

## STABILITY STUDY OF OMEPRAZOLE

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### Abstract

We carried out a stability study of omeprazole in accordance with the stability testing of pharmaceuticals guideline approved by the Romanian National Drug Agency [1].

Omeprazole is sensitive to heat, humidity, light, and organic solvents; consequently, accelerated tests for stability evaluation were performed at  $40^{\circ}\text{C}\pm 2^{\circ}\text{C}$  and  $75\pm 5\%$  relative humidity (RH), according to the current official guideline. The samples were kept in a climatic chamber for 6 months in the conditions described above. Half of the samples were also exposed to light. The samples were withdrawn from the climatic chamber and analyzed periodically (0; 0.2; 0.4; 2; 4; 5; 6 months) by an HPLC method with UV detection. A standard statistical methodology was used to calculate the expiration date based on the analytical results obtained in the studied samples.

The purpose of this study was to use the results obtained in accelerated stability testing in order to estimate the expiration date in normal room temperature conditions ( $25^{\circ}\text{C}\pm 2^{\circ}\text{C}$ ).

### Rezumat

Evaluarea stabilității omeprazolului și estimarea perioadei sale de valabilitate a fost realizată conform metodologiei de testare aprobată de Agenția Națională a Medicamentului (ANM) [1].

Omeprazolul face parte din categoria substanțelor sensibile la temperatură, umiditate, lumină și solvenți organici. Ca urmare, conform ghidului ANM, în acest caz evaluarea stabilității s-a realizat în condiții de testare accelerată la o temperatură de  $40^{\circ}\text{C}\pm 2^{\circ}\text{C}$  și o umiditate relativă (UR) de  $75\pm 5\%$ . Probele au fost păstrate timp de 6 luni într-o cameră climatică în condițiile descrise mai sus; jumătate dintre probe au fost expuse și la lumină. Periodic (7, 14, 64, 128, 150, 180 zile) au fost prelevate probe care au fost analizate printr-o metodă HPLC cu detecție UV. Rezultatele obținute au fost prelucrate matematic și statistic în vederea stabilirii perioadei de valabilitate a omeprazolului.

Scopul acestui studiu a fost acela de a utiliza rezultatele obținute la testarea accelerată pentru estimarea perioadei de valabilitate a omeprazolului în condiții normale de temperatură ( $25^{\circ}\text{C}\pm 2^{\circ}\text{C}$ ).

**Keywords:** omeprazole, stability, humidity, light.

### Introduction

Omeprazole (OPZ), 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulphonyl]-1H-benzimidazole is a substituted benzimidazole compound and prototype anti-secretory agent. OPZ is the first “proton pump inhibitor” widely used in the prophylaxis and treatment of gastroduodenal ulcers and the treatment of symptomatic gastro-

esophageal reflux. It interacts with H<sup>+</sup>/K<sup>+</sup> ATPase in the secretory membranes of the parietal cells and it is very effective in the treatment of the Zollinger–Ellison syndrome.

OPZ is a lipophilic, weak base with pK<sub>a1</sub>= 4.2 and pK<sub>a2</sub>= 9 that may be degraded unless protected against acid conditions. It contains a tricoordinated sulphur atom in a pyramidal structure and therefore can exist in two different optically active forms, (S)- and (R)-omeprazole.

The number of decomposed products of omeprazole in different conditions has been identified and characterized by Brändström et al [2]. D. Castro and al. described derivative spectrophotometry and HPLC methods [3].

The HPLC method is the official one proposed by the United States Pharmacopeia (USP 25) for the determination of omeprazole and for its quantification from bulk material. This procedure can be used in stability studies as there is no interference between the drug and its decomposition products.

In order to shorten the development period of a pharmaceutical formulation, the chemical stability of pharmaceuticals was evaluated in accelerated storage conditions at high temperature and high relative humidity (RH) by a high-performance liquid chromatographic method [5,6].

Long-term stability during preservation at room temperature is generally predicted based on the obtained accelerated data, using the Arrhenius equation. Therefore, it is not easy to predict transformations at room temperature from the data obtained at a high temperature [4].

