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ARTICLES

Voltammetric Determination of Papaverine and Drotaverine

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Abstract—Isoquinoline derivatives (papaverine and drotaverine) are oxidized at a graphite electrode in a 0.1 M sulfuric acid solution to give voltammetric waves at 1.1 V for papaverine and at 1.05 and 1.28 V for drotaverine. Determination limits and linearity ranges of currents as functions of papaverine and drotaverine concentrations are estimated. Microgram amounts of papaverine and drotaverine are determined in model solutions (RSD = 1–4%). A procedure for the direct determination of papaverine and drotaverine in pharmaceuticals is proposed.

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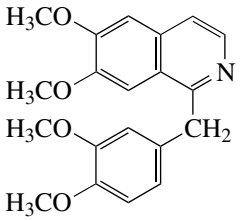
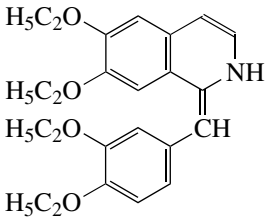
Papaverine [1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline] and drotaverine [1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline] are the derivatives of isoquinoline.



Papaverine



Drotaverine

Along with morphine, narcotine, codeine, thebaine, and narceine, papaverine belongs to alkaloids of the opium group. It was first isolated by Merck in 1848. Early in the 20th century, it was synthesized [1]. Drotaverine is a synthetic preparation.

Papaverine and drotaverine belong to myotropic antispasmodics and are used in medical practice. These preparations lowered tonus and reduced the contractile activity of smooth muscles. In significant doses, they reduced the excitability of the cardiac muscle and delayed intracardiac conduction [2].

The mechanism of the action of isoquinoline derivatives consists in the inhibition of phosphodiesterase, which caused the intracellular accumulation of cyclic 3',5'-adenosine monophosphate and decreased the ingress of ionized active calcium into smooth-muscle tissues. This, in turn, changed the contractility of smooth muscles and relaxed them during spastic states [3].

Chromatographic [4–7], electrochemical [8,9], and optical [10–12] methods were used to determine papaverine and drotaverine.

To determine papaverine, an ion-selective electrode with a polyvinyl chloride membrane plasticized with dioctyl phthalate and based on ion pairs formed by papaverine and heteropoly acids (tungstosilicic, molybdosilicic, tungstophosphoric, and molybdophosphoric acids), anions of organic salting out agents (sodium picrate and tetraphenyl borate), and complex salts (potassium tetraiodomercurate, potassium tetraiodobismuthate, and Reinecke salt) was created [13].

An ion-selective electrode with a liquid membrane based on papaverine tetraphenyl borate is available for determining papaverine [14]. Its potential is a linear function of papaverine concentration in the range 1×10^{-5} to 5×10^{-2} M. A procedure is developed for determining papaverine in ampoule preparations.

HPLC was used to determine drotaverine in blood serum. The detection limit was 50 ng/mL, RSD < 4% [15].

HPLC with photometric detection was applied to the determination of drotaverine in blood serum and urine [16]. Separation was carried out on a C_{18} column after extraction with an organic solvent and back extraction with a 0.1 M HCl solution. A mixture of 0.02 M dihydrogen phosphate–methanol (30 : 70, V/V) containing perchlorate ions (pH 3.2) was used as the mobile phase. The detection limit was 6 ng/mL (S/N = 3).

Potentiometric sensors for determining drotaverine in pharmaceuticals were described in [17–19].

A highly sensitive procedure for determining papaverine was developed. It is based on the indirect solid-phase enzyme immunoassay using a biotin–avidin intensifying system and photometric detection at 450 nm. The calibration graph was linear in the range from 0.02 to 1000 ng/mL papaverine. The detection limit was 0.008 ng/mL. The procedure was used to determine papaverine in pharmaceuticals [20].

It follows from the above-stated that chromatography, spectrophotometry, and potentiometry are most often used to determine isoquinoline derivatives. The use of voltammetry, a simple, sensitive, and rapid method, is promising.

