TECHNICAL NOTE

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Identification of Potassium Salts of Clorazepate by X-Ray Diffractometry

REFERENCE: Foster, R. L., Doms, D. J., and Lott, P. F., **"Identification of Potassium Salts of Clorazepate by X-Ray Diffractometry,"** *Journal of Forensic Sciences,* JFSCA, Vol. 25, No. 3, July 1980, pp. 666-670.

ABSTRACT: A technique has been developed that permits X-ray diffraction patterns to be obtained for the identification of the monopotassium and dipotassium salts of clorazepate in pharmaceutical products. The sample is not altered or destroyed; a single capsule of the material is sufficient for the analysis.

KEY WORDS: toxicology, clorazepate, radiography

The analysis of clorazepate and its salts has been a problem in forensic science laboratories because of the chemical nature of the drug. Furthermore, the excipients present in the sample may also interfere in traditional analytical methods.

Infrared analysis is impractical because of the excipients, and extraction is limited to water or ammonium hydroxide,[3] both of which convert the drug to desmethyldiazepam. Attempts to use these solvents result in spectra obviously different from the reference standards.

Mass spectrometry on both the desmethyldiazepam and the clorazepate forms produces complex fragmentation patterns with no observable molecular ion. The thermal stress in mass spectrometry decarboxylates the molecule, producing desmethyldiazepam. Thin-layer chromatographic analysis is ineffective because of the limited solvent systems and the tendency for the solvents to alter the drug. The solvent system recommended by Clark [*1*] for screening nitrogenous bases produces erratic and irreproducible results.

Optical crystallography is too sophisticated a technique for most forensic science laboratories. It is usually avoided because of the lack of trained personnel proficient in its application.

The drug analysis monographs edited by Florey [*2*] give a negative recommendation for the extraction of clorazepate and its salts. No technique is listed for the isolation and

Presented at the Symposium on Forensic Chemistry, Sixth Annual Meeting of the Federation of Analytical Chemistry and Spectroscopy Societies, Philadelphia, Pa., 1979. Received for publication 21 Sept. 1979; revised manuscript received 15 Nov. 1979; accepted for publication 17 Nov. 1979.

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[3] J. H. Siefert, State of Michigan Regional Crime Detection Laboratory, personal communication, Oct. 1977.

identification of the drug in its mixed, consumable form. A private communication from Abbott Laboratories (Chicago) stated that no solvent can be used with this drug that will not alter the compound. Even the traditional melting point approach is not practical because of the wide melting point range of the material.

The illegal source of the drug is usually diverted pharmaceutical production; consequently, the capsule coloring and marking are used as the method of identification by most forensic science laboratories.

In an attempt to overcome these problems, X-ray diffractometry was investigated as an identification technique.

Equipment and Procedure

A Philips-Norelco Model 3000 XRG X-ray diffraction instrument with proportional counter was used. A standard focus copper target tube was employed with a nickel filter to render the radiation monochromatic. The instrument settings for recording are listed on the patterns. Specimens included Endo 502 and 503 capsules, Abbott capsules, and standards of pure monopotassium clorazepate from Endo Laboratories, Inc. and dipotassium clorazepate from Abbott.

Because of the limited amount of sample from the capsules, a method of reducing the volume needed to fill a standard aluminum window slide was developed. Small squares of Plexiglas® of the same thickness as the slide were cut to dimensions of the height of the window opening and carefully filed down to where the inserted spacer would fit and stay within the window to each side so as to restrict the sample filling space to a central void (Fig. 1). It was found that by using these spacers as little as 100 mg of sample from an Endo capsule would produce an infinite thickness pattern with no obvious distortion or interference from the spacers or slide mount (Fig. 2). Because of the reduced amount of material in the mount, the intensity of the pattern is reduced to show only the major peaks of the drug and the peaks of the excipient. The alternative would have been to prepare a

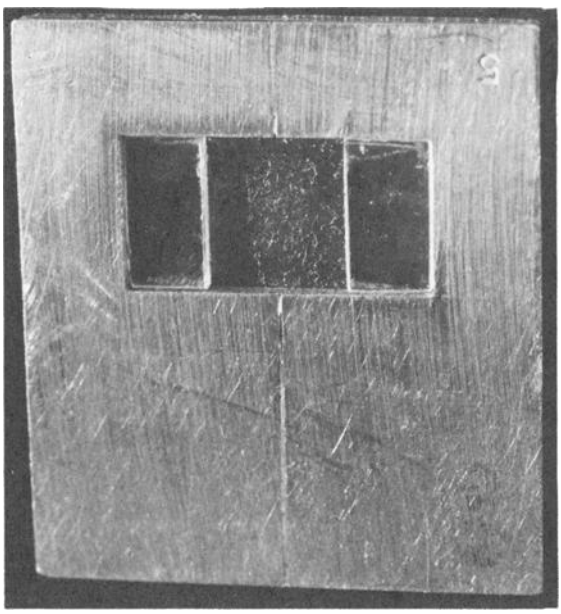

FIG. 1—*Philips standard small window slide with spacers.*

powder camera (Debye-Scherrer camera) capillary tube sample and perform a film exposure with a significant amount of time involved in obtaining the exposure, developing the film, and reading and analyzing the pattern arcs.

