X-RAY FLUORESCENCE SPECTROSCOPIC ANALYSIS OF BROMINE IN PHARMACEUTICAL FORMULATIONS

Maria Augusta RAGGI[a], Federico LUCCHINI[b] and Paolo Da RE[c]

[a] *Department of Pharmaceutical Sciences, University of Bologna, Italy*
[b] *Department of Mineralogical Sciences, University of Bologna, Italy*
[c] *Institute of Pharmaceutical and Toxicological Chemistry, University of Milan, Milan, Italy*

Received December 11, 1990
Accepted March 6, 1991

Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

A fast and accurate method is proposed for the determination of bromine in pharmaceutical formulations. The method is based on the application of X-ray fluorescence spectroscopy to solid samples and can be used for the assay of total bromine in various chemical media. It has high reliability provided that the appropriate matrix effect correction is employed, through the use of the scattered W-line from the X-ray tube as an internal standard.

A number of methods can be used to determine bromine in the various types of inorganic or organic matrices in pharmaceutical formulations. The classical Volhard titration, recommended by FU (ref.[1]), BP (ref.[2]) and AOAC (ref.[3]) is gradually being replaced by more sophisticated procedures such as electrochemical[4,5] and colorimetric[6-9] methods, neutron activation analysis[10], HPLC (ref.[11]) and X-ray fluorescence of liquid samples[12]. As these methods often require complex pretreatment, a more direct approach would seem preferable.

In a previous paper[13], we described a procedure for the determination of bromine, based on the application of X-ray fluorescence (XRF) spectroscopy to solid samples. The successful application of this method to the assay of traces of organic bromine in commercial sodium Diclofenac powder led us to extend this procedure to the determination of bromine in pharmaceutical formulations containing bromine in the active principle.

EXPERIMENTAL

Apparatus and Materials

A Philips PW 1450 manual X-ray spectrometer was employed, with a W target tube operating at 50 kV and 40 mA, an LiF (220) analyzing crystal and a scintillation counter as detector. A Retsch laboratory ball mill and Turbula type T2C planetary powder mixer were used. Analy-

tical grade NaBr and H_3BO_3 were obtained from C. Erba (Italy). The test pharmaceutical formulations were the commercial substances.

Preparation of Standards

For the construction of calibration curves, synthetic standards were prepared by adding NaBr powder to boric acid powder in the NaBr range 250—10 000 ppm (194—7 750 ppm Br). Separate portions of H_3BO_3 and NaBr were ground in a mortar and subsequently pulverized in an agate ball mill. Finally, an exactly weighed amount of NaBr was added to a weighed amount of H_3BO_3 and accurately mixed according to the method of geometric dilutions. The mixing process was completed in the planetary powder mixer and the homogeneity of the powder mixture was checked microscopically. The same procedure was employed using Diclofenac instead of H_3BO_3 to evaluate sample matrix effects.

Procedure

Pellets of standards, 25·4 mm in diameter, were obtained by pressing 0·500 g of the standards at 9 t cm^{-2} pressure on an H_3BO_3 support[14]. These pellets were measured in an XRF spectrometer and the intensities of the lines emitted at the angles characteristic for the K_α bromine line and the scattered WL_{γ_1} line of the X-ray tube as internal standard were measured. At least two pellets were prepared for each standard and each was analyzed twice, yielding an average of three readings (reading time 10 s).

RESULTS AND DISCUSSION

The XRF spectrum of bromine in the H_3BO_3 matrix is depicted in Fig. 1*a*; two radiation maxima typical for Br, corresponding to $2\theta = 42{\cdot}88°$ (K_α) and $2\theta = 38{\cdot}25°$

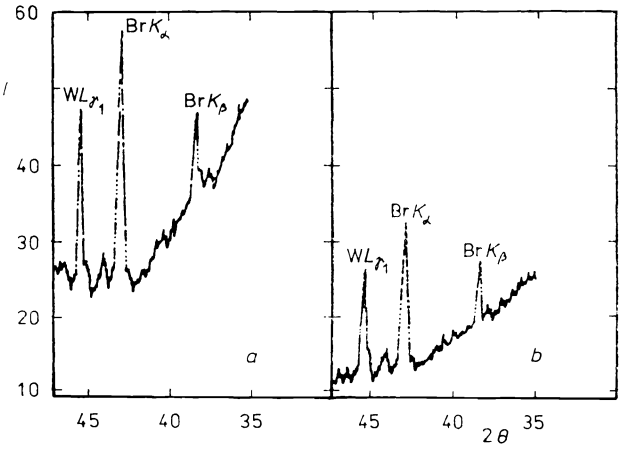

FIG. 1

XRF spectrum of bromine (775 ppm) and the WL_{γ_1} scattered line in H_3BO_3 matrix (*a*) and Diclofenac (*b*)

(K_β) are clearly visible. The K_α radiation was selected for the determination of bromine because of its better sensitivity.