The goal of this work was to find the specific features of the voltammetric behavior of papaverine and

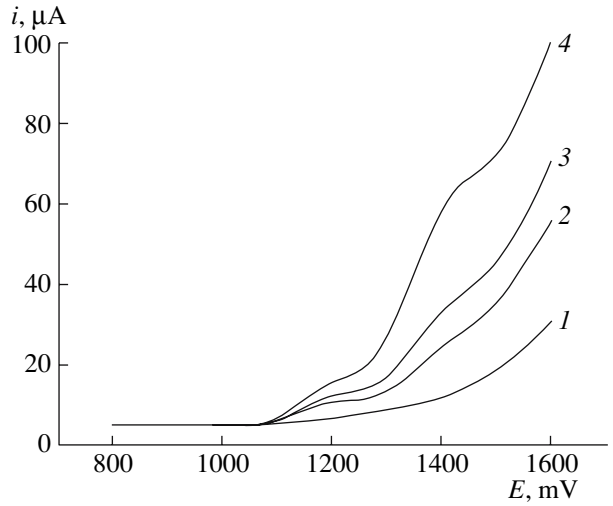


Fig. 1. Voltammograms of drotaverine oxidation at a graphite electrode in a 0.1 M H_2SO_4 solution (c (M): *1*, 0; *2*, 3.23×10^{-5}; *3*, 5.34×10^{-5}; *4*, 1.05×10^{-4}. Potential sweep rate, 50 mV/s).

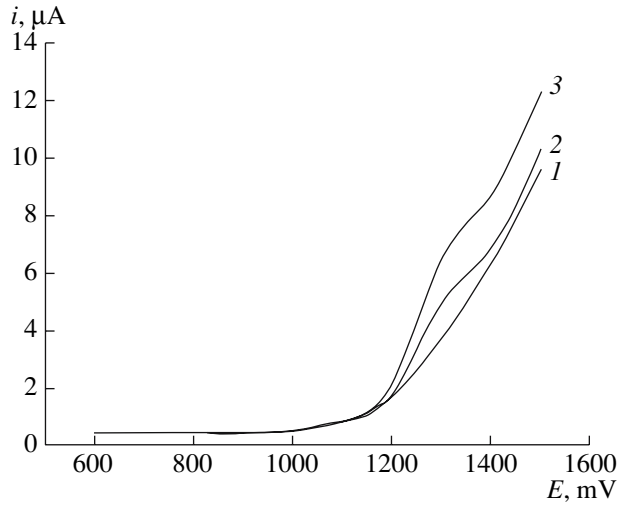


Fig. 2. Voltammograms of papaverine oxidation at a graphite electrode in a 0.1 M H_2SO_4 solution (c (M): *1*, 0; *2*, 1.95×10^{-5}; *3*, 3.82×10^{-5}. Potential sweep rate, 50 mV/s).

drotaverine at stationary electrodes and to develop a procedure for their direct determination in pharmaceuticals.

EXPERIMENTAL

The investigation was carried out using an Ekotest-VA voltammetric analyzer. A 20.0-mL portion of a 0.1 M H_2SO_4 solution and an aliquot of a test solution were placed in a 50.0-mL cell. The working, auxiliary (platinum-wire helix), and saturated silver–silver chloride reference electrodes were introduced; and anodic voltammograms were recorded with a linear potential sweep from 0.1 to 1.5 V.

Standard aqueous solutions of papaverine and drotaverine chlorides were prepared from accurately weighed samples.

Procedure for determining papaverine and drotaverine in pharmaceuticals. About 0.02 g (accurately weighed sample) of a powder of triturated tablets was dissolved in distilled water in a 50.0-mL volumetric flask. The solution obtained was filtered. A 0.7-mL aliquot portion of the solution was introduced into a cell containing a 0.1 M H_2SO_4 solution, and voltammograms were recorded.

