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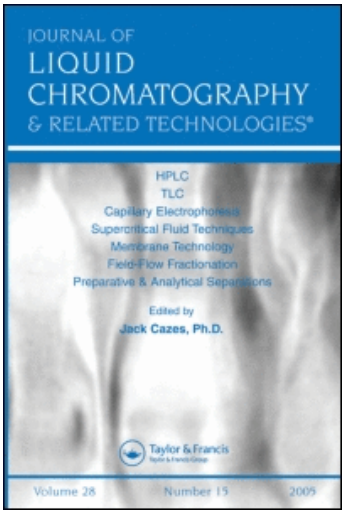

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A New High Performance Liquid Chromatographic Assay for Fluspirilene in Dosage Forms

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A NEW HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC ASSAY FOR FLUSPIRILENE IN DOSAGE FORMS

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ABSTRACT

A new method for the assay of fluspirilene (R 6218) in dosage forms using HPLC has been developed. The instrument used had a low volume positive displacement pump, a universal injector, a single wavelength (254 nm) detector, and a data module. The column was stainless steel 30 cm x 4 mm I.d. packed with microparticulate silica. The mobile phase consisted of equal volumes of chloroform and methanol at a flow rate of 1 ml per min. A linear relationship ($r = 0.999$) was obtained between peak area and concentration of fluspirilene in the range 10-200 µg per ml; no internal standard was used. Fluspirilene was extracted from injectable aqueous suspensions by membrane filtration, drying and dissolution in chloroform-methanol (1:1). Results of assaying fluspirilene in two commercial injectable suspensions by this method were 99.73 and 99.78% of labelled amount.

INTRODUCTION

Fluspirilene (R 6218), or 8-[4, 4-bis (p-fluorophenyl) butyl]-1-phenyl-1, 3, 8-triazaspiro [4, 5] decan-4-one, is a member of a class of neuroleptics, derived from 4, 4-diphenylbutyl-piperidine,

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of which pimozide is the prototype. In animals fluspirilene is relatively atoxic with a wide margin of safety (1). It is more effective than fluphenazine enanthate, and it has a duration of action of about 6 days following the intramuscular injection of an aqueous suspension (1). In humans, it was found effective in disorders of the affect, retardation in thought process, and lack of initiative (2). Fluspirilene is marketed in the form of a sterile aqueous suspension for injection containing 2 mg per ml. The recommended method for its assay is a spectrophotometric procedure (3) which, though somewhat sensitive, would not be adequate in the presence of decomposition products or other interfering substances.

The present work describes a simple, sensitive, and specific procedure for the assay of fluspirilene in dosage forms using high performance liquid chromatography (HPLC).

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EXPERIMENTAL

Chemicals and Reagents:

Fluspirilene standard (Janssen Pharmaceutica,Beerse, Belgium, Batch No: 58/1) was used as obtained. Chloroform (Fluka AG Chemische Fabrik CH-9470, Buchs) and Methanol (Fluka AG) were spectroscopic grade. Other chemicals were U.S.P. or Analytical Reagent grade and were used withou further purification. Injectable fluspirilene was purchased on the local market.

Instrumentation:

The liquid chromatograph (Model ALG/GPC 244 U, Waters Associates, U.S.A.) used had a low volume positive displacement pump (Model 6000 A, Waters Associates, U.S.A.), a universal injector (Model U6K, Waters Associates, U.S.A.), a single wavelength (254 nm) detector (Model 440, Waters Associates, U.S.A.), and a data module (Model 730, Waters Associates, U.S.A.).

The column was stainless steel 30 cm x 4 mm i.d. packed with microparticulate silica (Microporasil, Waters Associates, U.S.A.).

The mobile phase consisted of a 50:50 mixture of chloroform and methanol, and the flow rate was 1 ml per min. Experiments were conducted at ambient temperature (25°C).

Calibration Curve:

Standard solutions of fluspirilene were accurately prepared to contain 10, 20, 40, 60, 80, 100, and 200 µg per ml, using the mobile phase as the solvent. Duplicate injections of 10 µl were made, and peak area plotted against concentration. The line of best fit was calculated by least squares and used to determine concentration of test solutions. Standard solutions were interspersed with solutions obtained from extraction of dosage forms, and all were run on the same working day.

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Extraction of Fluspirilene:

The vial containing fluspirilene suspension for injection was shaken thoroughly, and then opened by the removal of the rubber stopper and the retaining almunium cap. Two ml of the suspension was pipetted and placed on a membrane filter system holding a 45mm membrane (Type AH, 0.45µm, Millipore Corporation, U.S.A.) and attached to a vacuum pump (Millipore Corporation, U.S.A.). The residue on the membrane was washed with about 10 ml of water, then dried at 105° for 30 min. The dried solid was then dissolved in 50 ml of chloroform, transferred to a 100-ml volumetric flask, and methanol was added to volume. Duplicate injections of 10 µl were made into the liquid chromatograph. This procedure was repeated with a second 2-ml aliquot from each vial.

RESULTS AND DISCUSSION

Figure 1 depicts the relationship between concentration of fluspirilene and peak area. The correlation coefficient of the least squares line was 0.999, and no internal standard was used. Under the experimental conditions described above, fluspirilene showed a single peak with a retention time of 5.15 min.