According to our present knowledge, no studies are available for the kinetics of decomposition or activation energy of omeprazole.

### **Materials and methods**

A sample of omeprazole (batch nr. 90807/BA22347) was obtained from Union Quimica Farmaceutica, Barcelona, Spain. The samples were kept in a climatic chamber for 6 months at 40°C±2°C and 75±5% relative humidity (RH); half of them were also exposed to light. The samples were withdrawn from the climatic chamber and analyzed periodically (0; 0.2; 0.4; 2; 4; 5; 6 months). Another set of omeprazole samples was stored for 6 months at three different temperatures: 30°C, 40°C and 50°C; the relative humidity was 75±5%.

HPLC grade acetonitrile, triethylamine and 85% orthophosphoric acid were purchased from Merck, Darmstadt, Germany. LC grade water was deionized using a Milli-Q equipment and then filtered using the Milli-Q

Academic, Millipore water purification system (Milford, MA, USA). All the other reagents were of analytical grade purity.

#### *Instrumentation*

The following were used: SanyoGallenkamp climatic chamber with light source (Xenon – Phillips 840), LC system - HPLC Agilent Series 1100, binary gradient pump, autosampler, column oven and an UV detector. The output signal was monitored and integrated using HP Chemstation software.

#### *Solutions*

*Mobile phase.* A. Water: 1% triethylamine with pH adjusted to 9.5 with 85% H<sub>3</sub>PO<sub>4</sub> filtered through a 0.45 µm nylon membrane filter prior to use and degassed for 15 min. B. Acetonitrile. The A/B ratio was 90:10v/v.

*Solution to dilution.* A mixture of 0.01M sodium tetraborate and acetonitrile - 3:1v/v ratio.

*Omeprazole standard solution.* 1.015mg/mL omeprazole stock standard solution was prepared in methanol and kept at +4°C, protected from light. In these conditions it was stable for two months. Omeprazole working solutions were prepared by dilution of the previously prepared stock standard solution at a concentration between 40 and 200µg/mL and then injected into the system.

*Sample solution.* 2mg/mL solution of omeprazole sample was prepared in methanol and diluted to 0.200µg/mL prior to injection into the system.

*Chromatographic conditions.* A Zorbax Extend C<sub>18</sub> analytical column (150mm×4.6 mm, 5µm packing) (Agilent) was used for analysis at 25°C. The mobile phase was pumped through the column at a flow rate of 0.8 mL/min. The gradient program was: 0 min (18%B), 7.2 min (18%B), 10.5 min (50%B), 12 min (50%B), 16 min (18%B) and 18 min (18%B). The sample injection volume was 20µL. The UV detector was set to a wavelength of 280 nm for the detection.

## **Results and discussion**

### *Kinetics of omeprazole decomposition*

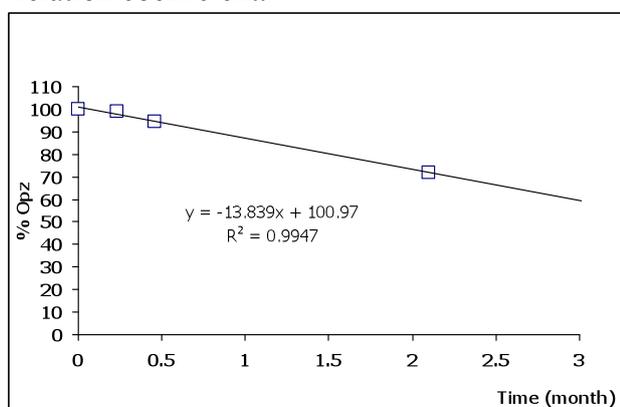
The stability properties of omeprazole were investigated in order to improve the pharmaceutical formulation.

The quantification of omeprazole by HPLC in the studied samples has shown zero order kinetics of decomposition for both light exposed samples and samples protected from light. The analytical results obtained for the samples which were stored protected from light are presented in table I.

