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**Title:** Formulation of Ibuprofen in Lipid-Crystal Nano-Particles Enhances Efficacy and Reduces Gastric Mucosal Erosions in a Rat Carrageenan-induced Paw Inflammation Model

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**Background:** Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly prescribed drugs in the world for their analgesic and anti-inflammatory properties. However, NSAID use is limited by gastrointestinal (GI) toxicity. NSAIDs injure the gut by causing topical injury to the mucosa and by systemic effects associated with mucosal prostaglandin depletion derived from COX inhibition. New formulations that prevent exposure of the NSAID to the GI mucosa may help reduce the GI toxicity associated with NSAIDs and maintain their anti-inflammatory effects.

**Objectives:** To demonstrate that ibuprofen formulated in two types of cochleates (lipid-crystal, nano-particles) provide enhanced anti-inflammatory effects while reducing the associated mucosal GI toxicity.

**Methods:** Male Sprague Dawley rats treated orally (one hour prior to right hind footpad injection of carrageenan) with vehicle or 50, 10, 2, 0.4, or 0.1 mg/kg of Ibuprofen, Ibuprofen Geodates or Ibuprofen Lipid-Crystal Cochleates (LCC) were evaluated for effects of treatment on inflammatory edema. Animals were terminated five hours after dosing with test articles (four hours after carrageenan injection). Efficacy evaluation was based on weight difference due to inflammation-induced swelling in injected (right) vs. uninjected (left) paws. In addition, gastric mucosa were evaluated for differences in incidence and severity of mucosal congestion and erosions.

**Results:** Treatment of rats with 50 mg/kg of all test articles or with 10 or 2 mg/kg Ibuprofen Geodates or 10 mg/kg Ibuprofen LCCs resulted in significant inhibition of paw weight difference when compared to the vehicle control group. The Ibuprofen LCC formulation was most effective ($ED_{50}$=6 mg/kg) followed by Ibuprofen Geodates ($ED_{50}$=7 mg/kg) and Ibuprofen ($ED_{50}$=30 mg/kg). Rats treated with 50 mg/kg Ibuprofen had significantly increased numbers of gastric lesions and increased total stomach lesion length. Some rats treated with 10 mg/kg Ibuprofen also had gastric lesions. Rats given 50 mg/kg Ibuprofen LCC had increased length and number of stomach lesions as compared to vehicle treated rats, but both parameters were significantly smaller when compared to Ibuprofen treatment alone. Rats treated with 50, 10 or 2 mg/kg Ibuprofen Geodates ($ED_{50}$=7 mg/kg) had significant inhibition of carrageenan-induced paw edema without evidence of gastric irritation. Treatment with LCCs at 10 mg/kg resulted in the greatest inhibition of paw edema for any formulation at this dose and there was no evidence of gastric irritation. There were no gastric lesions in rats given 2, 0.4 or 0.1 mg/kg of any formulation.

**Conclusions:** Results of this study demonstrated that Ibuprofen LCC ($ED_{50}$=6 mg/kg) had greater beneficial effects on carrageenan paw edema than did either Ibuprofen ($ED_{50}$=30 mg/kg) or Ibuprofen Geodates ($ED_{50}$=7 mg/kg). Gastric lesions occurred in some rats treated with single-dose 50 mg/kg (9 of 10) or 10 mg/kg (1 of 10) Ibuprofen whereas none were observed in rats given Geodates. Only 6 of 10 rats given 50 mg/kg LCC and none treated with 10 mg/kg had gastric lesions. Therefore both efficacy as well as incidence and severity of gastric irritation were significantly improved by cochleate formulations of Ibuprofen.

References: Patrignani P, Tacconelli S, Bruno A, Sostres C, Lanas A, Managing the Adverse Effects of Nonsteroidal Anti-Inflammatory Drugs, Expert Rev Clin Pharmacol. 2011;4(5):605-621.