

## A polarographic limit test for sulphoxide in chlorpromazine

G. S. PORTER

Twin cell subtractive cathode ray polarography can be used as a quantitative limit test for from 0.5% to 2.0% of chlorpromazine sulphoxide in chlorpromazine. 0.05% of the impurity is detectable by derivative polarography.

**E**XISTING chromatographic limit tests for sulphoxide in phenothiazine drugs are time consuming, imprecise and require great care in order to avoid oxidation and photodegradation of the parent compound. A polarographic method is suggested for chlorpromazine sulphoxide in chlorpromazine, based on the fact that the sulphoxide gives a cathodic wave in 0.5N hydrochloric acid whereas the drug does not (Porter & Beresford, 1966).

The characteristic direct sulphoxide wave is shifted to a more negative peak voltage in the presence of a large excess of chlorpromazine, and appears as an unreadable shoulder on the final current rise. Derivative operation, while giving a rough quantitative estimation of sulphoxide content, does not resolve the wave completely. Twin cell subtractive operation gives complete resolution of the wave given by the sulphoxide, enabling concentrations of it from 0.5  $\mu\text{g/ml}$  to 2.0  $\mu\text{g/ml}$  to be determined in the presence of 100  $\mu\text{g/ml}$  of chlorpromazine.

### Experimental and results

#### APPARATUS

A Davis differential cathode ray polarograph was used (A1660, Southern Analytical Ltd.) with mercury pool anodes, and capillaries balanced by the normal procedure. All solutions were prepared and examined in subdued daylight, used within 2 hr of preparation and flushed with nitrogen (10 min) before polarographing.

#### CHLORPROMAZINE AND CHLORPROMAZINE SULPHOXIDE

Both are available as pure bases and solutions were prepared (chlorpromazine 500  $\mu\text{g/ml}$ , chlorpromazine sulphoxide 25  $\mu\text{g/ml}$ ) in 0.005N hydrochloric acid. The chlorpromazine was examined polarographically in 0.5N hydrochloric acid at a concentration of 100  $\mu\text{g/ml}$  using the 50 msec derivative circuit and maximum instrument sensitivity. No cathodic wave was seen (Fig. 1A). The sulphoxide (0.5  $\mu\text{g/ml}$ ) gave the expected wave under the same conditions (Fig. 1B).

Inclusion of 0.2  $\mu\text{g/ml}$  of the sulphoxide with the chlorpromazine (100  $\mu\text{g/ml}$ ) produced a distinct wave using the 50 msec derivative circuit, maximum sensitivity and a start potential of  $-0.6$  V (Fig. 2A). The limit of detection for sulphoxide under these conditions was not greater than 0.05  $\mu\text{g/ml}$  (Fig. 2B).

From the School of Pharmacy, Liverpool Regional College of Technology, Byrom Street, Liverpool, 3.

## LIMIT TEST FOR SULPHOXIDE IN CHLORPROMAZINE

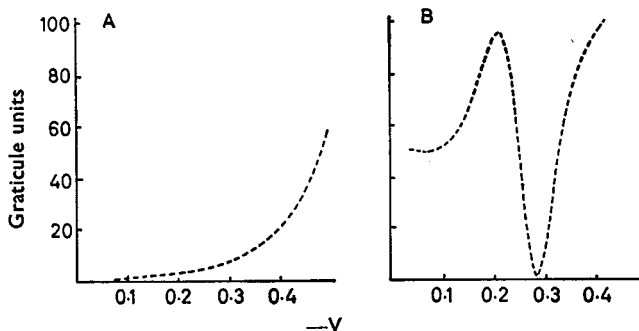


FIG. 1. Polarogram of (A) chlorpromazine (100  $\mu\text{g}/\text{ml}$ ), (B) chlorpromazine sulphoxide (0.5  $\mu\text{g}/\text{ml}$ ); 50 msec derivative, sensitivity maximum, start potential  $-0.6$  V, supporting electrolyte 0.5 N hydrochloric acid.

### PROCEDURE FOR CALIBRATION

Twin cell operation was carried out, the reference cell (cell 2) containing the base (100  $\mu\text{g}/\text{ml}$ ) in 0.5N hydrochloric acid. The test cell (cell 1) contained the base (100  $\mu\text{g}/\text{ml}$ ) and successive concentrations of the sulphoxide between 0.5  $\mu\text{g}/\text{ml}$  and 2.0  $\mu\text{g}/\text{ml}$  in 0.5N hydrochloric acid.

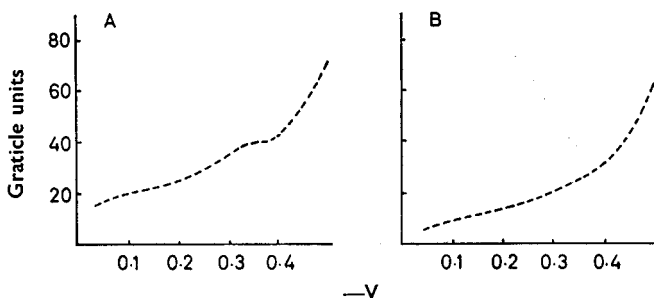


FIG. 2. Polarogram of chlorpromazine sulphoxide (A. 0.2; B. 0.05  $\mu\text{g}/\text{ml}$ ) in the presence of chlorpromazine (100  $\mu\text{g}/\text{ml}$ ); 50 msec derivative, sensitivity maximum, start potential  $-0.6$  V, supporting electrolyte 0.5 N hydrochloric acid.

