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Rapid Communication

Analysis of chlorcyclizine and related compounds by liquid chromatography for stability studies

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Summary

A rapid, specific and sensitive assay for the quantitation of chlorcyclizine hydrochloride and its degradation product by liquid chromatography is described. This method is used for stability studies. At 25 °C, the predicted shelf-life in aqueous solution of 115 days makes liquid dosage forms of the drug inappropriate for storage conditions.

Chlorcyclizine hydrochloride, 1-[(4-chlorophenyl)phenylmethyl]-4-methylpiperazine (**I**), is an H_1 blocker with a prolonged action and is available in oral solid dosage forms or ointments. Its determination has been described in the literature: gas-chromatographic and fluorimetric assays have been proposed for its separation in a series of antihistaminic drugs (Jensen and Pflaum, 1964; MacDonald and Pflaum, 1964). However, none of these methods permit the isolation of the drug in the presence of its degradation products.

The USP XXI (United States Pharmacopoeia, 1985) fails to mention any analytical method for impurities or degradation products while the Italian (FU IX, 1985) and British (BP, 1988) Pharmacopoeias report only a thin-layer chromatographic assay for *N*-methylpiperazine.

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We propose an HPLC method that can be used for the quantitation of its degradation product, 4-chlorobenzhydrol (**II**), and is suitable for stability evaluation of chlorcyclizine.

Chlorcyclizine hydrochloride was supplied by Sigma (St. Louis, U.S.A.) and 4-chlorobenzhydrol was from Aldrich (Milwaukee, U.S.A.). The acetonitrile HPLC grade (Carlo Erba, Italy) and double-distilled water were filtered through 0.45 μm Millipore membranes.

The high-performance liquid chromatograph used (Perkin Elmer, series 4) was equipped with a injector with a 20 μl loop (Rheodyne, model 7125), a variable-wavelength detector (Perkin Elmer, LC 75) and a strip chart recorder (Kipp Zonen, model BD 41). An analytical Lichrosorb RP 18 column (Perkin Elmer) of 250 mm length, 4.6 mm internal diameter and 10 μm particle size was also used.

The mobile phase consisted of a solution of acetonitrile and water (60 : 40 v/v) adjusted to pH 2.4. The flow rate of the mobile phase was 1.5 ml/min and the UV detector was set at 223 nm

with a sensitivity of 0.02–0.32 AUFS. The column temperature was ambient and the chart recorder set at a speed of 0.5 cm/min.

The proposed HPLC method is quite specific as evident from the separation of chlorcyclizine hydrochloride (**I**) and its degradation product (**II**) (Fig. 1).

Their retention times were found to be $3 \pm 5\%$ min for **I** and $6 \pm 5\%$ min for **II**. 4-Chlorobenzhydrol (**II**) showed a linear detector response throughout the concentration range tested (5–60 μg/ml) with a correlation coefficient of 0.9999. The accuracy of the method was established by determining the recovery of the degradation product (**II**) found to be 99.2% over the range 0.5–40 μg/ml with a relative standard deviation of 0.7%

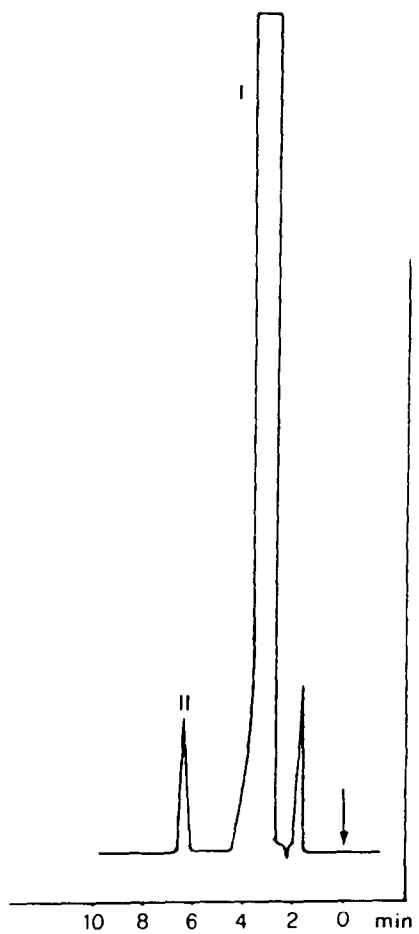

Fig. 1. Typical chromatogram of chlorcyclizine hydrochloride (**I**) and 4-chlorobenzhydrol, the degradation product (**II**).

TABLE 1

Percent recovery of 4-benzhydrol

Concentration (μg/ml)	Found (μg/ml)	Recovery (%)
0.5	0.5 (2.0)	100
1.5	1.48 (1.8)	98.6
3.0	3.02 (1.4)	100.6
4.0	3.94 (1.6)	98.5
5.0	4.93 (1.2)	98.6
7.0	6.95 (1.5)	99.2
10.0	9.90 (1.0)	99.0
20.0	19.80 (1.1)	99.0
40.0	39.80 (0.9)	99.5
	Mean recovery	99.2
	RSD %	0.7

(Table 1). The detection limit is 0.20 μg/ml. The reproducibility of three replicate injections of each sample is assured by a standard deviation ranging between 0.9 and 2.0%.

For stability studies, 2-ml samples of a 1% aqueous solution of **I** were introduced into vials and sealed. At appropriate intervals of time a vial was taken out and 1 ml of the solution was added to 1 ml of an ethanolic solution of phenylbutazone (internal standard) (0.1 mg/ml) into a 10 ml volumetric flask, diluted to volume with ethanol and chromatographed immediately.

Pseudo-first-order rate constants for the formation of the degradation product (**II**), determined from the slope of the linear plots of the logarithm of its concentration vs time, are 1.51×10^{-4}, 1.94×10^{-4} and 7.79×10^{-4} h^{-1} at 45, 55 and 75 °C, respectively.

In order to predict the stability of chlorcyclizine hydrochloride in aqueous solution at normal storage temperature, the Arrhenius equation was elaborated (Fig. 2) and a k value of 3.64×10^{-5} h^{-1} at 25 °C was obtained.

On the basis of these data, it is possible to estimate the shelf-life (as time required to form 10% of the degradation product) of aqueous solutions of **I**. The calculations show that a value of 115 days is achieved at 25 °C.

In conclusion, the proposed HPLC method is a precise, specific and reproducible procedure on the basis of its ability to separate chlorcyclizine hydrochloride from its degradation product. This

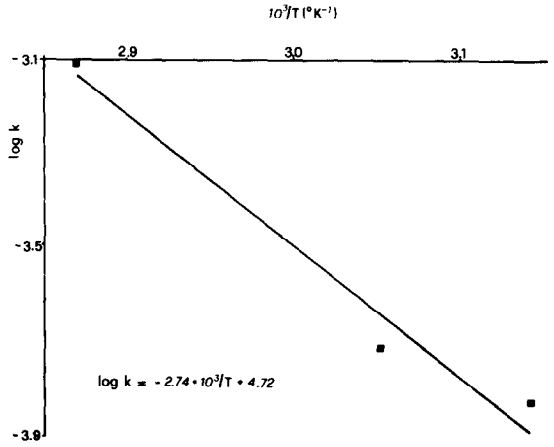

Fig. 2. Arrhenius plot of the rate of formation of degradation product (**II**) in aqueous solution.

method used for stability studies allowed the estimation of a shelf-life of 115 days for an aqueous solution of chlorcyclizine hydrochloride at 25 °C. Thus, this drug cannot be formulated as liquid dosage forms.

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