

NANOSTRUCTURED LIPID CARRIERS ENHANCE TOPICAL ANTI-INFLAMMATORY EFFICACY OF FLURBIPROFEN: *IN VIVO* STUDIES

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INTRODUCTION

Flurbiprofen (FB) is a water insoluble NSAID drug. In order to improve its therapeutic efficiency, the development of novel delivery systems for topical instillation is a demand. Nanostructured lipid carriers (NLC) are a new generation of solid lipid carriers which possess a number of features advantageous for the topical route of application. They are well suited for use on damaged or inflamed skin because they are based on nonirritative and nontoxic lipids. The small particle size facilitates contact of encapsulated with the stratum corneum and ensures the occlusive effect due to film formation on the skin surface and can also enhance the penetration of drugs into the viable skin as we demonstrated in earlier investigations [1].

OBJECTIVE

The aim of the present study was to evaluate the topical anti-inflammatory efficacy of Flurbiprofen-loaded NLC in a mouse ear inflammation model induced by TPA (12-*O*-tetradecanoylphorbol 13-acetate).

METHODS

PRODUCTION METHOD

FB-loaded NLC were produced via high pressure homogenization (APV-2000 invensys, Denmark) [2], applying 3 cycles at 620 bars. Previously, the lipid mixtures with FB were subjected to a DSC analysis, in order to assess the melting point.

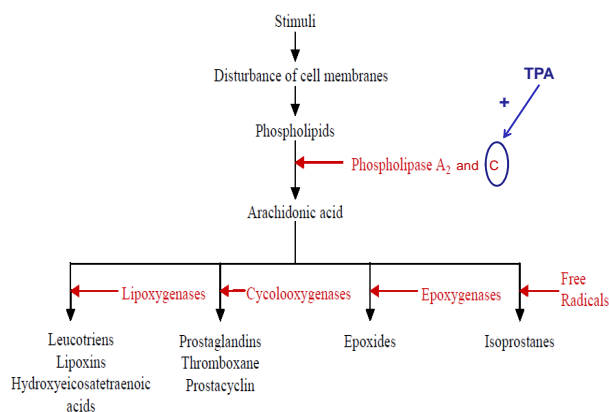
ANALYTICAL METHODS

Morphometrical properties and zeta potential (ZP) were measured using a Zetasizer nano ZS (Malvern Instruments, Malvern, UK). Differential scanning calorimetry (DSC) was performed on a Mettler DSC 823 e (Mettler Toledo, Spain). The FB concentration in the NLC was evaluated by reverse-phase high-performance liquid chromatography (RP-HPLC), after centrifugation / filtration.

IN VIVO STUDIES OF ANTI-INFLAMMATORY EFFICACY



Mouse ear edema was using groups of three male CD-1 mice. Edema was induced by topical application of 2.5 μ g per ear of TPA (12-*O*-tetradecanoylphorbol 13-acetate) dissolved in EtOH [3]. NLC formulations and the free FB (FB in PBS solution) as reference, were applied to both sides of the right ear (10 μ L each side) simultaneously with TPA. The ear swelling was measured before TPA application and 4 h after, and the edema was expressed as the increase in thickness.



RESULTS AND DISCUSSION

Composition of NLC formulations for topical administration of flurbiprofen (FB).

Sample	Composition (%)						
	Stearic acid	Compritol ATO 888	Miglyol 812	Castor oil	Flurbiprofen	Tween® 80	Water
FB-C888NLC	—	6.83	2.05	0.88	0.25	3.20	86.8
FB-SANLC	6.83	—	2.05	0.88	0.25	3.20	86.8

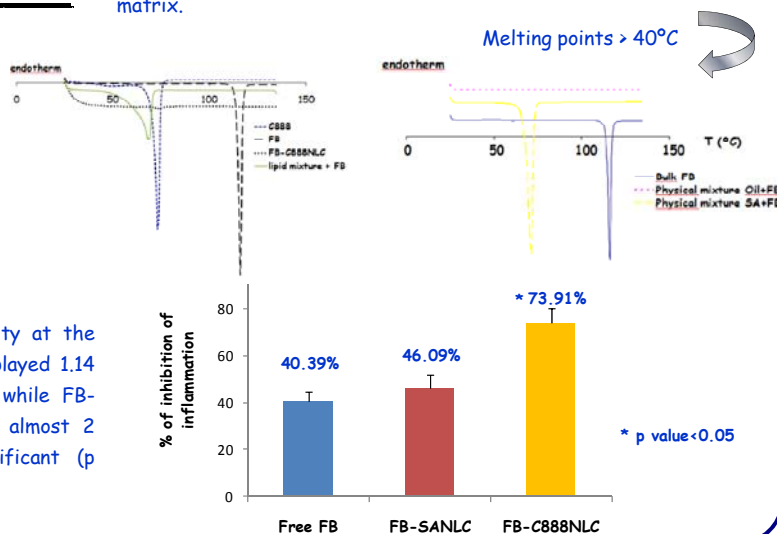
*FB-C888NLC, FB loading Compritol® ATO 888 (C888) based NLC
**FB-SANLC, FB loading stearic acid (SA) based NLC

The lipid mixtures with FB, as well as both kind of FB-NLC formulations were subjected to a DSC analysis in order to assess their melting points. These ones must be higher than 40°C, being the prerequisite to develop formulations for topical application. In addition, the melting event of FB (115°C) was not observed in the lipid mixtures. This result supports that FB is solubilized in the lipid matrix.

The physical properties were also evaluated.

PHYSICAL PROPERTIES	FB-C888NLC	FB-SANLC
Particle size (nm)	179.7 \pm 3.102	257.0 \pm 6.351
PI (polydispersity)	0.152 \pm 0.010	0.181 \pm 0.022
ZP (mV)	-23.0 \pm 0.569	-33.3 \pm 0.321
Entrapment Efficiency (%)	88.7 \pm 0.622	89.4 \pm 0.719

All the formulations showed *in vivo* anti-inflammatory activity at the concentration of 0.25% of FB. Nevertheless, FB-SANLC displayed 1.14 times higher anti-inflammatory activity than the free FB, while FB-C888NLC inhibited markedly the TPA-induced inflammation almost 2 times higher than the free FB, being statistically significant (p value < 0.05) according to the ANOVA test.



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