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Short communication

Acid and base degraded products of ketorolac

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ABSTRACT

The stability of ketorolac tromethamine was investigated in acid (0.5 M HCl) and alkaline conditions (0.5 M NaOH), using the same procedure reported by Devarajan et al. [2]. The acid and base degradation products were identified by liquid chromatography–mass spectrometry (LC–MS).

1. Introduction

Ketorolac tromethamine is one of the most potent anti-inflammatory and analgesic drugs but its use has been strongly limited owing to the high incidence of adverse effects reported, particularly in the gastrointestinal tract. Using the prodrug approach, which allows the reduction of toxicological features of the parent drug without altering its pharmacological properties, we have already synthesized an orally administrable prodrug of ketorolac by means of its reversible conjugation to D-galactose (ketogal) [1]. In the course of these studies on the stability of ketorolac prodrugs we have also investigated the stability of the parent drug, referring to a previous study, which shows the likely degradation products in acid–base. The stability was studied in acid (0.5 M HCl) and alkaline conditions (0.5 M NaOH) [2]. Using the same procedure reported by Devarajan et al., we further investigated the degradation products by LC–MS. The products obtained do not correspond to those reported in the work of reference, where the identification was carried out by HPTLC (Fig. 1).

2. Materials and methods

2.1. Materials

Ketorolac tromethamine was obtained from Sigma–Aldrich. HPLC grade acetonitrile, methanol and LC–MS reagent 0.1% formic acid were purchased from Baker.

2.2. Standard solution

Standard solutions of ketorolac tromethamine were prepared in methanol at a concentration of 1000 μg/ml. Standard solutions of 100 μg/ml in methanol and 50 μg/ml in acid or base were used for analysis.

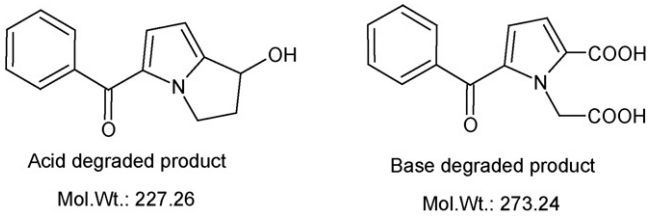

Fig. 1. Structure of acid and base degraded products reported by Devarajan et al. [2].

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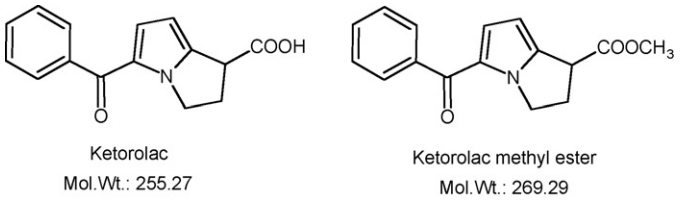

Fig. 2. Chemical structure of ketorolac and ketorolac methyl ester.

2.3. Sample preparation

The stability study of ketorolac tromethamine was carried out in 0.5 M HCl and 0.5 M NaOH, using two different procedures:

Method A 10 ml of ketorolac tromethamine solution (100 μg/ml) in methanol was boiled for 10 min with an equal volume of acid or base [2].

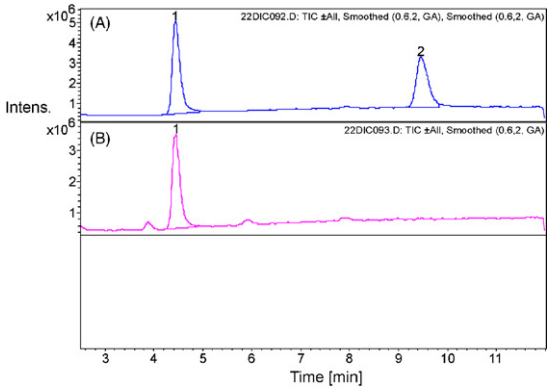

Fig. 3. Chromatograms of ketorolac in acid conditions: (A) 10 ml of ketorolac tromethamine solution (100 μg/ml) in methanol was boiled for 10 min with an equal volume of 0.5 M HCl and (B) 10 ml of ketorolac tromethamine solution (50 μg/ml) in 0.5 M HCl was boiled for 10 min.