**Table I**  
Omeprazole samples protected from light

Days	OPZ %	Degraded OPZ %
0.00	100.00	0.00
7.00	99.106	0.89
14.00	94.332	5.67
64.00	71.820	28.18
128.00	4.110	95.89
150.00	0.441	99.56
180.00	0.001	99.99

Figure 1 presents the linear regression for the following equation:  $C=f(t)$  where  $C=\%OPZ$  and  $t=time (month)$  was  $Y=-13.893 X+100.97$  with  $R^2=0.9947$  correlation coefficient.



**Figure 1**

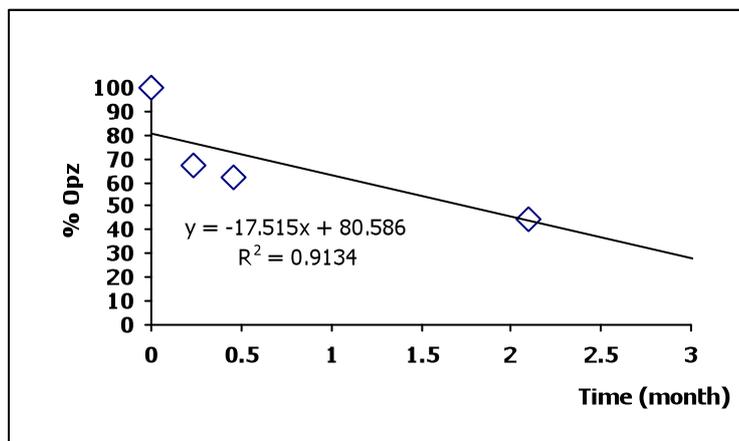
Kinetics of omeprazole decomposition – protected from light

The analytical results obtained for the samples which were stored exposed to light are presented in table II.

**Table II**  
Omeprazole samples exposed to light

Days	OPZ %	Degraded OPZ %
0.00	100.000	0.00
7.00	67.020	32.98
14.00	61.910	38.09
64.00	44.580	55.42
128.00	0.001	99.99
150.00	0.001	99.99
180.00	0.000	100.00

Figure 2 shows the linear regression for the following equation:  $C=f(t)$  where  $C=\%OPZ$  and  $t=time (month)$  was  $Y= -17.515 X+80.586$  with  $R^2=0.9134$  correlation coefficient.



**Figure 2**

Kinetics of omeprazole decomposition – exposed to light

However, decomposition was faster when the samples were exposed to light, although it has the same order in both cases.

*Activation energy  $E_a$  calculation – the Arrhenius equation*

If rapid results are desired for a given product, it may be stored at elevated temperatures. Thus, sufficiently large degrees of decomposition are obtained in order for the degradation product to be accurately assessed. Arrhenius plotting is carried out in order to estimate the expiration date in normal conditions. The temperature influence on a chemical reaction follows the so-called Arrhenius equation given by (eq.1):

$$\ln[k] = -(E_a/RT) + \ln[Z] \quad (\text{eq.1})$$

where:

$E_a$  – activation energy

$R$  – gas constant

$T$  – absolute temperature ( $^{\circ}K$ ) obtained by adding  $273.15^{\circ}$  to the degrees Celsius (centigrade)

$Z$  – potency (% of degraded omeprazole)

