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Note

Gas–liquid chromatographic determination of methadone in sustained-release tablets

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The need for accurate determination of small quantities of methadone, as a result of its widespread use, led to the development of a number of methods. Wallace *et al.*[1] proposed a UV spectrophotometric determination based on oxidation of methadone, having a low molar absorptivity of $\varepsilon_{max.} = 554$, to benzophenone, which exhibits a higher molar absorptivity of $\varepsilon_{max.} = 18{,}713$. McGonigle[2] reported a fluorometric method including treatment of methadone with formaldehyde in sulfuric acid. Beckett *et al.*[3] detected methadone and its metabolites with gas–liquid chromatography (GLC) using a glass 2-m × 1/8-in.-O.D. column, packed with 80–100 mesh Chromosorb G AW-CDMS, coated with SE-30. They also used a stainless-steel 1-m × 1/8-in.-O.D. column packed with Chromosorb G AW-CDMS, coated with 5% w/w potassium hydroxide and 2% Carbowax 20M. Inturrisi and Verebely[4] described a method employing solvent extraction and GLC, which was claimed to be able to detect as little as 0.015 μg of methadone per milliliter of human plasma. A 6 ft. × 2-mm-I.D. spiral glass column was packed with Gas-Chrom Q, 80–100 mesh, coated with SE-30; β-diethylaminoethyldiphenylpropyl acetate hydrochloride was used as internal standard. A number of other methods also appeared in the literature[5–7]. Presently a gas–liquid chromatographic (GLC) technique for the detection of methadone, released from prolonged-action tablets, is described.

EXPERIMENTAL AND RESULTS

Sustained-release tablets were prepared according to the methods outlined elsewhere[8,9]. Dissolution fluids for the *in vitro* evaluation of the tablets were prepared according to the techniques described in U.S.P. XVIII[10] and N.F. XIII[11]. Each of five dissolution media were prepared by mixing the volumes of gastric fluid and intestinal fluid indicated in Table I.

Two tablets from each prepared formulation were placed in two 90-ml screw-capped bottles, each containing 60 ml of dissolution medium, pH 1.2, previously heated to 37°. The bottles were then tightly capped and placed in the clamps on the shaft of the rotating bottle apparatus and rotated at 40 ± 2 rpm in a water-bath maintained at 37° ± 0.5 °. At the end of 1 h the apparatus was stopped and the

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TABLE I

COMPOSITION OF DISSOLUTION MEDIA

Dissolution fluid pH	*Gastric fluid (ml)*	*Intestinal fluid (ml)*	*Test time (h)*
1.2	100.0	0	0–1
2.5	46.0	54.0	1–2
4.5	39.0	61.0	2–3.5
7.0	17.5	82.5	3.5–5
7.5	0	0	5–7.5

bottles were removed. The pH 1.2 dissolution fluid from each bottle was decanted through a 40-mesh metal screen, retaining as much residue in the bottle as possible. Any residue remaining on the screen was returned to the original bottle and 60 ml of pH 2.5 dissolution fluid were added, while the decanted pH 1.2 dissolution fluid was retained for assay. The process was repeated at the end of 2 h, 3 h 30 min, 5 h, and 7 h 30 min, using pH 2.5, pH 4.5, pH 7.0 and pH 7.5, respectively.

