MICROEMULSION FOR IMPROVED SKIN DELIVERY AND IN VIVO ANTI-INFLAMMATORY EFFECT

Praça FSG[1] , Bentley MVLB[1] , Medina WSG[2] .

[1] First Author Affiliation (University of São Paulo, Br) [2]Second Author Affiliation (University of Padre Albino, Br)

ABSTRACT

We have designed a microemulsion (ME) containing Ketoprofen (KET) for antiinflammatory effect evaluated using the rat paw edema model. The ME was prepared by adding propylene glycol (PG) loaded with 1% KET/water (3:1, w/w), to a mixture of sorbitan monooleate and polysorbate 80 (47.0%) at 3:1 (w/w) and canola oil (38.0%). These results demonstrated that the ME formulation is an alternative strategy for improving KET skin permeation for anti-inflammatory effect. Furthermore, our findings are promising considering that the developed ME was loaded with only 1% KET, and the formulation was able to keep a similar release profile and in vivo effect compared to the commercial gel with 2.5% KET. Therefore, the KET-loaded developed herein ME is likely to have a decreased side effect compared with that of the commercial gel, but both presented the same efficacy.

BACKGOUND

Topical administration of nonsteroidal anti-inflammatory drug, such as Ketoprofen, has shown a series of advantages over oral or systemically administration owing to treatment acceptance by patient as well as drug delivery to affected tissues with limited side effects especially in prolonged drug therapy (1). Because Ketoprofen (KET) is a poor water-soluble compound, its skin absorption becomes limited. To overcome this drawback, oil-based formulations have been reported to successfully improve both solubility of KET and its skin permeation (2–4). Nanostructured delivery systems have been used to deliver several non-steroidal anti-inflammatory across the skin and among them the most promising are deformable liposomes, lipid nanoparticles, microemulsions, and nanoemulsions (3–8).

METHODS

The ME was prepared by adding propylene glycol (PG) loaded with 1% KET/water (3:1, w/w), to a mixture of sorbitan monooleate and polysorbate 80 (47.0%) at 3:1 (w/w) and canola oil (38.0%). The physicochemical characterization of KET-loaded ME involved particle size and zeta potential determination, entrapment efficiency, calorimetric analysis, and in vitro drug release. The in vivo anti-inflammatory study employed male Wistar rats. Measurement of the foot volume was performed using a caliper immediately before and 2, 4, and 6 h after injection of Aerosil. KET-loaded ME showed particle size around 20 nm, with zeta potential at -16 mV and entrapment efficiency at 70%. Moreover, KET was converted to the amorphous state when loaded in the formulation and it was shown that the drug was slowly released from the ME. Finally, the in vivo biological activity was similar to that of the comm ercial gel, but ME better controlled edema at 4 h.

RESULTS

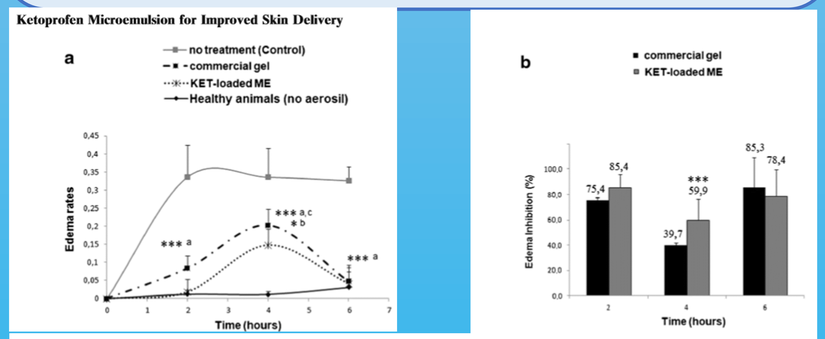


Fig. 2. Anti-inflammatory activity. Measurements of paw edema induced with Aerosil injection (a) and edema inhibition (%) after topical administration of Ketoprofen from commercial gel and microemulsion (b). The concentration of Ketoprofen applied was 7.1 and 2.8 mg/kg for the commercial gel and microemulsion, respectively. Statistical analyses were done using ANOVA followed by Tukey's Multiple Comparison Test; asterisks show a significant difference from group a, topical conventional Ketoprofen gel treatment group b, and healthy animals (c).*p < 0.05, **p < 0.01, and ***p < 0.001

