4′ oder 5′-H); 7.57 (t, $^3J = 7,5$ Hz, 1 H, 4′ oder 5′-H); 7,76 (d, $^3J = 8,0$ Hz, 1 H, 3′ oder 6′-H); 7,82 (d, $^3J = 8,0$ Hz, 1 H, 3′ oder 6′-H); 11,65 (s, 1 H, OH). UV/Vis (CH_2Cl_2, nm): λ_{max} (log ε) = 328 (4,14), 428 (4,08).
$C_{17}H_{11}Cl_3N_2O$ (364,4)

2.2. 8-Hydroxy-1,4,4a,8a-tetrahydro-4a,7,8a-trichlor-5,6-[N,N′(4′,5′-dimethylphen-1,2-diyl)]-diimino-1,4-methano-naphthalen (**12b**)

Ausbeute: 76 mg (19,4%) gelbe Kristalle vom Schmpt. 158 °C. MS (E.-I.) m/z (rel Int., Angaben beziehen sich auf ^{35}Cl): 392 (M^+, 8), 329 (25), 328 (21), 327 (71), 314 (99), 326 (100), 322 (78). IR (KBr, cm^{-1}): 3367, 2984, 1623, 1588, 1570, 1540, 1510, 1470. ^1H NMR (DMSO-d_6, δ, ppm): 1,93 (d, $^2J = 10,2$ Hz, 1 H, 9-H); 2,34 (s, 3 H, CH_3); 2,37 (s, 3 H, CH_3); 2,53 (d, $^2J = 9,8$ Hz, 1 H, 9-H); 3,69 (s, 1 H, 1 oder 4-H); 3,93 (s, 1 H, 1 oder 4-H); 5,90–5,92 (m, 1 H, 2 oder 3-H); 6,10–6,13 (m, 1 H, 2 oder 3-H); 7,06 (s, 1 H, 3′ oder 6′-H); 7,60 (s, 1 H, 3′ oder 6′-H); 11,57 (s, 1 H, OH). UV/Vis (CH_2Cl_2, nm): λ_{max} (log ε) = 238 (4,36), 329 (4,18), 437 (4,15), 457 (4,03).
$C_{19}H_{15}Cl_3N_2O$ (392,7)

2.3 8-Hydroxy-1,4,4a,8a-tetrahydro-4a,7,8a-trichlor-5,6-[N,N′-naphthalen-1,2-diyl)]-diimino-1,4-methano-naphthalen (**12c**)

Ausbeute: 70,6 mg (17%) orange Kristalle vom Schmpt. 300 °C (Zers). MS (E.-I.) m/z (rel Int., Angaben beziehen sich auf ^{35}Cl): 414 (M^+, 2), 350 (48), 86 (48), 84 (68), 57 (100). IR (KBr, cm^{-1}): 3291, 1606, 1594, 1577, 1559, 1508, 1465. ^1H NMR ($CDCl_3$, δ, ppm): 1,95 (d, $^2J = 8,4$ Hz, 1 H, 9-H); 2,39 (d, $^2J = 9,7$ Hz, 1 H, 9-H); 3,55 (s, 1 H, 1 oder 4-H); 3,92 (s, 1 H, 1 oder 4-H); 6,08–6,15 (m, 2 H, 2, 3-H); 7,50 (t, $^3J = 8,4$ Hz, 1 H, 6′ oder 7′-H); 7,60 (t, $^3J = 7,9$ Hz, 1 H, 6′ oder 7′-H); 7.92 (d, $^3J = 8,4$ Hz, 1 H, 5′oder 8′-H); 8,06 (d, $^3J = 7,9$ Hz, 1 H, 5′ oder 8′-H); 8,16 (s, 1 H, 3′ oder 9′-H); 8,41 (s, 1 H, 3′ oder 9′-H); 11,55 (s, 1 H, OH). UV/Vis (CH_2Cl_2, nm): λ_{max} (log ε) = 257 (4,41), 333 (4,44), 390 (4,14), 410 (4,15), 460 (4,05).
$C_{21}H_{13}Cl_3N_2O$ (414,7)