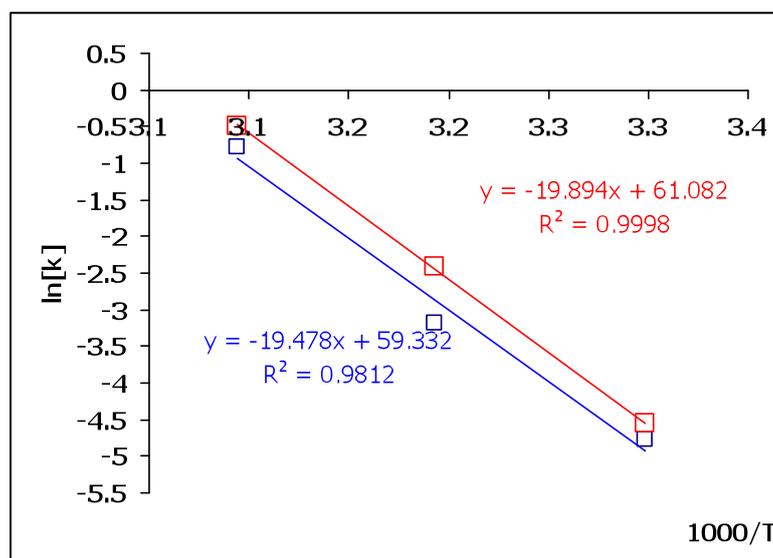
The omeperazole samples were stored for 6 months at three different temperatures:  $30^{\circ}C$ ,  $40^{\circ}C$  and  $50^{\circ}C$  and  $75 \pm 5\%$  relative humidity; half of the samples were also exposed to light. The samples were analyzed and the degradation rate of omeprazole was calculated.

The results obtained after 6 months of storage in the described conditions are presented in Table III.

**Table III**  
Least square fit parameters from data treated by zero order kinetics

°C	°K	1/T x 10 <sup>3</sup>	k (mol <sup>-1</sup> )	Ln [k]
<b>Protected from light</b>				
30	303.15	3.299	8.50E-03	-4.76769
40	313.15	3.193	4.13E-02	-3.18689
50	323.15	3.095	4.58E-01	-0.78089
<b>Exposed to light</b>				
30	303.15	3.299	1.05E-02	-4.55638
40	313.15	3.193	8.95E-02	-2.41352
50	323.15	3.095	6.09E-01	-0.49594

In order to calculate the  $E_a$ , the results were plotted  $\ln[k]=f(1/T)$ , for both the samples exposed to light and those protected from light. The plot obtained is shown in figure 3.



**Figure 3**  
Data from table III calculated using the Arrhenius equation

The Arrhenius equations for the two types of plotting are:  
 $\ln[k_1]=59.332-19.478(1000/T)$ ,  $R^2=0.9812$  for the samples which were

exposed to light and  $\text{Ln}[k_2]=61.082-19.894(1000/T)$ ,  $R^2=0.9998$  for the samples which were stored protected from light.

The activation energy was calculated based on the  $(-E_a/R)$  slopes of the above equations:

$$E_{a1} = 19.478 \times R = 19.478 \times 1.987 = 38.76 \text{ Kcal/mol}$$

$$E_{a2} = 19.894 \times R = 19.894 \times 1.987 = 39.58 \text{ Kcal/mol}$$

#### *Stability of omeprazole*

An active substance is usually considered stable as long as the percentage of degraded substances is below 10 when the substance is stored in certain conditions.

Based on the results obtained in accelerated stability testing, the decomposition rate of omeprazole was extrapolated to 25°C, which is considered the regular storage temperature.

The degradation rates of omeprazole were calculated at 25°C as follows:

$$\text{Ln } [k_{25}] = 59.332 - 19.478 \times 3.356 = -6.03 \quad k_{25}^1 = 0.0023907$$

$$\text{Ln } [k_{25}] = 61.082 - 19.894 \times 3.356 = -5.68 \quad k_{25}^2 = 0.0034058$$

The omeprazole decomposition rate is known to have zero order kinetics in both situations. Therefore, equation 2 was used to calculate for how long the concentration of omeprazole active substance was higher or equal with 90% ( $0.206 \text{ mol}^{-1}$ ), if stored at 25°C.

$$C = C_0 - K_0 \times t \quad \text{or} \quad t = (C_0 - C) / K_0 \quad (\text{eq.2})$$

In the described conditions, omeprazole reaches 90% concentration after 12.11 months, if stored protected from light and 8.50 months, if stored exposed to light.

#### **Conclusions**

To sum up, this study established the kinetics of decomposition and activation energy  $E_a$  for omeprazole.

In addition, the long-term stability during preservation at room temperature was predicted using the Arrhenius equation on the accelerated data.

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