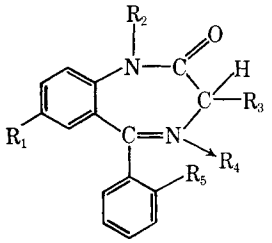
Polarographic Determination of Oxazepam

F. RAYMOND FAZZARI and OSCAR H. RIGGLEMAN

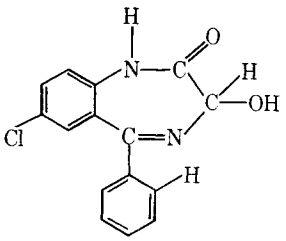
Abstract □ Oxazepam was extracted from dosage form and polarographed in a methanol–methylene chloride solvent system. Well defined cathodic waves were obtained at the dropping mercury electrode and the diffusion current was shown to be proportional to the concentration. The method is rapid and reasonably specific. Recoveries ranged from 97.0–104.0% with an average of 99.9%.

Keyphrases □ Oxazepam dosage forms—analysis □ Methanol–methylene Cl solvent—oxazepam determination □ Polarography—analysis

Oxazepam, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one, belongs to the chemical class referred to as the benzodiazepines.

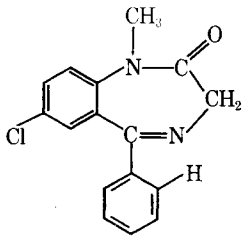


General Structure



Oxazepam

Senkowski *et al.* (1) have reported a large amount of data concerning the polarographic behavior of the benzodiazepines. These authors used 0.1 *N* HCl in 20% methyl alcohol as the solvent, and included in their report the results of the polarography of diazepam, the compound most closely related to oxazepam.



Diazepam

In addition, Oelschlager (2), using aqueous Britton-Robinson buffers as solvents, compiled data on the related compound chlordiazepoxide hydrochloride.

Because the applicability of polarographic techniques for the analysis of benzodiazepines is thus well established, and because of the need for a rapid, accurate analytical method for oxazepam, the authors have applied polarography to this compound. The entire procedure, including extraction and the recording of the polarogram, is very rapid and simple. An electrochemical read-out is applied directly to the sample extract without additional manipulation except for dilutions; this is more suitable than extracting with solvents that must be removed before the determinative step. Because oxazepam is extracted from the dosage form, polarographed in a well-controlled solvent system, and quantitated at its characteristic half-wave potential, the method is adequately specific. Similar compounds that would interfere in the analysis would not be expected to be present in the same dosage form.

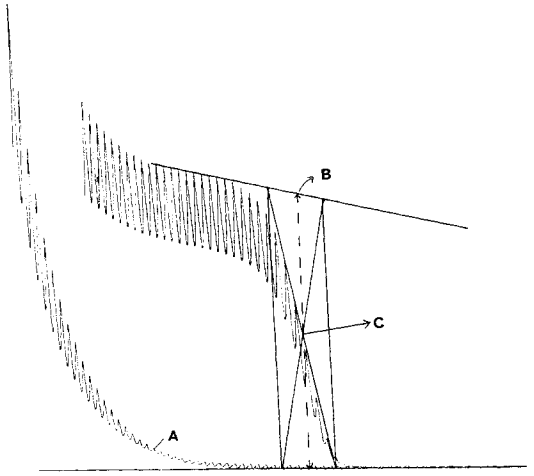


Figure 1—*Illustration of reduction wave and calculation of the limiting current.* A, *blank;* B, I_D = *1.72 μamp.;* C, $E_{1/2}$ = *−1.02 v.*

Well-defined cathodic waves (see Fig. 1) were obtained at the dropping mercury electrode in a mixture of methylene chloride–methyl alcohol solvent. The diffusion current was found to be linear at a limiting current of 0–3.4 μamp. over the range of interest (Fig. 2), thus permitting quantitative results. With the recommended instrument operating parameters, the sensitivity of the method is 0.5 mg./50 ml. of solvent.

EXPERIMENTAL

Apparatus—A recording polarograph[1] was used to obtain the curves for the analysis of polarographic waves. An electrolysis vessel with a capacity of approximately 20 ml. and a silver/silver chloride wire reference electrode were used. The electrode capillary delivered the mercury at 1.85 mg./sec. at a column height of 50 cm. The drop time was 4.5 sec. and the capillary constant, $m^{2/3}t^{1/6}$, was 1.90 mg./sec. The constants were obtained at ambient temperature with the mercury dropping into the solvent system. The sensitivity of the instrument was 2×10^{-8}A/mm. (0.02 mamp./mm.), the voltage span −0.5 to −2.0 v., the damping 5.0, and the bucking current 0.

Reagents and Standard—*Extraction Solvent*—0.1 *N* HCl and methylene chloride.

Polarographic Solvent—Prepare the following stock solutions: 0.2 *M* acetic acid in methyl alcohol; and 0.2 *M* sodium acetate (27.199 g. of the trihydrate per liter) in methyl alcohol. Mix 5.9 ml. of the 0.2 *M* acetic acid with 14.1 ml. of the 0.2 *M* sodium acetate.

Suppressor—A 0.1% solution of alkyl polyethoxy ethanol[2] in the polarographic solvent.

Supporting Electrolyte—0.1 *M* tetraethylammonium bromide in the polarographic solvent.

Oxazepam Standard Solution—Dissolve 25 mg. of standard oxazepam in 50 ml. of methylene chloride.

[1] Metrohm Polarecord E-261 with E-354 polarographic cell assembly.
[2] Triton X-100, Rohm & Haas, Philadelphia, Pa.

