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A valid high-performance liquid chromatography method for oxprenolol stability studies

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Abstract

An isocratic technique was developed for the analysis of oxprenolol 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 oxprenolol HCl at room temperature (25°C) was 48.9 days.

Keywords: Oxprenolol hydrochloride; HPLC; Stability; Nonlinear regression; Kinetic order; Shelf-life

Oxprenolol HCl is a non-cardioselective β-blocker with agonist intrinsic sympathomimetic activity (ISA) and membrane-stabilizing activity, used in the treatment of hypertension and angina pectoris (Reid, 1988). It is an orally active lipophilic β-blocker with rapid and complete absorption. However, the controlled-release form is clinically as effective as the conventional-release form and improves patient compliance (Gupta et al., 1991).

No literature data on the stability of oxprenolol HCl were found. The aim of the present study was to develop a method for the quantification of oxprenolol HCl and to determine its stability in solution. Our method allowed the rapid determination of oxprenolol HCl in solution using a suitable chromatographic column and mobile phase.

Oxprenolol HCl was obtained from Ciba-Geigy Laboratory (Barcelona, 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.

The analytical technique for the determination of oxprenolol HCl consisted of a mobile phase

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composed of acetonitrile and Sorensen phosphate buffer with 0.2% triethylamine adjusted to pH 3 with 85% phosphoric acid (30:70, v/v). Oxprenolol HCl was eluted isocratically at a flow rate of 0.8 ml/min and an injection volume of 40 μl. The UV detection was set at 224 nm.

Stock solutions of oxprenolol 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 of the determination of the same concentration range of oxprenolol 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 the precision of the assay three concentrations of oxprenolol 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 at 5 days (reproducibility assay).

In the linearity assay, the regression equation obtained by the least-squares method was $y = 0.548x - 0.176$, 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. C.V. for the linearity assay was 4.1%. The results obtained for repeatability and reproducibility assays were no greater than 1.4%. The data 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, 80 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.

Results of the unaltered concentration of active principle at the temperatures of the study as a function of time indicated degradation of oxprenolol HCl, as shown in Fig. 1.

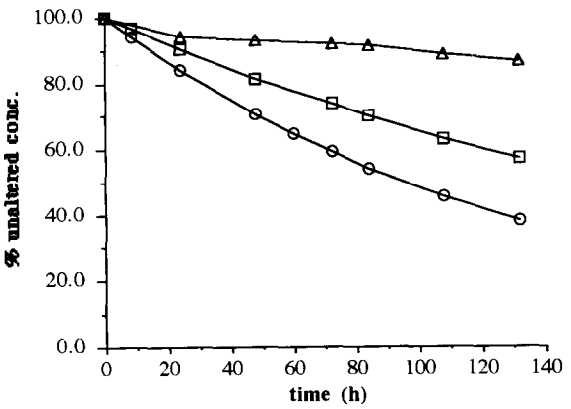

Fig. 1. Unaltered concentration of oxprenolol HCl at 60 (△), 80 (□) and 90°C (○).

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

Table 1 summarizes the parameter values of the drug degration process for each assayed kinetic order and temperature of study. Subsequently, Akaike Information Criteria values (AIC) (Akaike, 1973; Yamaoka et al., 1978) were calculated.

The AIC values were −1.01 and −1.20 at 60°C, 12.17 and 14.03 at 80°C and 20.52 and 19.77 at 90°C for zero-order and first-order kinetics, respectively.

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

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	80°C	90°C
Zero-order	C_0 (μg/ml)	21.59	19.13	21.26
	K (μg/ml per h)	2.20E−2	6.43E−2	1.18E−1
	r^2	0.83	0.96	0.92
First-order	C_0 (μg/ml)	21.60	19.34	21.67
	K (h^{-1})	0.11E−2	0.42E−2	0.73E−2
	r^2	0.84	0.95	0.93

AIC values ($P = 0.487$). Therefore, the process of oxprenolol HCl degradation was indistinctly explained according to zero-order or first-order kinetics under the conditions of the study. We assumed first-order kinetics with the aim of comparison with other β-blockers that are currently being studied in our laboratory (Modamio et al., 1994).

The first-order rate constants for degradation at each temperature were $1.07E-3$, $4.23E-3$ and $7.26E-3$ (h^{-1}) at 60, 80 and 90°C, respectively.

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

The parameters of the Arrhenius equation obtained were: $E_a = 6.09E04$ (J mol^{-1}) and $A = 4.23E06$. Rate constants at 37, 25, 0 and −4°C, determined from these values by extrapolation, and the degradation half-life ($t_{1/2}$) and 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.

In conclusion, an HPLC method for the determination and quantification of oxprenolol HCl was developed. The method was validated and the C.V. obtained were below the maxima permitted. The accelerated study of stability in solution demonstrated that oxprenolol HCl degradation evolved indistinctly according to zero-order or first-order kinetics under the conditions of our study. Apparent rate constants for first-order kinetics of degradation at each temperature were determined by non-linear regression.

From the Arrhenius equation, the shelf-life of oxprenolol HCl at 25°C was calculated to be 1173 h. This value is nearly 4-times greater than our previously reported value for celiprolol (Modamio et al., 1994).

Table 2
Summary of apparent first-order rate constants for the degradation of oxprenolol HCl at temperatures of 37, 25, 0 and −4°C

Temperature (°C)	K_d (h^{-1})	$t_{1/2}$ (h)	$t_{90\%}$ (h)
37	$2.32E-4$	2989	453
25	$8.95E-5$	7741	1173
0	$9.43E-6$	73520	11139
−4	$6.33E-6$	109565	16600

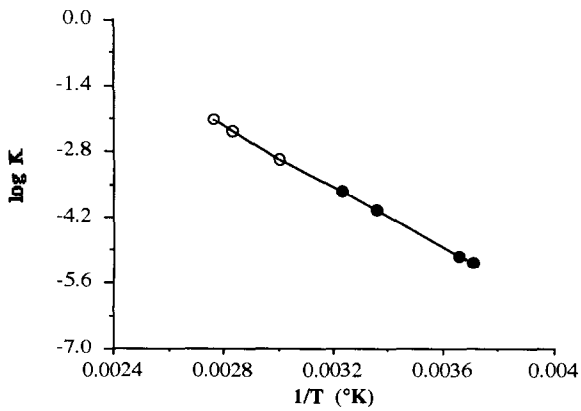

Fig. 2. Arrhenius plot of log K vs $1/T$. (○) Experimental log K (●) theoretical log K.

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