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# Determination of 5-methoxy-2-methylindole-3-acetic acid in indomethacin by derivative UV-spectrophotometry

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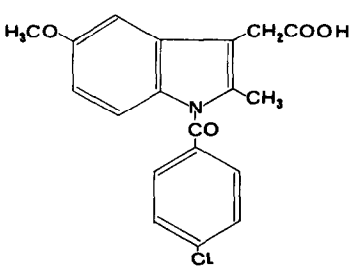
## Summary

A method for the determination of 5-methoxy-2-methylindole-3-acetic acid in indomethacin (bulk material and pharmaceutical formulations) by third-derivative ultraviolet spectrophotometry is described. The procedure is simple and rapid and allows accurate and precise results.

## Introduction

Indomethacin (**I**) (Shen et al., 1963), or 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, is a non-steroidal anti-inflammatory agent, widely used as an analgesic drug in the treatment of rheumatoid arthritis and other degenerative joint diseases, gout and acute musculo-skeletal disorders. It has also been used as antipyretic to reduce symptoms in some febrile conditions.

Together with *p*-chlorobenzoic acid, 5-methoxy-2-methylindole-3-acetic acid (**II**) is the main decomposition product of the drug (Hajratwala and Dawson, 1977; Krasowska et al., 1973) in bulk material and in its pharmaceutical formulations.

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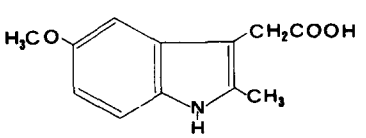


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Previously, the two decomposition products have been identified without quantitation by TLC (Ejima et al., 1984; Krasowska et al., 1973; Noda et al., 1975; Pawelczyk et al., 1979) or determined in a semi-quantitative way by TLC (Curran et al., 1980). The determination of these substances has been carried out in pharmaceutical formulations by HPLC (Ejima et al., 1984; Kwong et al., 1982; Rowe and Carless, 1983) or spectrophotometrically by measuring their additive absorptions (Pawelczyk and Knitter, 1976).

This paper describes a method for the determination of 5-methoxy-2-methylindole-3-acetic acid in indomethacin by derivative UV-spectrophotometry. This technique has been previously utilized for the analysis of indomethacin as the active component in mixture with other drugs, without determination of its decomposition products (Mahrous et al., 1985).

## Materials and Methods

*Apparatus and conditions*

Perkin-Elmer Model Lambda 5 UV-vis spectrophotometer. Zero-order spectra: scan speed 60 nm/min; spectral slit width 2 nm. Derivative conditions: scan speed 60 nm/min; spectral slit width 2 nm; $\Delta_\lambda$ 6.

*Reagents and chemicals*

Ethanol was of spectroscopic reagent grade. All other solvents were of analytical reagent grade. Indomethacin (Sigma Chemical Co., St. Louis, U.S.A.) was further purified by several recrystallizations from ethanol–water without heating or exposure to light. 5-Methoxy-2-methylindole-3-acetic acid was purchased from Aldrich Chemical Co., Milwaukee, WI, and used without further purification. Indoxen suppositories and capsules were obtained from Sigma-Tau, Industrie Farmaceutiche Riunite, Roma (Italy).

*Standard solutions and calibration curve*

Standard solutions were ethanolic solutions containing indomethacin ($5 \times 10^{-5}$ M) and 5-methoxy-2-methylindole-3-acetic acid with concentrations in the range $5 \times 10^{-8}$–$5 \times 10^{-7}$ M.

The determination of 5-methoxy-2-methylindole-3-acetic acid can be carried out, in the concentration range examined, by utilizing the peak–trough amplitude between 222 and 235 nm in the third-derivative spectrum and by using the following equation, obtained through regressional analysis of data for the standard solutions previously reported:

$$y = 1.66 \cdot 10^5 x + 0.350 \quad (r = 0.996)$$

where $y$ = peak–trough amplitude between 222 and 235 nm in the third-derivative spectrum, measured on the scale $\pm 0.5$; and $x$ = concentration of 5-methoxy-2-methylindole-3-acetic acid (mol/l).

*Samples analysis*

*(a) Bulk material.* The powdered bulk material was dissolved in ethanol in such a way as to obtain a $5 \times 10^{-5}$ M solution of indomethacin. After filtration, the solution was analysed by derivative UV-spectrophotometry by using the equation previously reported.

*(b) Pharmaceutical formulations.* The contents of 10 capsules were removed, weighed and combined. An amount of powder equivalent to about 100 mg of indomethacin was accurately weighed into a screw-capped tube, 10 ml of ether–water (1 : 1) was added and the mixture was shaken vigorously for 15 min. The ether layer was removed, dried and evaporated under reduced pressure. The residue was dissolved in ethanol in such a way as to obtain a $5 \times 10^{-5}$ M solution of indomethacin and analysed by derivative UV-spectrophotometry as previously reported.

Five suppositories were crushed and combined. An amount of material equivalent to about 100 mg of indomethacin was accurately weighed and treated as described previously for the capsules.

## Results and Discussion

Fig. 1 shows the derivative spectrum utilized for the determination of 5-methoxy-2-methylindole-3-acetic acid in indomethacin. The minimum concentration of this impurity detectable by the described procedure was 0.1%.

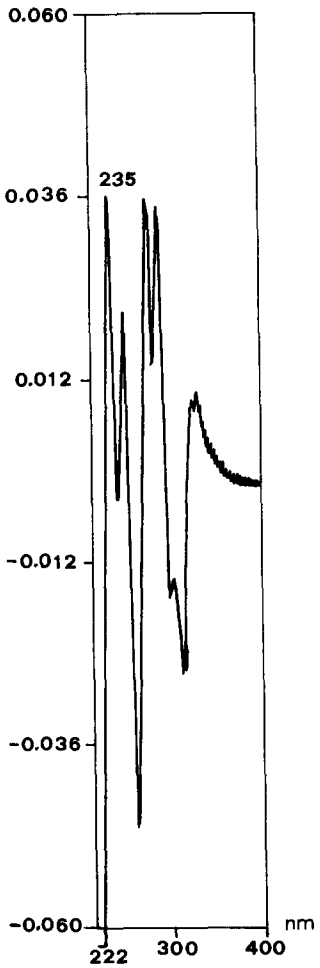


Fig. 1. Third-derivative ultraviolet spectrum of a $5 \times 10^{-5}$ M ethanolic solution of indomethacin containing 5-methoxy-2-methylindole-3-acetic acid ($5 \times 10^{-8}$ M).

TABLE 1

*Determination of 5-methoxy-2-methylindole-3-acetic acid in indomethacin*

Results are averages of 5 determinations for each sample.

| Sample | 5-methoxy-2-methylindole-3-acetic acid found (%) |
|---|---|
| Bulk material | 0.1 |
| Bulk material | 0.15 |
| Suppositories | 0.1 |
| Capsules | 0.2 |

The data employed for the calibration curve are the average of a minimum number of 5 determinations for each sample. The relative standard deviation observed by utilizing this technique was ca. 2%.

Table 1 gives the results obtained in the analysis of samples of commercial bulk material and of pharmaceutical formulations (suppositories and capsules) containing the drug. Also in these determinations the relative standard deviation observed was ca. 2%. The described procedure is very simple and rapid.

## Acknowledgement

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