Literatur

1 Ott, R.: Mh. Chem. **90**, 827 (1959)
2 Lindenbaum, S.: Ber. Dtsch. Chem. Ges. **34**, 1050 (1901)
3 Ott, R.; Lachnit, R.: Mh. Chem. **104**, 15 (1973)
4 Kallmayer, H.-J.; Doerr, M.: Sci. Pharm. **68**, 87 (2000)
5 Green, M.; Lucken, A. E.: Helv. Chim. Acta **45**, 1870 (1962)
6 Belg. Pat. 635723 (1964), Farbw. Hoechst; C. A. **61**, 13246 (1964)
7 Kallmayer, H.-J.; Doerr, M.: Sci. Pharm. **66**, 297 (1998)

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Prof. Dr. Hans-Jörg Kallmayer
Postfach 1150
D-66041 Saarbrücken

Department of Analytical Chemistry, Faculty of Pharmacy, Anadolu University, Eskisehir, Turkey

Pulse polarographic determination of meloxicam

G. Altiokka, Z. Atkosar and M. Tuncel

Meloxicam, (**1**, [4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a non-steroidal anti-inflammatory drug of the oxicam class [1, 2]. A limited number of studies have been reported for the determination of **1** including first-derivative spectrophotometry and TLC densitometry [3], spectrophotometry and flow-injection [4] and HPLC [5].

The aim of this study was to investigate the optimum polarographic conditions for the determination of **1** based on the reduction of enol group of the molecule and to apply the method to pharmaceutical preparations. The optimum polarographic parameters were elucidated and **1** was determined using differential pulse (DP), superimposed increasing amplitude pulse (SIAP) and superimposed constant amplitude pulse (SCAP) polarographic techniques in tablets. The experiments were conducted in the aqueous supporting electrolyte containing 0.2 mol/l KCl and 0.2 mol/l buffer solution. Well-defined and one-stepped reduction wave was appeared in the pH range of 7.23 and 11.95. The process was found to be irreversible according to the criteria of Birke et al. [6], and the control of the polarographic current was diffusional at pH 10.3. The effect of temperature was investigated in the range of 15 and 45 °C. The variation of limiting current confirm that the polarographic current is diffusional [7]. The stability of **1** in KOH was examined; the drug was stable for at least one week.

The calibration studies were performed using DP, SIAP and SCAP polarographic techniques.

The variation of **1** concentration in the range of 1.1×10^{-4}–5.5×10^{-4} mol/l was investigated. The equations were calculated measuring the current at the maximum of the waves or peaks.

At −1720 mV for DP; $i_{lim}(\mu A) = 2137.2\ C(mol/l) - 0.043$; $r = 0.9997$; At −1800 mV for SIAP; $i_{lim}(\mu A) = 6720.4\ C(mol/l) - 0.17$; $r = 0.9996$. At the peak maximum for SCAP; $i_{lim}(\mu A) = 6570.6\ C(mol/l) - 0.147$; $r = 0.9994$. The detection limit was calculated to be 1×10^{-5} mol/l (S/N = 3).

The methods were applied to pharmaceutical preparations of **1**. The determination was performed in filtered and unfiltered solutions. The drug was also analysed by UV-spectrophotometry for comparison. All the results were statistically evaluated using F and t tests (Table). High reproducibility was observed and insignificant differences were found between the polarographic techniques and UV-spectrophotometry at the 95% probability level. These results confirm the suggestions regarding the validity of the polarographic method in both filtered and unfiltered solutions [8].

The method proposed in this study is accurate, precise and rapid. Therefore, it can be suggested for the routine analysis of **1** in the field of quality controls.

