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Determination of celiprolol by high-performance liquid chromatography and stability in solution

P. Modamio, C.F. Lastra, E.L. Mariño *

Pharmacotherapy Unit, Department of Pharmacy, Faculty of Pharmacy, University of Barcelona, Avda Juán XXIII s / n, 08028 Barcelona, Spain

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Abstract

An isocratic technique was developed for the analysis of Celiprolol HCl using high-performance liquid chromatography (HPLC) with UV detection and a C_{18} reverse-phase column. The coefficient of variation (C.V.) for precision and proportionality assays was lower than 5% for all concentrations studied. The stability of the drug in solution was studied. We deduced that the shelf-life ($t_{90\%}$) of Celiprolol HCl at room temperature (25°C) was 13.8 days.

Key words: Celiprolol hydrochloride; HPLC; Stability; Nonlinear regression; Kinetic order; Shelf-life

Celiprolol HCl is a highly cardioselective β-adrenoceptor blocking drug which shows partial β_2-agonist (intrinsic sympathomimetic) activity, α_2-antagonist and no membrane stabilising activity that is used in the treatment of hypertension (Opie, 1991).

Celiprolol HCl provides effective blood pressure control with once daily dosage (Taylor, 1988) and its pharmacokinetic and pharmacological properties may offer advantages to some patients (Sirtory et al., 1989).

Few data about the stability of β-blockers and in particular on Celiprolol HCl were available. Therefore, the aim of the present study was to develop a method for the quantification of Celiprolol HCl and to determine its stability in solution. Our method allowed the rapid determination of Celiprolol HCl in solution using a suitable chromatographic column and mobile phase.

Celiprolol HCl was obtained from Rhone-Poulenc Pharma Laboratory (Madrid, Spain). All solvents and reagents were of analytical grade except acetonitrile and methanol, which were HPLC grade.

The chromatographic system consisted of a Kontron (Kontron Instruments S.A., Barcelona, Spain) equipped with an automatic sampling system, a UV-visible detector with variable wavelength and a computerized integration system. Chromatographic analysis was performed on a 5 μm C_{18} column (125 × 4 mm i.d.) (Technokroma, Barcelona, Spain) operating at room temperature.

* Corresponding author: Tel. (3)-4024544; Fax (3)-4021886.

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The analytical technique for the determination of Celiprolol HCl consisted of a mobile phase composed of acetonitrile and Sorensen phosphate buffer with triethylamine 0.1% adjusted to pH 3 with 85% phosphoric acid (30:70, v/v). Celiprolol HCl was eluted isocratically at a flow rate of 0.8 ml/min. and an injection volume of 20 μl. UV detection was performed at 232 nm.

Stock solutions of Celiprolol were prepared at 0.25 mg/ml in Sorensen phosphate buffer at pH 7.4. The concentration ranges of the calibration curves were 25–0.78 μg/ml.

Validation of the analytical method was based on proportionality (linearity assay) and precision (repeatability and reproducibility assay). The linearity assay consisted in the determination of the same concentration range of Celiprolol HCl as the calibration curve: 25, 12.5, 6.25, 3.125, 1.56 and 0.78 μg/ml and each concentration was analysed in triplicate.

To evaluate precision three concentrations of Celiprolol HCl (25, 6.25 and 1.56 μg/ml) were chosen. Five standard solutions of each concentration were prepared and analysed in triplicate (repeatability assay). This assay was repeated on 5 days (reproducibility assay).

In the linearity assay, the regression equation obtained by the least-squares method was: $y = 0.644x - 0.228$ with a correlation coefficient of 0.999. The response factors, expressed by the coefficient of variation (C.V.), were calculated in all validation data of the assay procedure. The C.V. for the linearity assay was 4.3%. The results obtained for repeatability and reproducibility assays were not greater than 2.5%. The results proved this analytical method had acceptable precision and linearity between the peak area and concentration.

An accelerated study of stability in solution was carried out by subjecting working solution aliquots (pH 7.4) to temperatures of 60, 70 and 90°C in a water bath, which were withdrawn at specified times and frozen at −20°C until analysis by HPLC. Each sample obtained at the different temperatures and times was analysed in triplicate.

The results on the unaltered concentration of active principle at the temperatures of the study as a function of time indicated degradation of Celiprolol HCl, as shown in Fig. 1.

