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Note

Purity assay of ketoprofen by high-performance liquid chromatography

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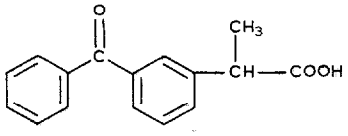
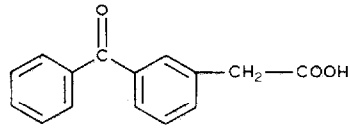
Among the propionic acid derivatives, ketoprofen (I) is a widely prescribed anti-inflammatory drug[1], for which numerous high-performance liquid chromatographic (HPLC) methods have been developed [2,3]. However, no method is available for the determination of ketoprofen-related impurities. These may include the by-products, 3-benzoylphenylacetic acid (II) and 2-[3-(4-methylbenzoyl)phenyl]propionic acid (III), and the precursor, 2-(3-benzoylphenyl)propionitrile (IV) (Fig. 1).

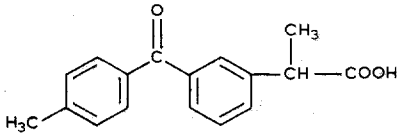
The purpose of this note is to report a reversed-phase HPLC method for the quality control of ketoprofen.



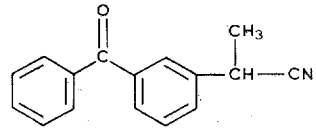
I



II



III



IV

Fig. 1. Structural formulae of ketoprofen (I), 3-benzoylphenylacetic acid (II), 2-[3-(4-methylbenzoyl) phenyl]propionic acid (III) and 2-(3-benzoylphenyl)propionitrile (IV).

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EXPERIMENTAL

Materials

Ketoprofen raw materials were from various sources. Ketoprofen-related impurities were obtained from SIMS (Firenze, Italy). The structure of III was confirmed by nuclear magnetic resonance spectroscopy, which allowed the methyl group to be assigned to the 4-position of the benzoyl ring. Ethyl 4-hydroxybenzoate (internal standard) was from Aldrich (Steinheim, F.R.G.). Acetonitrile was of HPLC grade (Chromasolv; Riedel de Haën, Hannover, F.R.G.). Water was distilled in glass and passed through a 0.45-μm membrane filter (Type HA, Millipore).

Solutions

Stock solutions of I–IV were prepared with a final concentration of 4 mg/ml (I) and 1 mg/ml (II, III, IV) in ethanol. Ethyl 4-hydroxybenzoate, as internal standard, was dissolved in ethanol to give a concentration of 0.008 mg/ml. Standard solutions of I (2 mg/ml) and II–IV (0.02–0.001 mg/ml) containing 8 μg/ml of internal standard were prepared from the stock solutions.

Chromatographic conditions

The system consisted of a Model 590 pump equipped with a Model U6K universal injector, a Model 440 ultraviolet detector and a Model 730 data module (Waters Assoc., Milford, MA, U.S.A.). Ultraviolet absorption was measured at 254 nm (0.05 a.u.f.s.). Samples were chromatographed on an Hibar LiChrocart RP C_{18} (12.5 cm × 4 mm) (Merck, Milano, Italy) using acetonitrile–water (37:63), pH 2.7 with 50% phosphoric acid, as eluent. The flow-rate was 2 ml/min. A pre-column of LiChrocart PVDF (4 cm × 4 mm) was used, to extend the column life.

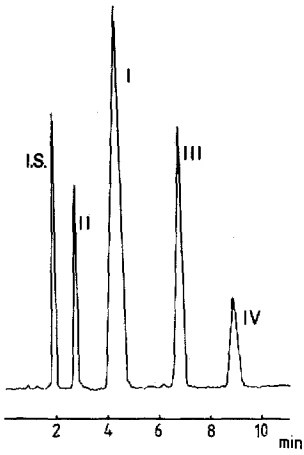

Fig. 2. Chromatogram of a synthetic mixture of compounds I–IV and ethyl 4-hydroxybenzoate (IS, internal standard). See text for chromatographic conditions.

RESULTS AND DISCUSSION

The resolution of compounds II–IV from ketoprofen using acetonitrile–water (37:63, pH 2.7) as mobile phase is shown in Fig. 2. Ethyl 4-hydroxybenzoate was chosen as internal standard, because it is stable and well resolved from other components. Linearity was established by chromatographing standard solutions over the range 200–10 ng.

Four lots of ketoprofen raw materials were examined for the presence of related compounds. A typical chromatogram obtained from one of these lots is presented in Fig. 3. The main impurity was III (*ca.* 0.4%), while the content of II was about 0.05%, IV was almost absent.

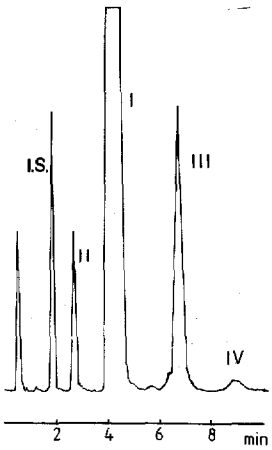

Fig. 3. Chromatogram of a ketoprofen raw material. Peaks as in Fig. 2.

The reproducibility of the method was determined by replicate analyses of the same samples in two different laboratories and was found to be 2.3%.

In conclusion, this specific and reproducible assay can be applied to industrial process control and to pharmaceutical quality control, and can replace the semi-quantitative thin-layer chromatographic purity test.

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