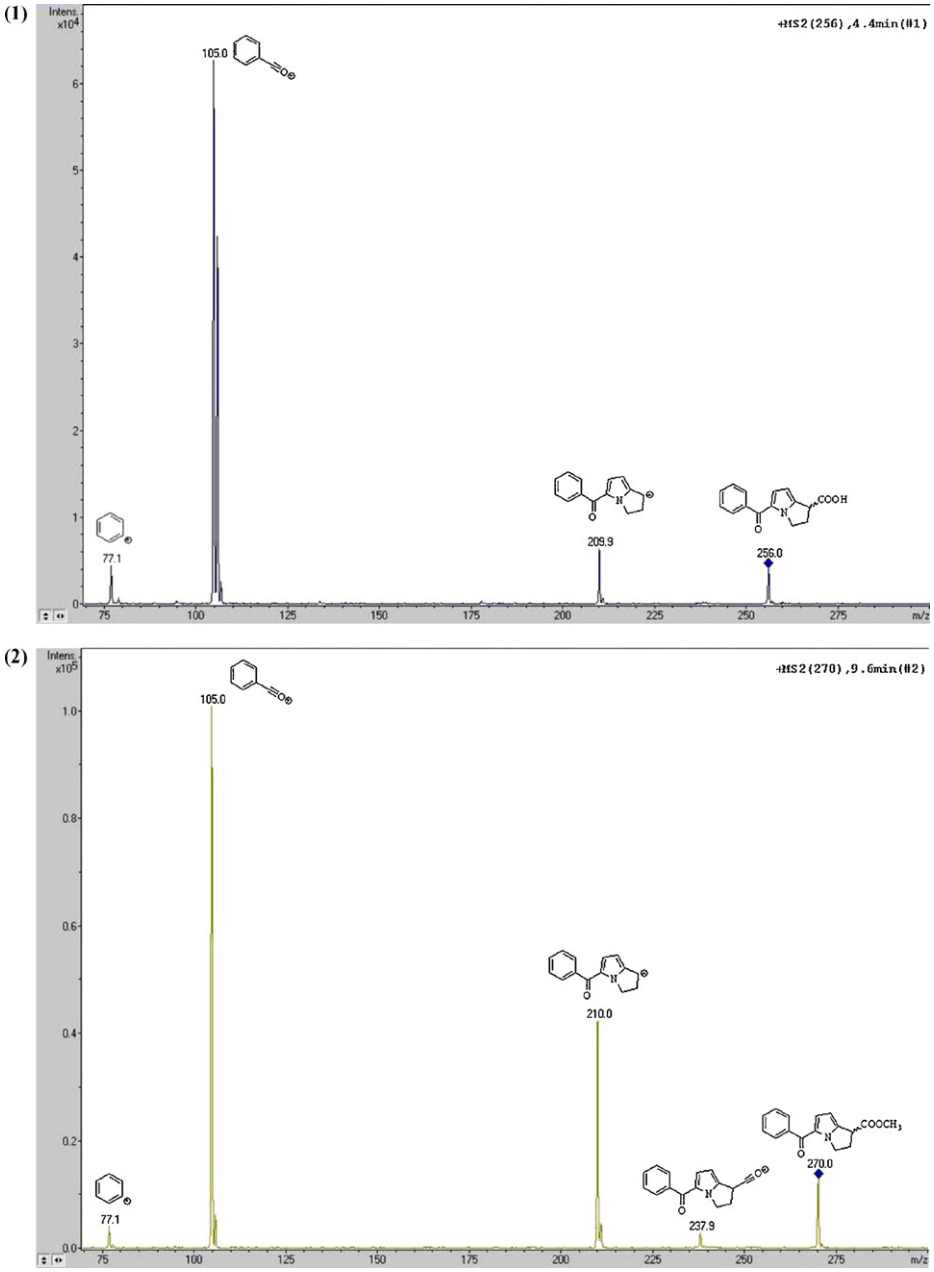

Fig. 4. Mass spectra of ketorolac (1) and ketorolac methyl ester (2).