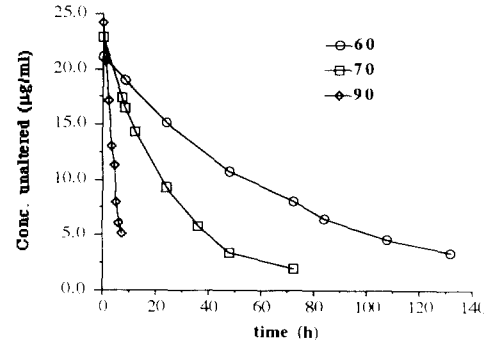

Fig. 1. Unaltered concentration of Celiprolol HCl at 60, 70 and 90°C.

Apparent rate constants for the zero-order kinetics of degradation were determined by linear regression analysis and the first-order kinetics were determined by a non-linear regression program, created from the ADAPT (University of Southern of California L.A.) program package (D'Argenio and Schumitky, 1979).

Table 1 summarizes the parameter values of the drug degradation process for each kinetic order assayed and temperature of study. The AIC values were 26.72 and −14.48 at 60°C, 42.54 and −1.44 at 70°C and 21.71 and 12.98 at 90°C for the zero-order and first-order process, respectively.

Subsequently, Akaike Information Criteria values (AIC) (Akaike, 1973; Yamaoka et al., 1978) were calculated.

After the application of Student's t-test, significant differences were found between the AIC

Table 1
Summary of the parameters fitted for zero-order and first-order kinetics by linear regression and non-linear regression analysis respectively, at the temperatures of study

		60°C	70°C	90°C
Zero-order	C_0 (μg/ml)	19.16	16.25	23.02
	K (μg/ml per h)	0.14	0.16	2.79
	r^2	0.95	0.76	0.97
First-order	C_0 (μg/ml)	21.18	22.76	25.05
	K (h^{-1})	0.01	0.04	0.22
	r^2	1.00	1.00	0.99

Table 2
Summary of apparent first-order rate constants for the degradation of Celiprolol HCl

Temperature (°C)	K_d (h^{-1})	$t_{1/2}$ (h)	$t_{90\%}$ (h)
37	$0.13E-2$	530	80
25	$0.32E-3$	2169	328
0	$0.11E-4$	60736	9202
−4	$0.63E-5$	109582	16603

values ($p = 0.0182$). Therefore, the Celiprolol HCl degradation process was correctly explained according to first-order kinetics under the conditions of the study.

In order to determine the kinetic parameters of drug degradation, the estimated rate constant values were treated according to the Arrhenius equation (Florence and Attwood, 1988) to obtain the thermodynamic parameters of the drug degradation process: the activation energy (E_a) and the frequency factor (A) and, by extrapolation, the desired rate constant values such as room temperature in Climatic Zone II (25°C), in which Spain is included (Cartwright, 1989; PMA's Joint QC-PDS Stability Committee, 1991).

The first-order rate constants for the degradation at each temperature were $1.39E-2$, $3.82E-2$ and $2.16E-1$ (h^{-1}) at 60, 70 and 90°C, respectively. The parameters of the Arrhenius equation obtained were: $E_a = 0.90E05$ (J mol^{-1}) and $A = 2.02E12$. The rate constants at 37, 25, 0 and −4°C, determined from these values by extrapolation, and the degradation half-life ($t_{1/2}$) and the shelf-life ($t_{90\%}$) parameters are also summarized in Table 2. A typical Arrhenius plot of the log of the observed and theoretical rate constants as a function of the reciprocal of the absolute temperature is shown in Fig. 2.

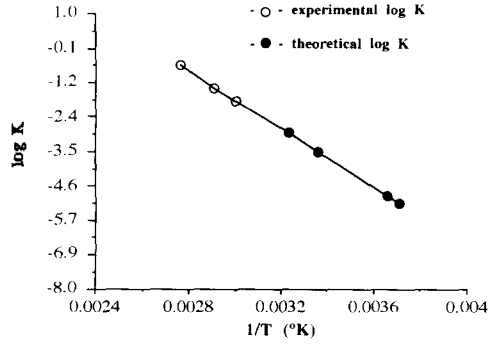

Fig. 2. Arrhenius plot of log K vs $1/T$.

In conclusion, an HPLC method for the determination and quantification of Celiprolol HCl has ben developed. The method was validated and the C.V. obtained was below the maxima permitted.

The accelerated study of stability in solution demonstrated that Celiprolol HCl degradation evolved according to first-order kinetics under the conditions of our study.

Apparent rate constants for the first-order kinetics of degradation at each temperature were determined by non-linear regression.

From the Arrhenius equation, the shelf-life of Celiprolol HCl at 25°C was calculated to be 328 h.

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