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Note

High-performance liquid chromatographic analysis of methadone hydrochloride in pharmaceuticals

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Methadone is a widely used drug possessing potent analgesic properties, but having a reduced sedative action compared with morphine. It is now being used extensively in narcotic drug substitution therapy programmes, a common formulation being 1 mg/ml methadone hydrochloride in a suitable vehicle, commonly referred to as methadone mixture DTF. Where large volumes of the mixture are prepared in closely monitored production facilities, a rapid and precise method of analysis is required for the finished product. The British Pharmacopoeia 1980 specifies an extraction–acid titration method for methadone injection and tablets and an extraction–UV spectroscopic determination for the linctus[1]. However, in recent years there has been a move away from the use of chloroform as a preservative and instead methylhydroxybenzoate (MHB) is increasingly used. This results in interference with the methadone assay and the MHB is also not quantified. The United States Pharmacopoeia 1985 gives two methods for the analysis of methadone in methadone hydrochloride oral concentrate and methadone hydrochloride oral solution[2]. The former assay is a reversed-phase high-performance liquid chromatographic (HPLC) method using gradient elution over a period of 10 to 20 min. Five replicate injections of a single test solution have to be performed hence the analysis is lengthy and wasteful of solvents. The latter assay requires an ether extraction and washing with water to prepare the test solution before using an isocratic reversed-phase HPLC system. Again the total assay procedure is lengthy. Beasley and Ziegler[3] described a reversed-phase HPLC system similar to that described for methadone hydrochloride oral concentrate which suffers from the same disadvantages. Derendorf and Garrett[4] described an HPLC method for the analysis of methadone, phencyclidine and their metabolites using a fluorescent ion-pairing agent. Although this method is sensitive for very low levels of drug and metabolites in biological matrices, it does not suit the requirements for routine pharmaceutical analysis. Hsieh *et al.*[5] have described a reversed-phase HPLC system using an ion-pairing agent (sodium pentanesulphonate) for the analysis of methadone in sustained release preparations.

The purpose of this paper is to describe an improved method for the simultaneous analysis of methadone and MHB in an oral solution.

MATERIALS AND METHODS

Chromatography

All assays were performed using an ACS (Luton, U.K.) Model 740 Pump, a Perkin-Elmer (Beaconsfield, U.K.) LC75 variable-wavelength detector and a Hewlett-Packard (Wokingham, U.K.) 3900A integrator. Injection was via a Rheodyne (Cotati, CA, U.S.A.) 7125 injector fitted with a 20-μl loop. A 25 cm × 5 mm I.D. Spherisorb 5CN column (Hichrom, Reading, U.K.) was used, the flow-rate was 2 ml/min and the detection wavelength was 259 nm.

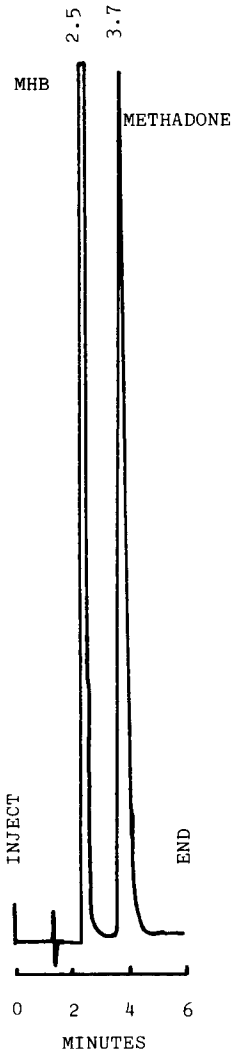

Fig. 1. Typical chromatogram of diluted methadone mixture with MHB as preservative (0.1 mg methadone per ml, 0.1 mg MHB per ml).

Reagents

Methadone hydrochloride was purchased from The Wellcome Foundation (London, U.K.) and assayed before use. Acetonitrile was obtained from Rathburn (Walkerburn, U.K.). Sodium octanesulphonate and methylhydroxybenzoate were obtained from Sigma (St. Louis, MO, U.S.A.). Glacial acetic acid was reagent grade and potassium dihydrogen orthophosphate "AnalaR" grade (BDH, Poole, U.K.).

The mobile phase was acetonitrile–0.01 *M* potassium dihydrogen orthophosphate (60:40). To the final solvent was added 0.1% (w/v) sodium octanesulphonate and the pH was adjusted to 3.5 with glacial acetic acid.

Procedure

Solutions of methadone, with both chloroform and MHB as preservatives, were diluted to give a final concentration of 10 mg methadone hydrochloride in 100 ml (0.1 mg/ml). Standards were prepared from both methadone and MHB in water to give similar concentrations. Samples were injected via the injector and the areas under the peaks determined. Replicate sample and standard solutions were injected to test for system reliability.

RESULTS

A typical chromatogram for methadone and MHB is shown in Fig. 1. The first peak is MHB and the second is methadone (elution times of 2.5 and 3.7 min, respectively). The peaks are well resolved and the addition of the phosphate buffer reduced peak tailing. No chromatographic interference was seen with the colouring agents. The coefficient of variation of 10 replicate standard injections was 0.2%. Five replicate analyses of a freshly prepared methadone mixture (1 mg/ml) gave a mean recovery of 100.5% with a coefficient of variation of 0.25%.

DISCUSSION

The recent increasing manufacture of methadone mixture DTF, requiring routine quality control, coupled with the move away from the use of chloroform as a preservative, necessitated a sensitive and rapid method of analysis for methadone and MHB. An HPLC method using a nitrile column with an ion-paired mobile phase has been successfully developed and this system is now in constant use in this laboratory, allowing complete and rapid separation of the components. Furthermore, the method is simple and offers a reduction in expensive solvents and laboratory man hours compared with existing published methods.

REFERENCES

1 *British Pharmacopoeia*, Her Majesty's Stationery Office, Cambridge, 1980, pp. 637, 679.
2 *The United States Pharmacopoeia*, Mack Printing Company, Easton, PA, 21st revision, 1985, pp. 649–650.
3 T. H. Beasley and H. W. Ziegler, *J. Pharm. Sci.*, 66 (1977) 1749.
4 H. Derendorf and E. R. Garrett, *J. Pharm. Sci.*, 72 (1983) 630.
5 J.-W. Hsieh, J. K. H. Ma, J. P. O'Donnell and N. H. Choulis, *J. Chromatogr.*, 161 (1978) 366.