Cationic Diclofenac Lipid Nanoemulsion for Improved Oral Bioavailability: Preparation, Characterization and In Vivo Evaluation

Swapna Madishetty, Muzammil Afzal Syed, Prabhakar Kandadi and Kishan Veerabrahma*
Nanotechnology Research Lab, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India – 506009.
Received February 16, 2015; accepted March 29, 2015

ABSTRACT
Cationic nanoemulsions were reported to have increased bioavailability. The aim of present study was to prepare a cationic lipid nanoemulsion of diclofenac acid (LNEs) for improved oral bioavailability to treat arthritic conditions. The LNEs of diclofenac acid were prepared by using soya bean oil, egg lecithin, cholesterol and stearylamine. Stearylamine was used as positive charge inducer. The LNEs were processed by homogenization and ultrasonication. The formulation composition was selected based on earlier reports. The LNEs were characterized for size and zeta potential. The physical stability of LNEs was studied using autoclaving, centrifugal, desorption (dilution effect) stresses and on storage. The total drug content and entrapment efficiency were determined using HPLC. During in vivo studies in Wistar rats, the pharmacokinetic parameters of LNEs were compared with a prepared diclofenac suspension in sodium CMC mucilage. The selected formulations, F1, F2 and F3, were relatively stable during centrifugal stress, dilution stress and on storage. The drug content was found to be 2.38 ± 1.70 mg/ml for F1, 2.30 ± 0.82 mg/ml for F2, and 2.45 ± 0.66 mg/ml for F3. The entrapment efficiencies were 97.83 ± 0.53%, 97.87 ± 1.22% and 98.25 ± 0.21% for F1, F2 and F3 respectively. The cumulative percentage drug release from F1, F2 and F3 showed more release in pH 6.8 phosphate buffer than in pH 1.2 HCl. During oral bioavailability studies, the LNEs showed higher serum concentrations than a suspension. The relative bioavailability of the LNE formulations F1, F2 and F3 were found to be 2.35, 2.94 and 6.28 times that of F4 suspension and were statistically significant. Of all, the cationic lipid nanoemulsion (F3) was superior in improving bioavailability, when compared with plain emulsion (F1) and cholesterol containing LNE (F2). The study helps in designing the cationic oral nanoemulsions to improve the oral bioavailability of diclofenac.

KEYWORDS: Lipid nanoemulsion; Diclofenac acid; Oral bioavailability; Cationic emulsions; Anti-inflammatory drug.

Introduction
Submicron O/W lipid emulsions are potential drug carriers for lipophilic and amphiphilic drugs (Lundberg et al., 1996). The basic structure consists of a neutral lipid core (i.e., triglyceride) stabilized by a monolayer of amphiphilic lipid (i.e., phospholipids) such emulsions can solubilize considerable amount of lipophilic drugs in core or/amphiphilic ones in the surface monolayer (Lundberg, 1996). The average size of lipid nanoemulsion globules ranges between 200-600 nm.

Diclofenac sodium [O-(2, 6-dichlorophenyl)-amino-phenyl] acetate, is a water soluble (50 mg/ml) non-steroidal Anti-inflammatory drug (NSAID). It shows cyclooxygenase-inhibiting activity (Menassee et al., 1978). It is used to treat inflammation. Due to its analgesic properties, diclofenac sodium is used to reduce the pain in conditions of arthritis, kidney stones, gallstones, menstrual pain, dysmenorrhea and cancer. It is also widely used in long-term therapy of various arthritic conditions such as Rheumatoid Arthritis (Doreen et al., 1978), Osteoarthritis (Sing et al., 2006), Spondylarthritides and Ankylosing Spondylitis. But the biological half-life of diclofenac is short and varies from 1–2 h (Willis et al., 1979; Kendall et al., 1979; Kurowski et al., 1988). Therefore, multiple dosing is required to maintain a therapeutic concentration of drug for an extended period. Previous studies demonstrated that gastro intestinal (GI) toxicity of diclofenac was due to both local as well as systemic effects and enterohepatic recirculation. The induced upper and lower GI toxicity of diclofenac was formulation and time dependent. GI side effects of diclofenac may be reduced if it is administered as a complex with phospholipid. Diclofenac was orally administered as acid with DPCC complex and as sodium salt to reduce the mucosal toxicity. The protection offered by DPCC complex on mucosa could not last up to lower GI tract and limited to 1hr after post administration (Khazaeinia et al., 2003). Diclofenac parenteral lipid nanoemulsions were found to produce sustained effect in a pharmacodynamic study (Varshika et al., 2009).