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Electrochemical behaviour and determination of triprolidine and diphemanil in pharmaceutical formulations*

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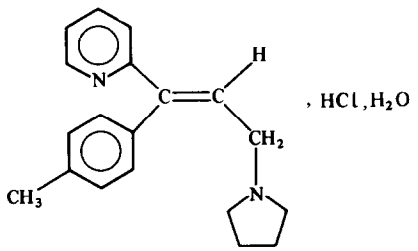
Introduction

Triprolidine hydrochloride, Actidilon® and diphemanil methylsulphate, Prantal® are widely used as antihistamine and anticholinergic agents. Various assay techniques have been applied, including gas–liquid chromatography (GLC) [1–3] and high-performance liquid chromatography (HPLC) [4]. However there are no studies of their quantitative determination in pharmaceutical formulations without prior separation.

Both compounds possess a double bond which is part of an extended π-system and may be reduced by electron transfer [5, 6]. In the present work, their electrochemical behaviour at the dropping mercury electrode in dimethyl sulphoxide and ethanol has been investigated, in order to develop a simple, rapid direct current polarographic method for their determination in tablets and creams.



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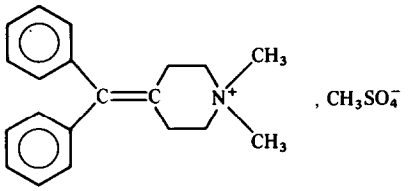

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Experimental

Solvents, electrolytes and reagents

Dimethyl sulfoxide (DMSO; spectroscopic grade) (Merck).

Ethanol (analytical grade) (Prolabo) purified by the procedure of Lund and Bjerrum [7].

Tetraethylammonium perchlorate (TEAP) (Fluka) purified by the method of Kolthoff and Coetzee [8].

Triprolidine hydrochloride (Wellcome) and diphemanil methylsulphate (Unilabo) were used without further purification. Their identity was checked by IR and NMR spectra and their purity by TLC.

Apparatus

Polarographic measurements were made on a PRG5 Tacussel potentiostat coupled with an EPL1 Tacussel recorder in conjunction with a three-electrode thermostated (25° ± 0.1°C) cell which consists of an MPO Tacussel dropping mercury electrode with an adjustable drop-time and a platinum wire auxiliary electrode. The Ag/AgCl reference electrode and sample compartment were separated by a TEAP/solvent bridge.

Cyclic voltammetric triangular wave forms were obtained from a GSTP3 Tacussel function generator. A hanging drop mercury electrode (Kemula type) was used as the working electrode, and the reference and counter electrodes were identical to those described above. Data were recorded on an R 5103M Tektronik oscilloscope.

For controlled potential electrolysis, a mercury pool approximately 1 cm deep and 12 cm^2 in area was placed in the cell and a large surface platinum auxiliary electrode was used in the anodic compartment separated by a solvent bridge containing background electrolyte. The reference electrode was the same as that described above. Potentials were applied by a PRT 202X Tacussel potentiostat. The quantity of electricity was measured using an IG5 Tacussel integrator.

Polarographic measurements

For all the experiments, the background electrolyte was 0.2 M TEAP. The solutions were purged with nitrogen and kept under atmosphere of nitrogen during the recording. Direct current polarographic data were obtained at a controlled drop-time of 1 s. Cyclic voltammograms were recorded at different potential scan rates (1–10 $V.s^{-1}$). For controlled potential electrolysis, nitrogen was continuously bubbled through the solution during electrolysis and a magnetic stirrer was used.

Standard addition method

10^{-5} mol of each drug (p mg) were accurately weighed into a polarographic cell and dissolved in 20 ml of TEAP solution in a suitable solvent. Nitrogen was bubbled for 10 min. Two polarograms for each solution were scanned and the net wave heights were measured. An average of these wave heights (i_a) was used for the calculations. The operations were repeated after adding q mg (10^{-5} mol) of reference standard and stirring with a nitrogen stream (i_b). The drug content was calculated as:

$$\frac{100 \times i_a \times q}{(i_b - i_a)\, p}$$

Assay of pharmaceutical preparations

Actidilon® tablets and Prantal® tablets and cream were introduced directly into the polarographic cell without prior separation.

Tablets: 20 tablets were weighed and powdered (P = average weight). An accurately weighed quantity of powder equivalent to 10^{-5} mol of drug (p mg) was shaken with 20 ml of TEAP solution in ethanol under a stream of nitrogen for 10 min and then assayed by the standard addition method. The drug content (mg per tablet) was calculated as:

$$\frac{P \times i_a \times q}{(i_b - i_a)\, p}$$

Prantal® cream: 20 ml of supporting electrolyte in DMSO was added to a quantity of cream equivalent to 10^{-5} mol (p mg) of diphemanil methylsulphate and shaken until dispersed. The suspension was assayed by the standard addition method.

Actilidon® cream: 10 ml of supporting electrolyte solution in DMSO were added to a quantity of the preparation equivalent to 10^{-5} mol (p mg) of triprolidine hydrochloride and shaken until the preparation was completely dispersed. The suspension was allowed to stand for 20 min, centrifugated for 5 min at 3000 r.p.m. and the upper phase was transferred to a polarographic cell. The procedure was repeated with a further two portions of 10 ml and the standard addition method was carried out on the combined supernatant solutions.

