Journal of Pharmaceutical & Biomedical Analysis
Vol. 7, No. 6, pp. 755–758, 1989
Printed in Great Britain

0731–7085/89 $3.00 + 0.00

Short Communication

Potentiometric and calorimetric assay of mephenoxalone

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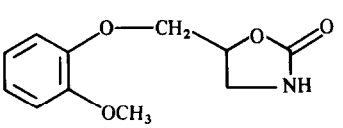
Keywords: *Mephenoxalone determination; coated-wire electrodes; potentiometric titration; differential scanning calorimetry.*

Introduction

Mephenoxalone (syn. Dorsiflex, Guayazolidona, Lenetran, etc. [1]), chemically 5-[(2-methoxyphenoxy)methyl]oxazolidin-2-one ($C_{11}H_{13}O_4N$, M_r = 223,23), is a tranquilizer and muscle relaxant. It is practically insoluble in water and the secondary nitrogen of oxazolidine ring is only slightly basic owing to the presence of two neighbouring oxygen atoms. For this reason the conventional determination by titration with perchloric acid in media such as acetic acid or acetic anhydride is not applicable. Nitrogen determination by the Kjeldahl procedure gives non-precise results because of the low content of organic nitrogen. UV-spectrophotometry has been suggested [2] but it is not accurate due to interference by light absorbing impurities. The same objection is valid for measurements by IR-spectra [3]. It should be mentioned that the mass spectra of mephenoxalone and some other drugs, biotransformation products and intermediates of illegal syntheses of narcotics have also been published [4]. A liquid chromatograph using UV-detection at two wavelengths was found to be useful when the absorbance signals were combined with retention times [5].

Having tested the stability of the substance in our laboratory, we found that mephenoxalone decomposed in alkaline medium to yield probably three products (these were qualitatively detected using thin-layer chromatography). Although the decom-



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position products were not identified, it was found that they could be precipitated with sodium tetraphenylborate. On this basis, an assay method for mephenoxalone was worked out in which simple potentiometric sensors were used to monitor the ion-pair formation titration [6, 7]. The substance purity was also followed using differential scanning calorimetry [8].

Experimental

Potentiometric measurements

The measuring cell consisted of the coated-wire electrode, prepared as described earlier [6, 9] by coating an aluminium wire with a membrane formed by poly(vinyl chloride) plasticized with 2,4-dinitrophenyl-*n*-octyl ether, and the saturated double-junction calomel electrode (Crytur RCE-102) with 0.01 M sodium nitrate as a salt-bridge electrolyte. Titrations were performed using a Potentiograph E 436 with Dosimat E 436 D arrangement (Methrom). Constant magnetic stirring was used.

Calorimetric measurements

The melting of the substance was followed using a differential scanning calorimeter DSC 1B (Perkin–Elmer). Conditions for recording the curves were as follows: weighed amount of a sample, ca. 0.8 mg; scan rate, 4°C min^{-1}; range, 2 mcal min^{-1}. The absolute purity was calculated according to a program [10, 11] for a desk calculator HP 9820.

Reagents

Sodium tetraphenylborate ($NaBPh_4$) solution (0.04 M) was prepared from a p.a. preparation (Lachema) as described earlier [6] and standardized by potentiometric titration against thallium(I) nitrate [12].

Sodium hydroxide solution (1 M) for the alkaline hydrolysis was prepared using a p.a. preparation (Merck). As the solution contained small amounts of potassium ($\leq$0.05% is guaranteed) which could interfere in titration with tetraphenylborate, its content was determined by titration and by atomic absorption spectrometry (using a Spectr AA-30 instrument, Varian) with a good agreement.

Procedures

Determination of mephenoxalone in the substance. The substance (ca. 40 mg) was weighed into a titration vessel, sodium hydroxide solution (5 ml) was added and the mixture was heated for 15 min on a boiling water bath under continual stirring. Then the mixture was cooled to room temperature, distilled water (20 ml) was added and cautiously neutralized with hydrochloric acid (20%) to the pH value of 3.0 ± 0.1. The protonized products of hydrolysis were potentiometrically titrated with sodium tetraphenylborate. The mephenoxalone content in the substance [in %(m/m)] was calculated according to

$$p(\text{Meph}) = [V(NaBPh_4) \cdot c(NaBPh_4) - n(K^+)] \cdot M(\text{Meph}) \cdot 100/m(\text{sample}),$$

where $V(NaBPh_4)$ is the volume (ml) of titrant required, having a molar concentration of $c(NaBPh_4)$ [mmol ml^{-1}], $n(K^+)$ is a correction on the content of potassium [mmol] in the dosed volume of sodium hydroxide, M(Meph) is the molar mass of mephenoxalone [mg $mmol^{-1}$], and m(sample) is the mass [mg] of the substance weighed.