Samples from capsules were removed and ground to the same consistency by using an agate mortar and pestle. Standards were treated likewise. Where sample volumes were sufficient, a standard Philips-Norelco small window aluminum slide was packed with the sample and mounted for analysis. When volumes required, the previously mentioned spacers were used. This was the case with the Endo suspect capsule sample since only one capsule was available, providing 100 mg of sample (Fig. 2). Figures 3 and 4 show the patterns of a conventional slide mount filled with Endo 502 and Endo 503 prescription material.

Figure 5 gives the structural formulas of the two materials. The comparison of the monopotassium (Fig. 6) and dipotassium (Fig. 7) salt diffraction patterns shows distinct differences even though the structural differences between the two compounds are subtle. In the standards the monopotassium form has its major peak located at 4.8 deg 2θ (where 2θ is a standard notation for the angular relationship between the source beam and the sample), while the dipotassium form is at 5.2 deg 2θ. These differences can also be observed in the capsule samples. The Abbott capsule pattern (Fig. 8) shows a diminutive major peak at about 5.2 deg 2θ while the Endo capsule sample has its peak at 4.8 deg 2θ. The excipients have much higher peak intensities, being, of course, in greater concentration in the formulation. The Abbott capsule sample also produces four peaks in the pattern from 24 deg 2θ to 27 deg 2θ (labeled with x marks beneath the peaks), which correspond to peaks in the standard dipotassium clorazepate pattern. These peaks are not observed in the Endo capsules or the monopotassium clorazepate patterns, which exhibit peaks at 15.6, 19.2, and 21.2 deg 2θ. The results clearly indicate that these materials can be discriminated by X-ray diffractometry.