The following GLC method for the determination of methadone was developed. Exactly 10 ml of a filtered methadone-containing sample was transferred to a 125-ml separatory funnel, and a drop of phenolphthalein was added. Drops of 1 *N* sodium hydroxide solution were added until the phenolphthalein had changed color. 50 ml of trichloromethane, accurately measured, were pipetted in, and the separatory funnel was shaken vigorously for 3 min. After the layers had been separated, about 30 to 35 ml of the trichloromethane layer was transferred to a stoppered 50-ml conical flask. About 1 g anhydrous sodium sulfate was added and the flask shaken. A 10-ml volume of this solution, exactly measured, was transferred to a stoppered 25-ml conical flask, and 2 ml of reference solution (a trichloromethane solution of base atropine), accurately measured, was added. The volume of the resulting solution was reduced to approximately 2 ml in a steam-bath using dry compressed air to facilitate evaporation. Finally, the solution was evaporated to dryness, using compressed air only, to avoid possible loss of methadone due to overheating. The residue was dissolved in 2 ml of trichloromethane, accurately measured, and the flask was stoppered immediately. A volume of 1 to 2 μl was injected in-column, using a siliconized spiral glass column 3 ft. long × 2 mm I.D. packed with 100–120 mesh Supelcoport coated with GP 3% SP-2250-DB. The oven temperature was set at 235°, the injector temperature was 290°, and that of the detector was 285°. Helium was used as carrier gas at a flow-rate of 35 ml/min, while the hydrogen flow-rate was set at 30 ml/min and that of air at 300 ml/min. The gas chromatograph used was Aerograph Model 2740 equipped with a flame ionization detector and connected to a Varian Instruments Model 30 variable-speed recorder. Under these conditions the retention times were 1.60 min for methadone and 2.45 min for atropine (Fig. 1). Triplicate injections were made for each sample. The determination of methadone was based on the ratio of methadone peak height to reference (atropine) peak height, using the formula

$$\frac{q_m}{q_a} = \frac{p_m}{p_a} \cdot \frac{mr_a}{mr_m}$$

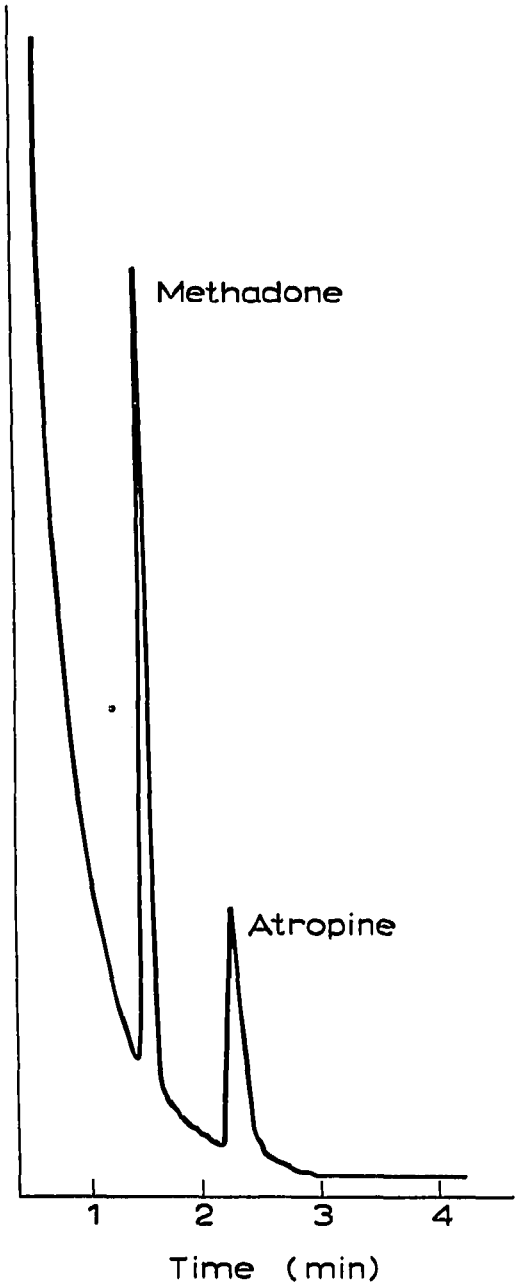

Fig. 1. GLC of methadone (atropine was used as reference).

where q_m is the quantity of methadone in the solution, q_a is the quantity of atropine, p_m/p_a is the average peak height ratio of methadone to atropine, mr_a is the molar response of atropine and mr_m is the molar response of methadone. The calculated

values were 0.3800 for mr_m and 0.5855 for mr_n [peak height units $\times$ (100 ml/mg)]. The results were reproducible.

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