TABLE I

Results of Br assay of pharmaceuticals

Commercial substance	Active principle	Br Content given ppm	Br Content found ppm	% Br found/given
A	Brotizolam	334	335	100·29
B	Clidinium bromide	2 030	2 050	100·98
C	Bromocriptine	2 180	2 210	101·37
D	Bromperidol	7 390	7 340	99·32

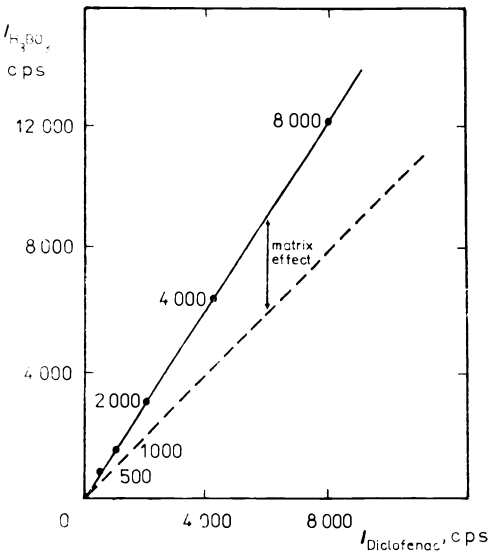

FIG. 2

Plot of the bromine K_α net intensities of standards in H_3BO_3 ($I_{H_3BO_3}$) against standards in Diclofenac ($I_{Diclofenac}$): experimental (full line) and theoretical (dashed line). ● ppm NaBr

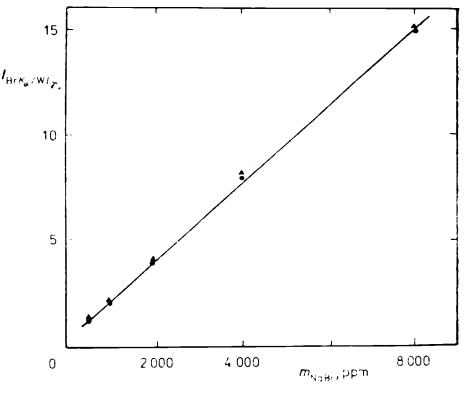

FIG. 3

Example of the calibration curve (NaBr content, m_{NaBr}, vs intensity ratios of BrK_α and WL_{γ_1} lines, $I_{BrK\alpha/WL\gamma_1}$) obtained using both standard series: ● H_3BO_3, ▲ Diclofenac

Figure 1*b* depicts the XRF spectrum for an NaBr sample in Diclofenac. The matrix effect is clearly visible from comparison of spectra *a* and *b*. Both the background and the peak height of the scattered WL_{γ_1} line are greater in the H_3BO_3 matrix than in Diclofenac. These results are consistent with the lower density of H_3BO_3 compared with Diclofenac.

Figure 2 gives the dependence of the net BrK_α intensity of the NaBr standards in Diclofenac matrix on the values in H_3BO_3, indicating higher values in H_3BO_3 than in Diclofenac at the same NaBr level.

Several method have been suggested[15] for overcoming the "matrix effect" (dilution, mathematical correction, internal or external standards). The spectra in Fig. 1 suggest that either the background value or the scattered WL_{γ_1} line of the X-ray tube can be used as a standard. The latter was selected because of its higher efficiency in correcting for matrix effects, reflected in the linearity of the calibration curve obtained using both standards in Diclofenac and H_3BO_3 (Fig. 3). The method was employed for the analysis of various commercial substances. Tablets and coated tablets containing different active principles and various amounts of Br in a number of excipients were examined. It can be seen from Table I that the method yields good recovery from all the substances examined (% Br found compared to declared amount equalled 99·32–101·37%). The precision of the method was also good, yielding satisfactory relative standard deviation values (minimum value: 0·5% for 7 750 ppm Br; maximum value: 1·4% for 194 ppm Br).

Thus, the proposed method is suitable for Br assay in pharmaceuticals; its accuracy and precision are satisfactory and it can be reliably employed for pharmaceutical quantitative analysis provided than a correction is employed for matrix effects. It is easily used as no solubilization or pretreatment of the sample is required. The total bromine in pharmaceutical preparations can be found irrespective of its molecular form (organic, inorganic, ionized, molecular).

REFERENCES

1. *F. U. Farmacopea Ufficiale della Repubblica Italiana*, 9th ed., Vol. II, p. 274. Istituto Poligrafico e Zecca dello Stato, Roma 1985.
2. *BP. British Pharmacopoeia*, Vol. I, p. 452. Her Majesty's Stationery Office, London 1988.
3. *AOAC. Official Methods of Analysis*, 14th ed. Association of Official Analytical Chemists, Arlington 1984.
4. Bailey P. L.: *Analysis with Ion-Selective Electrodes*, p. 95. Heyden, London 1976.
5. Bezilla B. M.: Diss. Abstr. Int., B *47*, 1025 (1986).
6. *Standard Methods. Water and Wastewater*, 13th ed., p. 75. American Public Health Association, Washington 1971.
7. Feuersenger M., Müller G.: Dtsch. Lebensm. Rundsch. *59*, 69 (1963).
8. Kretzschmann F., Engst R.: Nahrung *12*, 135 (1968).
9. *Standard Methods of Chemical Analysis*, 6th ed., Vol. IIA, p. 1082. Van Nostrand, New York 1963.

10. Alfassi Z. B., Lavi N.: Radiochem. Radioanal. Lett. *53*, 173 (1982).
11. De Kleijn J. P.: Analyst *107*, 223 (1982).
12. Rastegar F., Maier E. A., Heimburger R., Christophe C., Ruch C., Leroy M. J. K.: Clin. Chem. *30*, 1300 (1984).
13. Raggi M. A., Da Re P., Lucchini F., Parisi F., Salvi A.: J. Pharm. Biomed. Anal., in press.
14. Volborth A.: Nevada Bur. Mines Report *6A*, 1 (1963).
15. Jenkins R., De Vries J. L.: *Practical X-Ray Spectrometry*, p. 136. Macmillan, London 1972.

Translation revised by M. Štulíková.