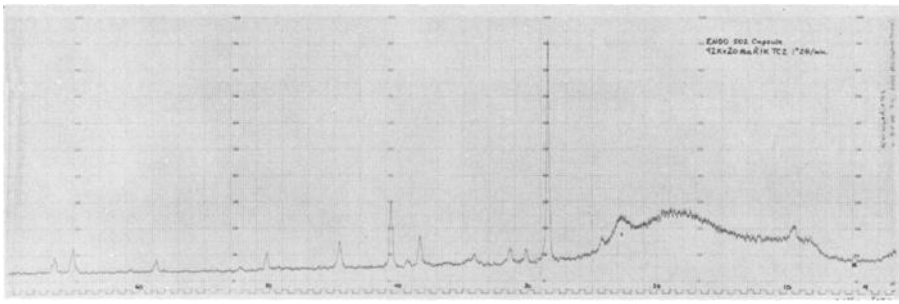

FIG. 2—*Endo 502 suspect capsule pattern using spacers.*

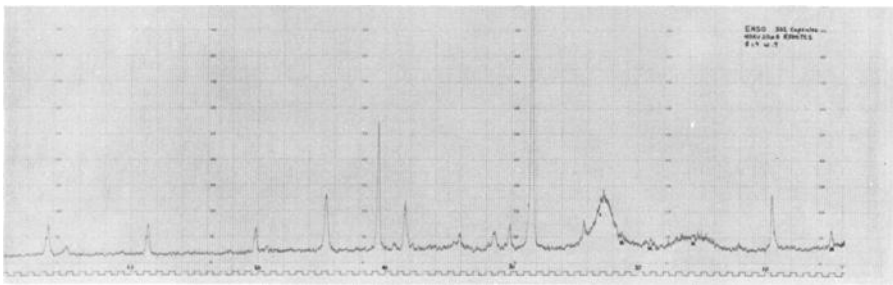

FIG. 3—*Pattern of Endo 502 capsule material using full Philips slide.*

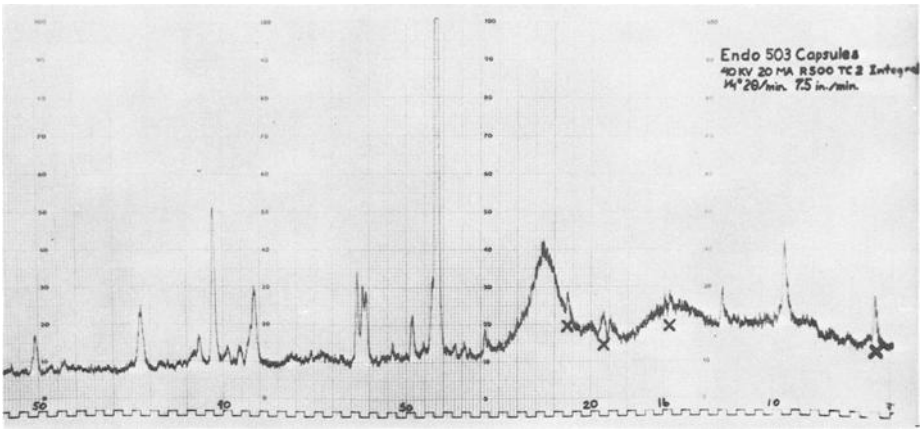

FIG. 4—*Endo 503 capsule material using full Philips slide.*

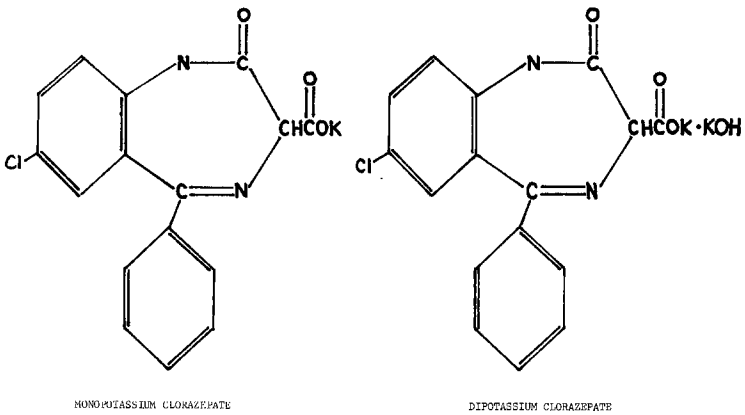

FIG. 5—*Structural formulas of monopotassium and dipotassium clorazepate.*

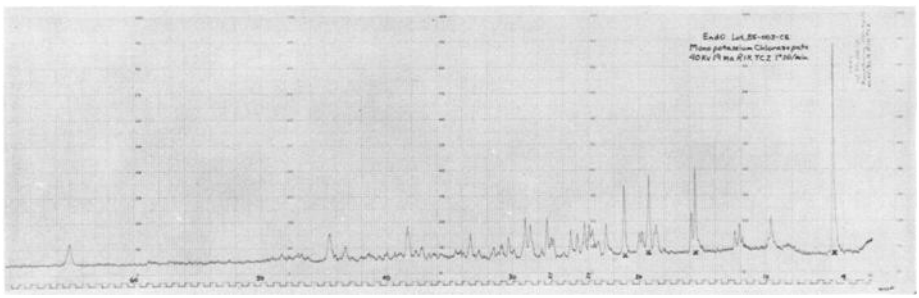

FIG. 6—*Endo standard monopotassium clorazepate pattern.*

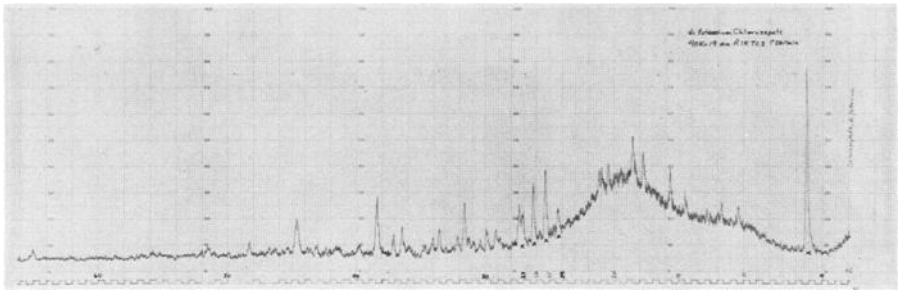

FIG. 7—*Abbott standard dipotassium clorazepate pattern.*

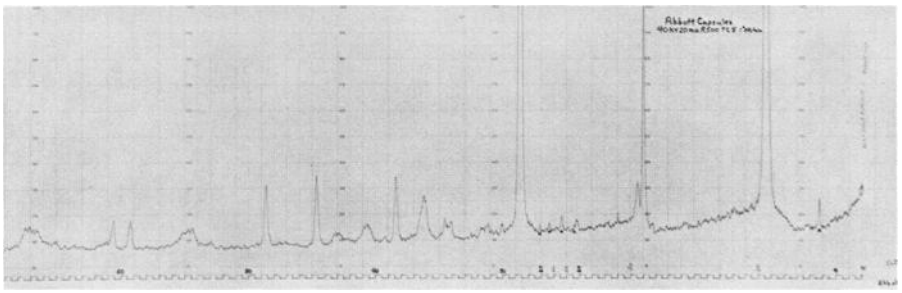

FIG. 8—*Abbott capsule material pattern.*

References

[1] Clark, E. G. C., Ed., *The Isolation and Identification of Drugs*, Vol. 1, The Pharmaceutical Press, London, 1969, p. 46.
[2] Florey, K., Ed., *Analytical Profiles of Drug Substances*, Vol. 4, Academic Press, New York, 1975, pp. 92–112.

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