With a start potential of  $-0.6$  V the subtractive wave peak occurred at about  $-0.93$  V and a peak current/sulphoxide concentration graph was constructed, using the mean of five determinations at each sulphoxide concentration level (Table 1).

TABLE 1. CALIBRATION FOR TWIN CELL POLAROGRAPHY OF CHLORPROMAZINE SULPHOXIDE IN THE PRESENCE OF CHLORPROMAZINE (100  $\mu\text{G}/\text{ML}$ )

Sulphoxide concentration ( $\mu\text{g}/\text{ml}$ )	Peak current (graticule units)		Sensitivity	Peak current at maximum sensitivity
	Mean	Standard deviation		
0.5	56	2.4	0.4 max.	140
1.0	67	1.3	0.25 "	268
1.5	70	1.1	0.16 "	420
2.0	92	1.0	0.16 "	552

Polarograms for cells 1 and 2 and the subtractive wave for  $0.5 \mu\text{g/ml}$  sulphoxide as shown in Fig. 3A-C, respectively.

#### LIMIT TEST FOR SULPHOXIDE IN CHLORPROMAZINE HYDROCHLORIDE

A solution is prepared of the sample under test ( $112 \mu\text{g/ml}$ ) in  $0.5N$  hydrochloric acid. If no wave is seen on 50 msec derivative operation at maximum sensitivity, the sample does not contain more than  $0.1\%$  sulphoxide. If a wave is seen in the  $-0.93 \text{ V}$  region, twin cell operation is carried out, using as reference either pure chlorpromazine base ( $100 \mu\text{g/ml}$ ) or the pure hydrochloride ( $112 \mu\text{g/ml}$ ) in  $0.5N$  hydrochloric acid.

The peak current of the resolved wave should not be greater than that of a standard solution containing  $100 \mu\text{g/ml}$  of pure chlorpromazine base (or an equivalent amount of pure hydrochloride) and the required concentration of the sulphoxide. A fresh reference solution is used for each determination.

Application of the test to a prepared solid mixture of sulphoxide ( $1\%$ ) in chlorpromazine, gave a peak current reading of 280 graticule units at maximum sensitivity.

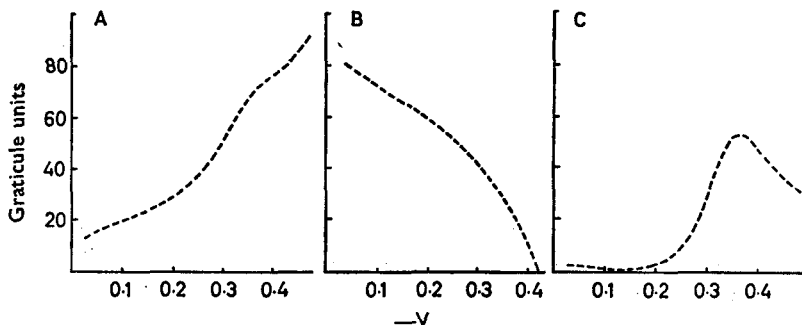


FIG. 3. A. Direct polarogram of chlorpromazine sulphoxide ( $0.5 \mu\text{g/ml}$ ) and chlorpromazine ( $100 \mu\text{g/ml}$ ). B. Direct polarogram (inverted) of chlorpromazine ( $100 \mu\text{g/ml}$ ). C. Subtractive sulphoxide wave ( $0.5 \mu\text{g/ml}$ ), sensitivity  $0.4$  maximum, start potential  $-0.6 \text{ V}$ , supporting electrolyte  $0.5N$  hydrochloric acid.

## Discussion

The method is rapid ( $\frac{1}{2}$  hr), accurate, sensitive, and has been applied successfully to promethazine and fluphenazine. A wave due to  $0.2 \mu\text{g/ml}$  chlorpromazine sulphoxide can readily be resolved.

The method will not, of course, distinguish between the sulphoxide and any other reducible decomposition product which generates an inseparable wave, but this consideration is not of prime importance as the total quantity of such decomposition products may be expressed in terms of sulphoxide.

No polarographically detectable deterioration occurred with either chlorpromazine or its sulphoxide in  $0.5N$  hydrochloric acid under the conditions employed. Solutions exposed to normal laboratory bench

## LIMIT TEST FOR SULPHOXIDE IN CHLORPROMAZINE

daylight conditions for 8 hr developed in the case of chlorpromazine a wave indistinguishable from the sulphoxide wave, whereas sulphoxide solutions under these conditions showed a diminution in height of the characteristic wave. Solutions kept in the dark showed no deterioration for some days.

*Acknowledgement.* The chlorpromazine and chlorpromazine sulphoxide samples were kindly supplied by Messrs. May and Baker Ltd., Dagenham.

### Reference

Porter, G. S. & Beresford, J. (1966). *J. Pharm. Pharmac.*, **18**, 223-227.