Table: Assay results of 1 in tablets[a]

	DPP		SIAPP		SCAPP		UV
	Filtered	Unfiltered	Filtered	Unfiltered	Filtered	Unfiltered	
Mean[b] (mg)	14.8	14.9	14.9	15.0	14.8	14.9	14.9
SD	0.13	0.17	0.15	0.19	0.22	0.16	0.13
CL ($p = 0.05$)	±0.2	±0.2	±0.3	±0.1	±0.3	±0.2	±0.2
F-test of significance	1.74	3.16	2.23	2.76	3.22	4.05	4.12 (table)
t-test of significance	0.47	1.27	0.83	1.91	1.34	2.01	2.14 (table)

a: Each tablet contains 15 mg of **1**
b: Each value is the average of eight determination
SD: standard deviation
CL: confidence limit

Experimental

1. Apparatus and chemicals

The polarographic system comprised of a Polaropulse Model PRG-5; the electrodes dual function EGMA type cell stand for polarography and voltammetry, with dropping Hg as working, Pt wire as auxiliary and saturated Ag/AgCl as reference electrodes were used (all Tacussel). The polarograms were recorded by a Model SE 790 X-Y recorder (BBC Goertz Metrawatt). A model WTW Multiline P4 Universal pH-meter cabled WTW Sen-Tix 97 T pH electrode (Germany) was adjusted the pH of the solutions. Spectrophotometric studies were done using a Model UV-2401 PC (Shimadzu). Standard **1** (99.8%) and tablets (Melox®) were kindly supplied from Nobel Ilac. A. S. (Istanbul, Turkey), The standard sample was used without further purification. The other chemicals were of analytical grade (E. Merck).

2. Procedures

2.1. Preparation of the stock solution

An aqueous solution of **1** (1×10^{-3} mol/l) in 0.02 mol/l KOH was prepared and dilutions were made from this solution. The final concentration of the supporting electrolyte was 0.2 mol/l KCl and 0.2 mol/l phosphate buffer. The pH of the buffers were adjusted by 2 mol/l KOH or 2 mol/l HCl solutions.

2.2. Polarographic procedure

Ten ml supporting electrolyte containing 5.5×10^{-4} mol/l **1** was put into the polarographic cell and purified N_2 was passed through the solution for 10 min. 5.5×10^{-4} mol/l **1** was employed to investigate the effect of pH on the limiting current and the other polarographic parameters. The polarographic examinations were carried out by scanning cathodically in the range of 0 mV and −2000 mV against saturated Ag/AgCl reference electrode potential. The optimum conditions were: initial potential 0 mV, potential rate $10\ mV \cdot s^{-1}$, pressure applied to the mercury reservoir $1000\ dyne \cdot cm^{-2}$, pulse height 50 mV and drop time of 0.8 s.

2.3. Application to the tablets

Twenty tablets were separately weighed and the average weight of a tablet was calculated. The tablets were powdered in a mortar. A sample equivalent to one tablet was weighed and transferred to a 100 ml calibrated flask. Two ml 1 mol/l KOH solution was added and the volume was made up with bidistilled water. Following vigorous shaking, half of the solution was filtered. The first 10 ml portion was discarded and the remaining solution was employed for the determination of **1** using the techniques mentioned above. The spectrophotometric assays were carried out dissolving in KOH. The calibration equation was found to be $A = 18940\ C(mol/l) + 0.024$ ($r = 0.9999$) at 360 nm under the mentioned conditions.

References

1 Türck, D.; Roth, W.; Busch, U.: Brit. J. Rheumatol. **35** (suppl. 1), 13 (1996)
2 Davies, N. M.; Skjodt, N. M.: Clin. Pharmacokinet. **36**, 115 (1999)
3 Bebawy, L. I.: Spectrosc. Lett. **31**, 797 (1998)
4 Garcia, M. S.; Sanchez-Pedreno, C.; Albero, M. I.; Marti, J.: Eur. J. Pharm. Sci. **9**, 311 (2000)
5 Offringa, M.; Van der Kam, H. J.; Brouvers, J. R. B. J.: Ziekenhuisfarmacie **13**, 63 (1997)
6 Birke, R. L.; Kim, M. H.; Strassfeld, M.: Anal. Chem. **53**, 852 (1981)
7 Bauer, H. H.; Christian, G. D.; O'Reilly, J. E.: Instrumental Analysis. Allyn and Bacon Inc., Boston, 1978, p. 56.
8 Volke, J.: Bioelectrochem. Bioenerg. **10**, 7 (1983)

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Dr. Göksel Altiokka
Department of Analytical Chemistry
Faculty of Pharmacy
Anadolu University
26470 Eskisehir
Turkey
galtiokk@anadolu.edu.tr.