RESULTS AND DISCUSSION

Platinum, graphite, and glassy-carbon stationary electrodes were tested for the voltammetric determination of papaverine and drotaverine. A 0.1 M H_2SO_4 solution served as a supporting electrolyte. It is known that, in alkaline solutions, the substances under study are virtually insoluble and precipitate. For this reason, isoquinoline derivatives are obtained by recrystallization from acids as hydrochlorides.

Papaverine is oxidized at graphite and glassy-carbon electrodes, whereas drotaverine is oxidized only at a graphite electrode. The hydrochloride fragment is electrochemically inert under the conditions of our experiments.

Two oxidation waves at 1.05 and 1.28 V were observed in the voltammograms of drotaverine obtained at a graphite electrode (Fig. 1). The limiting current of the first wave was a linear function of the drotaverine concentration in the solution. The determination limit for drotaverine was 2.16×10^{-5} M.

A wave at 1.1 V was observed in the voltammogram of papaverine oxidation at a graphite electrode. The limiting current of the wave was a linear function of the papaverine concentration in the solution (Fig. 2). The determination limit for papaverine was 7.88×10^{-6} M.

Papaverine is oxidized at a glassy-carbon electrode at 1 V, but the dependence of the oxidation current on the papaverine concentration in the solution was not linear.

The parameters of calibration graphs for determining isoquinoline derivatives are presented in Table 1.

The results of the voltammetric determination of papaverine and drotaverine in model solutions are summarized in Table 2. The accuracy of the determination was verified by the added–found method.

A procedure for the direct determination of papaverine and drotaverine in tablets of these pharmaceuticals is proposed. The results obtained (Table 3) were compared with the data of the coulometric analysis of these preparations. As can be seen from Table 3, the results are in good agreement to each other.

Table 1. Parameters of calibration graphs for determining isoquinoline derivatives from oxidation current at a graphite electrode in a 0.1 M H_2SO_4 solution

Compound	Analytical range, M	Regression equation $y = a + bx$		R
		a	$b \times 10^{-4}$	
Papaverine	1.18×10^{-5}–1.06×10^{-4}	1.8 ± 0.3	12.1 ± 0.5	0.99624
Drotaverine	2.23×10^{-5}–5.34×10^{-5}	$-(6.0 \pm 0.8)$	25 ± 2	0.99764
	7.55×10^{-5}–2.92×10^{-4}	4 ± 1	7.3 ± 0.5	0.99448

Table 2. Determination of papaverine and drotaverine in model solutions ($n = 5$, $P = 0.95$)

Compound	Added, μg	Found, μg	RSD, %
Papaverine	101	101 ± 2	2
	168	162 ± 2	1
	337	331 ± 3	1
	1010	1004 ± 5	1
Drotaverine	323	322 ± 2	1
	538	537 ± 2	1
	1076	1072 ± 10	1
	2153	2151 ± 12	1

Table 3. Determination of papaverine and drotaverine in pharmaceuticals as hydrochlorides ($n = 5$, $P = 0.95$)

Sample	Concentration of the active substance, mg	Manufacturer*	Found by voltammetry, mg	RSD, %	Found by coulometry, mg	RSD, %
Tablets of papaverine hydrochloride	40	1	38.9 ± 0.8	2	37 ± 1	3
		2	39 ± 1	2	40.7 ± 0.8	2
		3	38 ± 1	2	38.2 ± 0.7	2
Tablets of drotaverine hydrochloride	40	4	39.38 ± 0.09	1	39.6 ± 0.2	1
		5	40.4 ± 0.3	1	39 ± 1	1
		6	39.7 ± 0.3	1	40 ± 3	3
		7	40.10 ± 0.02	1	40 ± 1	2

* 1, 4: ZAO Pharmaceutical Production Company Obnovlenie, Novosibirsk; 2, 7: OAO Irbit Chemicopharmaceutical Plant, Irbit; 3: OAO ICN Tomskkhimfarm, Tomsk; 5: OAO Tatkhimfarmpreparaty, Kazan; 6: No-spa, Chinoin Chemical Pharmaceutical, Hungary.

