 4. The assignments correspond to the numbered structure shown in Fig. 6. Bidimensional spectra (COSY, HSQC and HMBC) were also obtained and confirmed the correlations. The evaluation of the spectra indicates the structure of DP-19 is the benzimidazolone.

The ^{1}H and ^{13}C 200 MHz NMR data for the main signals of DPchloroform are given below. The assignments correspond to

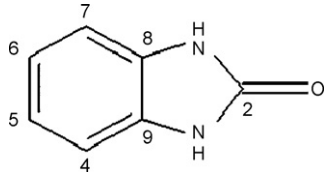

Fig. 6. Structure of degradation product DP19 (benzimidazolone).

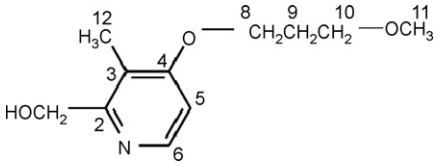

Fig. 7. Structure of degradation product DPchloroform [4-(3-methoxy-propoxy)-3-methyl-pyridin-2-yl]methanol.

the numbers in the structure shown in Fig. 7. The analysis of the spectra indicates (Table 5) the structure of DPchloroform is the [4-(3-methoxy-propoxy)-3-methyl-pyridin-2-yl]methanol.

According to the work by DellaGreca et al. [32], lansoprazole and omeprazole aqueous dispersions, when irradiated by solar simulator for 72 and 43 h, respectively, gave several degradation products: the benzimidazole, the benzimidazolone and the pyridine-derivative, among others substances. The benzimidazolone is also formed at pH 4.0 in the dark, what suggests that it could be also one of the degradation products formed under acidic conditions in our preliminary studies, as shown by the HPLC chromatogram in Fig. 2. None of the products elucidated have structures similar to the impurities studied by Reddy et al. [22].

Tests were done using the commercial benzimidazole in order to find out if DP-19 (benzimidazolone) could be formed by the oxidation of DP-16 (benzimidazole). Thus, the reagent was dissolved in methanol and exposed to UV-254 nm lamp for 90 min. Also, aliquots of the solution were treated with hydrogen peroxide at 30% concentration. The samples were analysed by HPLC. The benzimidazole is not affected by the hydrogen peroxide, under the conditions studied, and not any other peak is observed in the chromatograms. However, after exposition to the UV lamp, one degradation product is formed with retention time of 18.3 min. Despite of the small modification in the retention time, this result suggests that it is possible to obtain the benzimidazolone from the benzimidazole under the UVC light exposition. The modification observed could be explained by the normal equipment variation.

The analysis of the powdered tablets exposed to the UVC-254 nm lamp demonstrated the photodegradation of rabeprazole in the solid form is slower than in solutions, but the products formed were the same. It was possible to observe degradation

Table 5
^{1}H and ^{13}C NMR assignments for photodegradation product DPchloroform in $CDCl_3$

Position[a]	^{1}H (ppm/J)	^{13}C (ppm)
1	–	–
5	6.75/1H, d	106.0
6	8.30/1H, d	146.0
7	–	–
8	4.2/2H, t	68.5
9	2.15/2H, m	29.0
10	3.6/2H, t	66.0
11	3.3/3H, s	58.0
12	2.0/3H, s	9.5
CH_2OH	4.7/2H, s	63.0

[a] According to Fig. 7: s, singlet; d, doublet; t, triplet; m, multiplet.

products only after 10 days of exposition; the HPLC analysis showed several very small peaks before the signal due to the DP-19, that was the main degradation product. The hereto described HPLC methodology is, then, appropriate to follow the photodegradation of the rabeprazole powdered tablets. On the other hand, the intact tablets, did not show any significant degradation after 50 days of irradiation. It is likely, that the excipients protect the drug from the light effects. In the solid state, the photochemical process takes place on the formulation surface. In most cases the interior of the preparation is unaffected independently of the exposure time [33].

4. Conclusions

Rabeprazole demonstrated to be relatively stable in the solid form, but very unstable in solution for different factors, such as heat, oxidation, acid and light. The photodegradation in solution follows a zero-order kinetics and the products isolated by preparative TLC and column chromatography were the benzimidazole and the benzimidazolone, originated, likely, from the cleavage of the rabeprazole structure at the sulphur atom. The other part of the molecule could be identified as the [4-(3-methoxy-propoxy)-3-methyl-pyridin-2-yl]methanol, by the NMR spectra of the reaction mixture, in which the solvent was distilled to dryness, and the solid residue dissolved in chloroform-*d*. Irradiation of the powdered rabeprazole tablets by the UVC lamp showed the same degradation products of the solution, whereas the intact tablets did not show any degradation after 50 days of light exposure. The photoinstability of the rabeprazole sodium showed by the present studies indicates that special care to avoid exposure of the drug to the light effects must be taken during the manufacture and storage of the pharmaceutical preparations.

Acknowledgments

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