INTRODUCTION
The proposed curative properties of copper based non-steroidal anti-inflammatory drugs (NSAIDs) have led to the development of copper(II) complexes of NSAIDs with enhanced anti-inflammatory activity and reduced gastrointestinal toxicity compared with their uncomplexed parent drugs. No copper(II) anti-inflammatory drug is currently available for oral human use, although a gel base of copper-salicylate (Alcusal™) is available for topical temporal relief of pain in inflammation in humans in Australia(1).

Copper is an essential trace element, taking part in all aspects of metabolism(2). It is believed to possess anti-inflammatory activity and has been proposed an increased demand for copper during inflammatory conditions(3).

Fenoprofen, 2-(3-phenoxyphenyl)propionic acid, is an antipyretic, analgesic and NSAID(4). Little is known about chemical structures of Fenoprofen complexes and copper drugs have yet to reach an extended human market, so in this work we present the enhanced anti-inflammatory activity of two new copper(II) complexes with Fenoprofen.

MATERIALS AND METHODS
Copper complexes, of formula Cu₂(Fen)₄(caf)₂ and Cu(Fen)₂(im)₂ (Fen: Fenoprofenate; caf: caffeine; im: imidazole), were synthesized from Cu₂(Fen)₄(dmf)₂(5) dissolved in acetone and by the addition of a solution of caffeine in ethanol and imidazole, in acetone respectively. The diffusion of acetonitrile led to the formation of crystals which were studied by physicochemical techniques to confirm their molecular structures.

The studies of the anti-inflammatory properties were carried out employing the carrageenan induced paw oedema in female mice described by Winter et al(6).

Test animals were administered orally an aqueous suspension of Cu₂(Fen)₄(caf)₂ (31 mg/kg), Cu(Fen)₂(im)₂ (28 mg/kg) and the calcium salt of Fenoprofen (21 mg/kg). The vehicle alone (carboxymethylcellulose and Tween80) was used as excipient for the control group. Drug and excipient were orally administered to each animal one-hour before inducing oedema in the left hind paw by sub-plantar injection of carrageenan.

The length of the paw was measured with a digital electronic caliper immediately before the injection of carrageenan and 3, 5, 7 and 9 hours after. The anti-inflammatory effect was expressed in terms of the percent inhibition of oedema produced by each drug-treated group.

RESULTS
The study of acute anti-inflammatory test showed that the percentages of inhibition of inflammation for Cu₂(Fen)₄(caf)₂ were 84.3, 81.0, 81.5 and 73.4% at the third, fifth, seventh and ninth hour from the beginning of the experiment, meanwhile for Cu(Fen)₂(im)₂, the percentages were 30.0, 33.3, 58.5, 40.5% respectively.

When Fenoprofen calcium salt was studied it presented 29.1, 42.3, 19.9, 10.5% of inhibition at the same hours.

DISCUSSION
Cu₂(Fen)₄(caf)₂ presented the highest inflammation inhibition percent, sustaining it during all the time of the experiment. Cu(Fen)₂(im)₂ presented highest action than Fenoprofen salt from the fifth hour. Both complexes maintained enhanced action until the end of the experiment when compared to Fenoprofen calcium salt, demonstrating a more sustain activity in time.

CONCLUSION
Both copper(II) complexes with Fenoprofen presented enhanced anti-inflammatory action than the uncomplexed parent drug, being this characteristic improved for the complex containing caffeine in its structure. Complementary studies, such as analgesic and toxicological effects are being carried out to improve the knowledge of therapeutic properties of this kind of potential new anti-inflammatory drugs.

REFERENCES