It is recommended that the rapid voltammetric procedure developed for determining papaverine and drotaverine in pharmaceuticals be introduced in the laboratories of pharmaceutical plants and centers of pharmaceutical quality control.

REFERENCES

1. Elad, D., D. Ginsburg, *J. Am. Chem. Soc.,* 1954, vol. 76, no. 1, pp. 312–313.
2. Mashkovskii, D.M., *Lekarstvennye sredstva* (Pharmaceuticals), Kharkov: Torsing, 1998, vol. 1.
3. *Registr lekarstvennykh sredstv Rossii. Entsiklopediya lekarstv* (Register of Russian Pharmaceuticals. Encyclopaedia of Medicine) Vyshkovskii, G.L., Ed., Moscow: RLS, 2002, no. 9.
4. Saushkina, A.S., Maksimenko, T.I., Klimenko, I.N., and Shcherbina, O.M., *Farm. Zh.*, 1992, vol. 2, p. 41.
5. Zavrazhnaya, T.A. and Kuleshova, M.I., *Farmatsiya*, 1982, vol. 31, no. 4, p. 32.
6. Singh, D.V., Prajapati, S., Bajpai, S., Verma, R.K., Gupta, M.M., and Kumar, S., *J. Liq. Chromatogr. Rel. Technol.*, 2000, vol. 23, no. 11, p. 1757.
7. Paul, B.D., Dreka, C., Knight, E.S., and Smith, M.L., *Planta Med.*, 1996, vol. 62, no. 6, p. 544.
8. Bjornsdottir, I. and Hansen, S.H., *J. Pharm. Biomed. Anal.*, 1995, vol. 13, nos. 4–5, p. 687.
9. Zarechenskii, M.A., Gaidukevich, O.M., and Georgievskii, V.P., *Farm. Zh.*, 1991, vol. 4, p. 65.

10. Abdel-Ghani, N.T., Shoukry, A.F., Issa, Y.M., and Wahdan, O.A., *J. Pharm. Biomed. Anal.,* 2002, vol. 28, no. 2, p. 373.
11. Tang, Y., Luan, J., Wang, Q., Wu, L., Cao, R., and Liu, S.H., *Acta Acad. Med. Sin.*, 2002, vol. 24, p. 413.
12. Metwally, F.H., Abdelkawy, M., and Naguib, I.A., *J. AOAC Int.*, 2006, vol. 89, no. 1, p. 78.
13. Kharitonov, S.V. and Gorelov, I.P., Abstract of Papers, *Vserossiiskaya konferentsiya po khimicheskomy analizu veshchestv i materialov* (All-Russia Conf. on Chemical Analysis of Substances and Materials), Moscow, 2000, p. 57.
14. Magnuszewska, B., Ostrowska, J., and Figaszewski, Z., *Chemia Analyticzna*, 2000, vol. 45, no. 1, p. 105.
15. Lalla, J.K., Shah, M.U., Jain, M.B., and Sharma, A.H., *J. Pharm. Biomed. Anal.*, 1993, vol. 11, nos. 4–5, p. 385.
16. Bolaji, O.O., Onyeji, C.O., Ogungbamila, F.O., Ogunbona, F.A., and Ogunlana, E.O., *J. Chromatogr. B*, 1993, vol. 622, no. 1, p. 93.
17. Ibrahim, H., Issa, Y.M., and Abu-Shawish, H.M., *Anal. Lett.*, 2005, vol. 38, no. 1, p. 111.
18. Kharitonov, S.V., *Anal. Bioanal. Chem.,* 2005, vol. 382, no. 7, p. 1642.
19. El-Saharty, Y.S., Metwaly, F.H., Refaat, M., and El-Khateeb, S.Z., *J. Pharm. Biomed. Anal.*, 2006, vol. 41, no. 3, p. 720.
20. Yan, J., Wang, L., Zhao, M.-P., and Chang, W.-B., *Anal. Lett.*, 2004, vol. 37, no. 14, p. 2977.