DIFFERENTIAL PULSE POLAROGRAPHY (DPP) IN THE DETERMINATION OF CLONAZEPAM AND NITRAZEPAM IN HOSPITAL FORMULATED SUSPENSIONS

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Recently Purkiss & Kayes (1981) described the extent of use by hospitals of specially formulated and prepared drug suspensions. These often require capsule or tablet powder to be suspended in a suitably viscous medium to produce an oral liquid preparation which is presented extemporaneously with little or no quality control. We are investigating the suitability of DPP as a precise, reliable means of quality control requiring a minimum of sample preparation for such formulations.

Nitrazepam and Clonazepam are both formulated in this manner at the Southern General Hospital (SGH), Glasgow, and although DC polarographic assays for these compounds have been reported [e.g. Vinh et al (1978)], there are no reports relating to liquid preparations, nor to DPP which is more sensitive than DC. The sterilized vehicle used at SGH for suspending the appropriate quantity of powdered solid includes methylcellulose 20 (0.74%), syrup B.P. (38%), the preservative Nipasept (0.1%), and a silicone based antifoaming agent (0.05%).

The assays were performed with a Princeton Applied Research Model 174A polarograph and Model 303 dropping mercury electrode assembly. Reduction voltage peaks at -0.090 V and -0.585 V with respect to the Ag/AgCl reference for Nitrazepam and Clonazepam respectively were used for analysis, the suspension samples being diluted 1 in 20 with methanol and then 1 in 5 with 0.1 mol l^{-1} HCl.

Calibration graphs prepared for both drugs in this solvent were linear over a wide concentration range (r=0.999, 8 replicates at each of 5 concentrations) which included the narrow range obtained when the suspensions were diluted. For comparison, crushed tablets were extracted with 100 cm^3 methanol and then diluted 1 to 5 with 0.1 mol l^{-1} HCl before analysis. A standard addition procedure for the suspensions was also used in which known weights of pure substances were added to the methanolic solutions before dilution with HCl.

		Results as % of theoretical amount	
Preparation		Direct comparison with graph. (4 assays ± coeff. of variation)	Standard Additions Method
Nitrazepam	Tablets	99.9 ± 1.0%	-
	0.5mg/5ml suspension	70.6 ± 1.6%	95.6%, r = 0.992
Clonazepam	Tablets	104.0 ± 1.19%	-
	0.5mg/5ml suspension	79.2 ± 0.52%	102.8%, r = 0.994

The discrepancies in the results for the suspensions analysed by the direct comparison method are probably caused by vehicle component interference. This is supported by comparison of pure drug substance calibration graphs with similar graphs obtained in the presence of 1% suspending agent in which a reduction in slope, corresponding to the low results, was observed although linearity was retained. Thus although interference was observed for the direct determinations more satisfactory results can be obtained by the standard additions method.

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