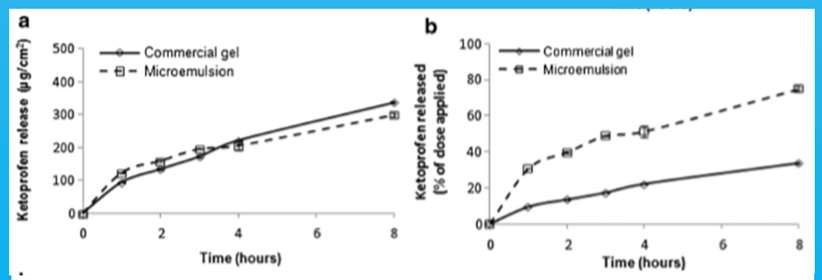


Fig. 1. In vitro release profiles of Ketoprofen from commercial gel or microemulsion. Amount of Ketoprofen released trough cellophane membrane (µg/cm2) and percentages (%) are showed in a and b, respectively

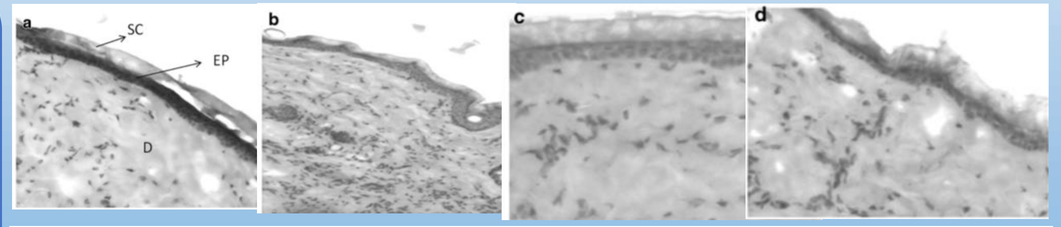


Fig. 3. Histological changes in edema paws 6 h after injection of Aerosil. Paws were harvested 6 h after injection of Aerosil and subjected to H&E staining of paw tissues. a Healthy animals (no Aerosil group). b No treatment (control group). c 2.8 mg/kg of KET from microemulsion. d 7.1 mg/kg of KET from commercial gel. Magnification ×200. SC stratum corneum, EP epidermis, D dermis

CONCLUSION

In this study, we have developed a topical microemulsion system for KET delivery to treat inflammatory conditions. The microemulsion formulation loaded with the drug displayed a very small particle size, with low polydispersity and negative zeta potential, all characteristics considered adequate for drug delivery. This microemulsion was compared to the commercial gel for in vitro release, and the percentage of KET released was advantageously higher for the microemulsion. The results of the anti-inflammatory study strongly indicate that KET-loaded ME has the ability to improve drug bioavailability, similarly to that of the marketed formulation in rats, even when less than 60% of the drug was used, confirming the therapeutic potential of the microemulsion formulation developed herein. Further studies, for instance, the evaluation of the ability of KET-loaded ME to suppress the production of myeloperoxidase enzyme (MOP) and cytokines (TNF-α) during the inflammatory process, could help elucidate the anti-inflammatory effect of the delivery system developed herein

ACKNOWLEDGEMENTS The authors thank Henrique Diniz and José Orestes del Ciampo for technical assistance during performance of the experiments.

COMPLIANCE WITH ETHICAL STANDARDS All the experimental procedures were done following the guidelines of the Institutional Animals Ethics Committee (IEAC) and the protocol of the animal study was approved by the Faculdades Integradas Padre Albino animal committee on care and handling animals (Authorization number 15.11.27-06).

REFERENCES

1. Leslie JC. Use of NSAIDs in treating patients with arthritis. Croff Ord Arthritis Res Therapy. 2013;15(3):S2. ; 2-Suraweera RK, Pasansi HGP, Sakeena MHF. Assessing the characterizations of Ketoprofen loaded and unloaded virgin coconut oil based creamy nanoemulsion. Asian J Pharm Clin Res. 2015;8(1):275–9.; 3-Noriaki N, Aya I, Shion T, Chiaki Y, Yoshimasa I. Pharmacokinetics and antiinflammatory effect of a novel gel system containing Ketoprofen solid nanoparticles. Biol Pharm Bull. 2015;38:1918–24. -4 Chourasia KM, Kang L, Chan SY. Nanosized ethosomes bearing ketoprofen for improved transdermal delivery. Results Pharma Sci. 2011;1:60–7. ; -5 Aichele CP. Characterizing water-in-oil emulsions with application to gas hydrate formation. 1st ed. Unites States: ProQuest LLC; 2009.; -6 Varshosaz J, Hajhashemi V, Soltanzadeh S. Lipid nanocapsulebased gels for enhancement of transdermal delivery of Ketorolac Tromethamine. J Drug Deliv. 2011;2011:571272.; -7 Francesca M, Maria LGR, Antonio MR, Paola M. Preparation and characterisation of liposomes encapsulating ketoprofen– cyclodextrin complexes for transdermal drug delivery. Int J Pharm. 2005;298(1):55–67;-8 Ritika A, Geeta A, Harikumar SL, Kirandeep K. Nanoemulsion based hydrogel for enhanced transdermal delivery of Ketoprofen. Adv Pharmaceutics. 2014;2014:468456.