Results and Discussion

Electrochemical behaviour

Triprolidine hydrochloride and diphemanil methylsulphate yield different cathodic waves at the dropping mercury electrode in DMSO and ethanol with tetraethylammonium perchlorate (TEAP) as supporting electrolyte. The polarogram of triprolidine hydrochloride was found to consist of a one electron wave ($E_{½}$ = 1.3V) followed by a second wave of about double the height of the first. A third step of equal height to the second was also observed. As the first monoelectronic transfer was absent in triprolidine base, it was unambiguously attributed to hydrochloride and was not further investigated. Vinyl pyridine exhibits two waves with similar half-wave potentials and intensities. Diphemanil methylsulphate and 1,1-diphenylethylene yield a single step corresponding to the first step of vinyl pyridine. Only this wave observed in the two drugs was investigated.

The number of electrons transferred estimated by exhaustive controlled potential electrolysis is two and no anodic wave was observed during coulometry. Irreversibility is confirmed by cyclic voltammetric measurements in which no anodic peak corresponding to the oxidation of the reduction product was observed at any scan rate (1–10 $V.s^{-1}$).

For each substance, ethanol which is a proton donor solvent, is more suitable than DMSO for the electron transfer (Table 1) which may be assigned to the reduction of the olefinic bond:

$$>C = C< + 2e^- + 2\,H^+ \rightarrow >CH - CH<$$

Table 1
Half-wave potential ($E_{1/2}$) in volts vs Ag/AgCl in different solvents (TEAP 10^{-1} mol.l^{-1})

$E_{1/2}$	Diphemanil	Triprolidine base	1,1-Diphenylethylene	Vinyl 2-pyridine
Ethanol	−2.33	−2.00	−2.30	−2.00
DMSO	−2.52	−2.35	−2.40	−2.35
DMSO + Phenol	−2.45	−2.25		

This hypothesis is strengthened by the shifts of $E_{1/2}$ to less negative potentials after the addition of a proton donor such as phenol to DMSO solutions.

The $E_{1/2}$ of diphemanil is more negative than vinyl pyridine in the two solvents and this is attributed to the positions of the antibonding orbitals of the double bond. As the pyridine ring in tripolidine hydrochloride and vinyl pyridine involves a lower unoccupied molecular orbital that is higher than that of the benzene ring in diphemanil methylsulphate and 1,1-diphenylethylene, the electronic transfer is easier.

Determination in pharmaceutical preparations

Calibration graphs of current intensities (i_{lim}) against concentrations (c) were plotted. The response was linear in the range 10^{-4}–5.10^{-3} mol.l^{-1} in the recommended electrolyte ($n = 6$)

$$\text{Tripolidine hydrochloride: } r = 0.999,\ Y(\mu A) = 7.71\ X(mg) + 1.29,$$
$$\text{Diphemanil methylsulphate: } r = 0.999,\ Y(\mu A) = 2.94\ X(mg) - 2.16.$$

Direct proportionalities of functions $i_{lim} = f(\theta)$ and $i_{lim} = f(c)$ prove the diffusion character of the polarographic current and permit the drug to be assayed.

The precision was ascertained by carrying out 10 replicate analyses on freshly prepared 5.10^{-4} mol.l^{-1} standard solutions. For evaluating the precision of the method the following equations were used:

$$\bar{X} = (\Sigma_{i=1}^{n} X_i)/n;$$

$$S = \sqrt{[\Sigma_{i=1}^{n} (X_i - \bar{X})^2]/n};$$

$$RSD = (S \times 100)/\bar{X}.$$

The relative standard deviations (RSD) for tripolidine hydrochloride and diphemanil methylsulphate were 0.9 and 1.0% respectively.

Pharmaceutical dyes and the following excipients which are commonly found in tablets and creams were checked for possible interference with the method: lactose, saccharose, microcrystalline cellulose, magnesium stearate, zinc stearate, polyethylene glycol, cetyl alcohol, gelatin, waxes, petrolatum, *p*-hydroxybenzoates. No reduction wave was observed at the $E_{1/2}$ of the drugs.

Five replicate analyses were performed on pharmaceutical preparations. Table 2 shows the results of the assay of commercial triprolidine (Actidilon) and diphemanil (Prantal) tablets and creams. The average values obtained are in good agreement with the stated amounts and relative standard deviations are less than 1.75%.

Table 2
Assay of triprolidine and diphemanil by D.C. polarography

Trade name*	Stated amount	Average found†	Recovery %	RSD
Actidilon® tablet	2.5 mg	2.45 mg	98.0	1.1
cream	0.2%	0.195%	97.6	1.6
Prantal® tablet	100 mg	99.4 mg	99.4	0.9
suppository	2%	19.8%	99.1	1.4

* Actidilon preparations contain triprolidine hydrochloride. Prantal preparations contain diphemanil methyl sulphate.
† Average of 5 determinations.

Conclusion

The polarographic reduction of vinyl groups conjugated with aromatic rings may be used for the assay of drugs in pharmaceutical preparations. The simple and accurate standard addition method proposed for the assay of triprolidine and diphemanil requires a minimum of sample preparation.

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