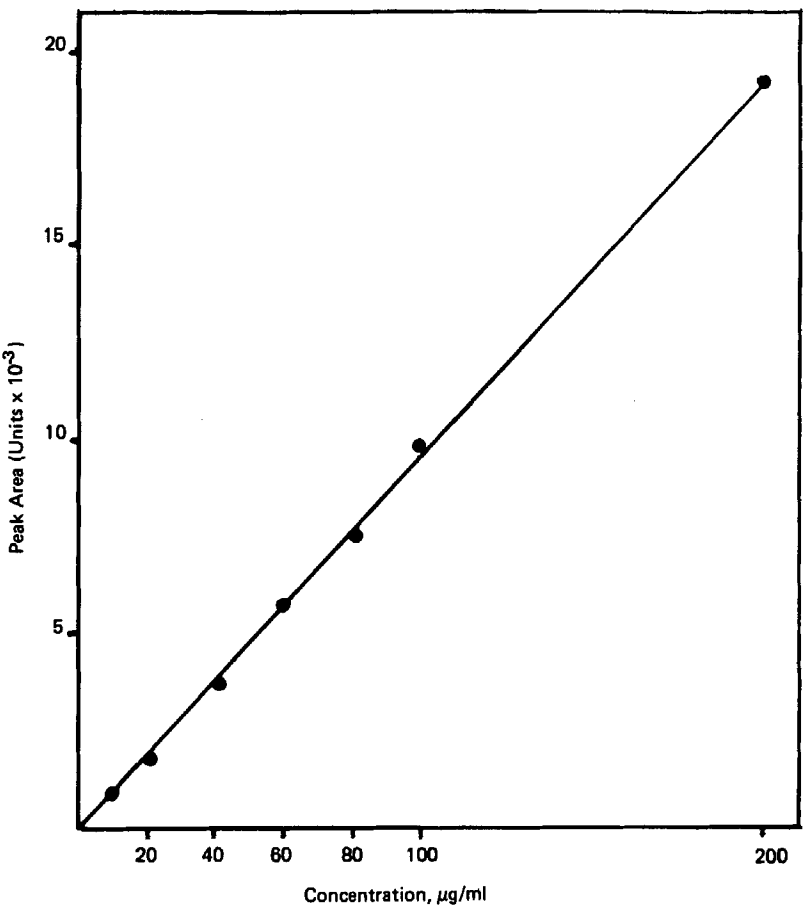

FIGURE 1

Relationship between peak area and concentration of fluspirilene.

Figure 2 shows a typical chromatogram obtained from extraction of fluspirilene from an injectable suspension. No interfering peaks were observed.

When the present procedure was applied to the determination of fluspirilene in two commercially available suspensions, the

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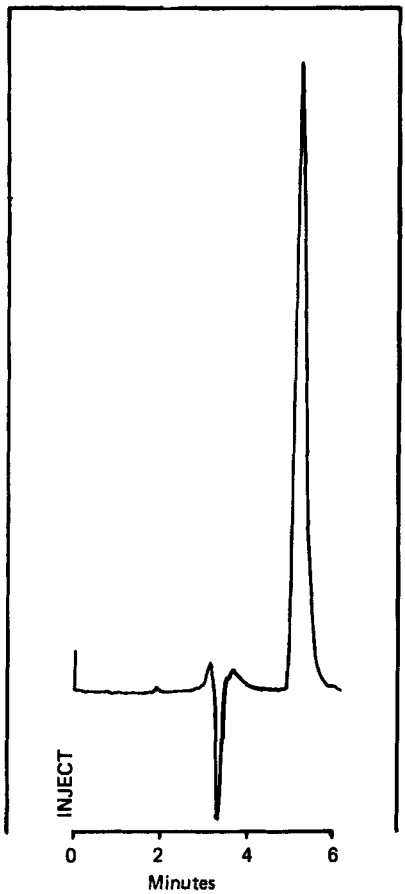

FIGURE 2

Typical chromatogram of fluspirilene extracted from injectable suspension.

results shown in Table I were obtained. In both of the commercial products, the labelled amount was 2 mg per ml. In product A, the amount found in 2 ml was 3.989 ± 0.088 mg, representing 99.73% of the labelled amount. In product B, the amount found in 2 ml was 3.991 ± 0.096 mg, representing 99.78% of the labelled amount.

TABLE 1

Assay of Fluspirilene in Injectable Suspension by HPLC.

Product	Labelled amount (mg/2 ml)	Amount found[c]	%
A[a]	4	3.989 ± 0.088	99.73 ± 2.2
B[b]	4	3.991 ± 0.096	99.78 ± 2.4

a- Redeptin®, Smith, Kline, and French Laboratories,Ltd.England, Lot No: JG 0105.

b- Imap®, Janssen Pharmaceutica, Beerse, Belgium, Lot No:80108/121.

c- Mean of 2 runs ± S.D.

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The procedure described is simple, accurate, and specific, and is more capable of detecting interfering substance, whether decomposition products or other, than a spectrophotometric assay.

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