Determination of mephenoxalone in tablets. The crushed tablets (ca. 70 mg) were weighed into a titration vessel, sodium hydroxide (10 ml) was added and the mixture was heated for 30 min on the boiling water bath. Cooling, neutralization and titration followed as described above. The mephenoxalone content (mg) per tablet was calculated as follows:

$$m(\text{Meph}) = [V(\text{NaBPh}_4)\cdot c(\text{NaBPh}_4) - n(\text{K}^+)]\cdot M(\text{Meph})\cdot \bar{m}(\text{tab})/m(\text{sample}),$$

where $\bar{m}$(tab) is the average mass of the one tablet [mg] (other symbols as above).

Results and Discussion

From the stability testing of the substance as mentioned above, it was presumed that the conditions for its alkaline hydrolysis need not be drastic. A reasonable amount of sodium hydroxide was optimal so that the reaction was quantitative, but the correction for the potassium(I) content should have a minimal value. However, the amount of sodium hydroxide sufficient for the hydrolysis of the substance was not large enough to hydrolyse the tablets. Therefore, the addition of sodium hydroxide for the hydrolysis of mephenoxalone in drug form had to be greater. It could be assumed that a part of the sodium hydroxide solution was consumed by the gelatine present in placebo. As the potential break of the titration curve near the end-point was not steep (ca. 10 mV/0.1 ml of the titrant), it was considered that the hydrolytic nitrogen-containing product had a lower molecular mass. In spite of this fact, the results were reproducible.

With regard to differential scanning calorimetry, it should be mentioned that the peaks of the recorded curves were decreased, extended and shifted to lower temperatures with increased amount of impurities in the sample measured (see Fig. 1). Thus, the DSC record contains information on the ratio of impurities when the energy differences needed for the equilibration of the temperatures between the measured and the reference samples were followed, and the sample purity can be expressed in molar percentages [11].

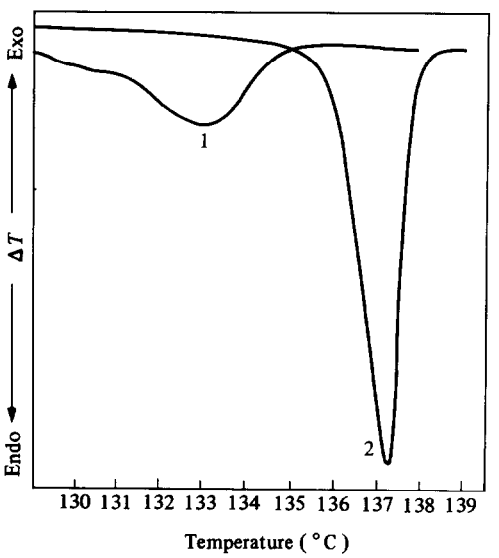

Figure 1
The differential scanning calorimetry curves of the sample No. 880120. (1) A crude sample; (2) a recrystallized sample.

As shown in Table 1, the results of both potentiometric and calorimetric assay procedures agreed quite well, although differently defined percentages were compared. The comparison of the results of the potentiometric determination of mephenoxalone in tablets with the content declared on the basis of UV-spectrophotometry (Table 2) is also satisfactory.

Table 1
Comparison of the assay values for mephenoxalone in substance

	Potentiometric titration			
Sample number	Number of titrations	Average content (%, m/m)	RSD (%)	DSC purity (%, n/n)
871209	3	99.2	0.3	99.2
870825	5	99.5	0.2	99.3
871111	3	100.1	0.3	99.1
871201	3	98.8	0.3	97.9
870715	3	97.9	0.6	98.2
880120/I	3	85.1	2.7	—
880120/II	3	78.7	14.1	—

Table 2
Determination of mephenoxalone in tablets

		Found by potentiometric titration		
Sample number	Content declared* (mg/tablet)	Number of titrations	Average content (mg/tablet)	RSD (%)
290687	199.3	2	195.6	0.5
271287	202.2	4	203.4	0.2

*Based on UV-spectrophotometry.

Conclusion

On the basis of the presented experiments, both potentiometric and calorimetric procedures can be recommended to assay mephenoxalone powder. The method of potentiometric titration can also be used for a control of crude products and for the determination of mephenoxalone in tablets.

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[Received for review 13 July 1988; revised manuscript received 1 December 1988]