Table I—Recovery of Added Oxazepam

Added, mg.	Found, mg.	Recovery, %
	Analyst I	
24.33	24.00	99.0
25.66	25.03	97.7
30.52	29.40	98.0
26.65	26.75	100.2
27.60	27.80	100.5
28.90	29.20	101.0
	Analyst II	
26.32	27.48	104.0
25.41	25.63	100.9
27.80	28.16	101.3
24.71	24.92	101.0
24.66	24.00	97.0
26.85	26.65	99.3
Average		99.9
SD		±2.64

Procedure—*Extraction*—Quantitatively transfer a representative portion of sample, equivalent to approximately 25 mg. of oxazepam, to a 125-ml. separator with small portions of methylene chloride. Add methylene chloride to a total volume of 25 ml. and shake the separator to dissolve the oxazepam (about 1 min.). To increase the solubility of the oxazepam and to remove the excipients, add 25 ml. of 0.1 *N* HCl to the separator and shake the mixture. gently for about 30 40 sec. Drain the organic phase into a 50-ml. volumetric flask and re-extract the acid phase with successive 15- and 10-ml. portions of methylene chloride, combining each portion in the volumetric flask. Dilute to volume with methylene chloride.

Filter the methylene chloride through a fast filtering filter paper, discarding the first 10–15 ml. Quantitatively transfer a 5-ml. aliquot of the filtrate to a 50-ml. volumetric flask. Using Mohr pipets, add 5 ml. of supporting electrolyte and 5 ml. of suppressor; then dilute to volume with the polarographic solvent.

Polarography—Place approximately 15 ml. of the sample solution in the polarographic cell equipped with the silver/silver chloride reference and the dropping mercury electrodes. Use a gentle stream of nitrogen, bubbled through a solvent scrubber and then through the cell, to deaerate the solution. After 5 min., record the polarogram, using the prescribed instrument parameters, while continuing to gently sweep the cell with nitrogen.

Determine the limiting current at the half-wave potential (about −1.02 v.). Refer to the sample polarogram, Fig. 1, to calculate the limiting current; compare to the limiting current of a standard prepared by taking a 5-ml. aliquot of the standard oxazepam solution and treating it in the same manner as the sample.

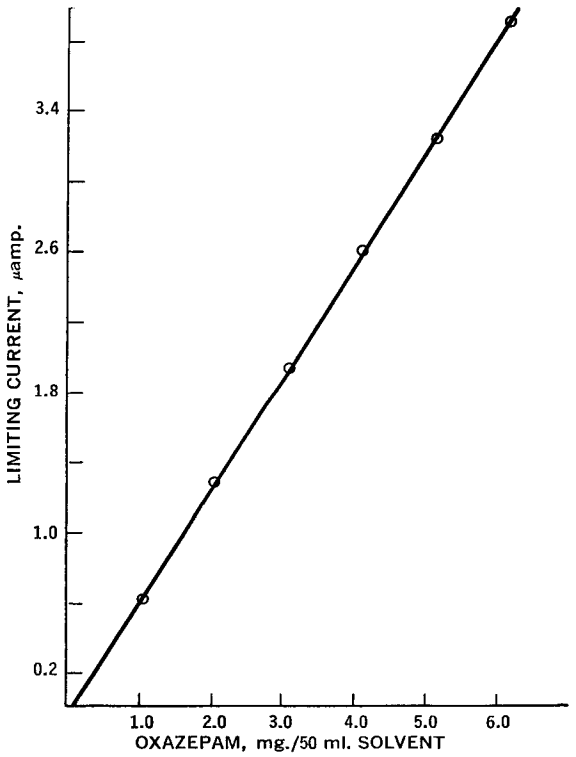


Figure 2—*Plot of oxazepam concentration* versus *limiting current.*

Table II—Analyses of Oxazepam Capsules

Sample Weight, mg.[a]	Mg./Capsule	% Declared
	Analyst I	
184.19	29.6	98.6
187.29	29.1	97.5
185.98	29.5	98.5
178.94	29.3	98.0
171.73	29.2	97.3
187.25	29.2	97.3
	Analyst II	
181.75	29.5	98.2
181.70	29.5	98.3
178.76	29.5	97.3
184.19	29.6	98.7
181.40	28.3	94.2
	Analyst III	
184.90	29.8	99.4
174.10	30.4	101.3
179.70	30.2	100.7
185.70	29.2	97.2
	Analyst IV	
182.10	29.3	97.6
181.20	28.8	96.0
181.50	29.9	99.7
183.20	30.0	100.0
179.70	29.8	99.4
Average	29.4	
SD	± 0.45	

[a] Equivalent to approximately 30 mg. of oxazepam.

RESULTS AND DISCUSSION

Recovery data, ranging from 97.0 to 104.0% at the 25-mg. level, are presented in Table I.

Table II shows the results of actual sample analyses performed by four different analysts. All data are based on a product declared to have 30 mg. of oxazepam per capsule. Assay weights were taken from a prepared composite. Results ranged from 28.3 to 30.4 mg. found per capsule, reflecting an average value of 29.5 mg. and a standard deviation of ±0.45 mg.

A sample weight equivalent to 25 mg. of oxazepam was selected since it resulted in a limiting current reflecting the midpoint of the linearity plot. However, a much smaller amount can be used. Because the sensitivity of the method is at least 0.5 mg./50 ml. of solvent, a sample equivalent to 10 mg., the lowest dosage form currently available, can be accurately analyzed. Therefore the method is applicable to the dosage forms of 10, 15, and 30 mg., not only for composite analysis but also for individual dose analysis.

REFERENCES

(1) B. Z. Senkowski, M. S. Levin, J. R. Urbigkit, and E. G. Wollish, *Anal. Chem.*, **36**, 1991(1964).

(2) H. Oelschlager, *Arch. Pharm.*, **296**, 396(1963).

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