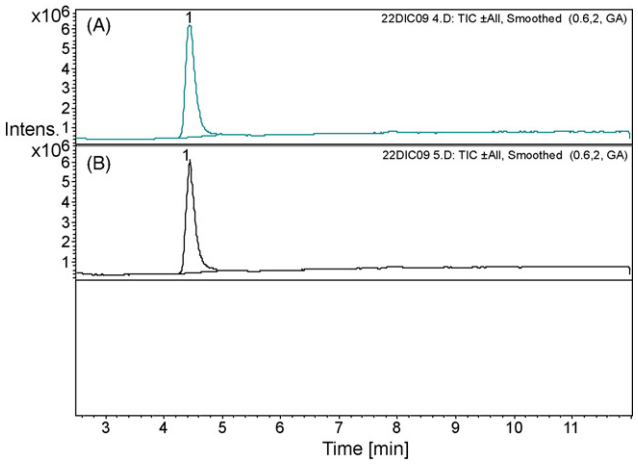

Fig. 5. Chromatograms of ketorolac in alkaline condition: (A) 10 ml of ketorolac tromethamine solution (100 μg/ml) in methanol was boiled for 10 min with an equal volume of 0.5 M NaOH and (B) 10 ml of ketorolac tromethamine solution (50 μg/ml) in 0.5 M NaOH was boiled for 10 min.

Method B 10 ml of ketorolac tromethamine solution (50 μg/ml) in acid or base was boiled for 10 min.

The four final solutions were neutralised before injection into the LC–MS system.

2.4. LC–MS

An Agilent Technologies (Palo Alto, CA, USA) 1100 series LC/MSD equipped with an autosampler (G1313A) was used for LC separation. The chromatographic separation was achieved on an LUNA C18 (2) column (150 mm × 2.0 mm, 3 μm) (Phenomenex, Torrance, CA, USA) using a mobile phase containing mixture of aqueous 0.1% HCOOH and acetonitrile (50:50, v/v). The column temperature was maintained at 25 °C. The flow rate was 0.2 ml/min.

The chromatographic system was coupled to an ion trap mass spectrometer LC-MSD-Trap-VL (Agilent Technologies, Palo Alto, USA) equipped with an electrospray ionisation source (ESI) working in positive ion mode. Optimised ESI source parameters were as follows: dry temperature (set) 350 °C, nebulizer (set) 40.00 psi, dry gas (set) 8.00 l/min, HV capillary 4500 V, Octapole RF amplitude 127.9 Vpp, lens 2 −47.2 V, capillary exit 91.2 V, skim 1 15.0 V, skim 2 6.9 V, lens 1 −2.5 V, cap exit offset 76.2 V, octopole 2.90 V, octopole delta 2.91 V, trap drive 33.2, scan begin 80 *m*/*z*, scan end 300 *m*/*z*, averages 5 spectra, max. acc. time 300,000 μs, ICC target 30,000.

3. Results and discussion

The objective of this study was to extend our understanding of the stability of ketorolac in acid and alkaline conditions. The studies were carried out in 0.5 M HCl/CH_3OH (50:50, v/v), 0.5 M HCl, 0.5 M NaOH/CH_3OH (50:50, v/v) and 0.5 M NaOH. We found that no decomposition products were isolated by LC–MS, contrary to what reported by Devarajan et al. [2].

When the hydrolysis was conducted in 0.5 M HCl/CH_3OH (50:50, v/v) we observed two products: the ketorolac and the ketorolac methyl ester (Fig. 2), while, when the hydrolysis was conducted in 0.5 M HCl no new product was observed. Fig. 3 shows chromatograms related to the treatment with 0.5 M HCl/CH_3OH (50:50, v/v) (Fig. 3A) and 0.5 M HCl (Fig. 3B), whereas the mass spectra of peaks of Fig. 3A are reported in Fig. 4.

Degradation was not observed in ketorolac tromethamine sample when subjected to alkaline hydrolysis in 0.5 M NaOH/CH_3OH (50:50, v/v) (Fig. 5A) and in 0.5 M NaOH (Fig. 5B).

Thus, these results indicate that ketorolac is highly stable in acid and alkaline conditions.

4. Conclusions

The data presented prove the stability of ketorolac: in those conditions no degradation takes place, contrary to what reported in previous papers [2,3].

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