Objectives: This work aimed at investigating the potential of solid lipid nanoparticles (SLN) as carriers for topical delivery of Ketoprofen (KP); evaluating a novel technique incorporating Artificial Neural Network (ANN) and clustered bootstrap for optimization of KP-loaded SLN (KP-SLN); and demonstrating a longitudinal dose response (LDR) modeling-based approach to compare the activity of topical non-steroidal anti-inflammatory drug formulations.
Methods: KP-SLN was fabricated by a modified emulsion/solvent evaporation method. Box–Behnken design was implemented to study the influence of glycerylpalmitostearate-to-KP ratio, Tween 80, and lecithin concentrations on particle size, entrapment efficiency, and amount of drug permeated through rat skin in 24 hours. Following clustered bootstrap ANN optimization, the optimized KP-SLN was incorporated into an aqueous gel and evaluated for rheology, in vitro release, permeability, skin irritation and in vivo activity using carrageenan-induced rat paw edema model and LDR mathematical model to analyze the time course of anti-inflammatory effect at various application durations.
Results: Lipid-to-drug ratio of 7.85 [bootstrap 95%CI: 7.63–8.51], Tween 80 of 1.27% [bootstrap 95%CI: 0.601–2.40%], and Lecithin of 0.263% [bootstrap 95%CI: 0.263–0.328%] were predicted to produce optimal characteristics. Compared with profenid_ gel, the optimized KP-SLN gel exhibited slower release, faster permeability, better texture properties, greater efficacy, and similar potency.
Conclusions: SLNs are safe and effective permeation enhancers. ANN coupled with clustered bootstrap is a useful method for finding optimal solutions and estimating uncertainty associated with them. LDR models allow mechanistic understanding of comparative in vivo performances of different topical formulations, and help design efficient dermatological bioequivalence assessment methods.