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PHOTOSTABILITY AND *EX-VIVO* PERMEATION STUDIES ON DICLOFENAC IN TOPICAL NIOSOMAL FORMULATIONS

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Abstract
Photostability studies were performed on topical formulations containing Diclofenac (DC). Niosomal gels were designed as photostabilization systems and ascorbic acid was also added to the new topical formulations because of its antioxidant property. Photodegradation tests were applied on commercial formulations containing DC and novel prepared gels, according to the ICH rules. The experiments were monitored by spectrophotometry and the data processed by multivariate curve resolution analysis to estimate the spectra and concentration profiles of evolved components. Characterization of niosomes was evaluated by size and distribution measurement, morphological analysis and encapsulation efficiency. Permeation experiments were performed across rabbit ear skin up to 24 h. Photodegradation rate of DC was found very fast in commercial formulation, with a residual content of 90% after only 4.38 min under a radiant exposure of 450 W/m^2. Photostability resulted increased significantly when the drug was entrapped in niosomal systems. The best results were obtained by reaching a 10% degradation after 50.00 min of light exposure after incorporation of DC in niosomes in presence of 5% ascorbic acid. Moreover, niosomal gel also influenced the permeation capability of DC by enhancing the transdermal delivery of the drug. The cumulative dose permeated of DC from niosomal gel was about three times that obtained with the commercial gel.

Keywords
Photodegradation studies; Photostabilization; Niosomal gel; Ascorbic Acid; MCR analysis; Percutaneous permeation study.

Chemical compounds studied in the article
Diclofenac sodium salt (PubChem CID: 5018304); Ascorbic Acid (PubChem CID: 54670067)

Abbreviations
DC, Diclofenac; AA, Ascorbic Acid; NSAID, non-steroidal anti-inflammatory drug; ICH, International Conference on Harmonization; MCR-ALS, Multivariate curve resolution-Alternating least squares; DLS, Dynamic Light Scattering; TEM, Transmission Electron Microscopy; MLVs, Multilamellar niosomal vesicles; CPP, Critical Packing Parameter; sc, *stratum corneum*.

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1. Introduction
Photosensitivity of many non-steroidal anti-inflammatory drugs (NSAIDs) is well known and several stability studies have been reported (Ioele et al., 2014; Jácome-Acatitla et al., 2014; Li, 2012; Mangesh Patil et al., 2013; Marotta et al., 2013; Ribeiro et al., 2013; Salgado et al., 2013; Szabó et al., 2011; Temussi et al., 2011; Zheng et al., 2011). In particular, the light sensitivity of Diclofenac (2-[(2,6-dichlorophenyl)amino] phenylacetate) (DC), has been proved in several works (Gaudiano et al., 2003; Hartmann et al., 2008; Hofmann et al., 2007; Zhang et al., 2011), detailing the formation of impurities as 1-(2,6-dichlorophenyl)indolin-2-one (Hájková et al., 2002) and other quinone derivatives (Salgado et al., 2013).
In a previous study (Ioele et al., 2014), we have defined the photodegradation profile of DC in solution and semi-solid commercial specialties and proposed photostabilization of the drug in gel formulations through addition of chemical UV-absorbers or incorporating the drug into cyclodextrins matrices. Liposomes have been also studied as light stabilizers of DC but limited to liquid formulations (Caddeo et al., 2013; Fujisawa et al., 2012; Jukanti et al., 2011; Manconi et al., 2009, 2011). Incorporation of DC in semisolid supramolecular systems for topical application is not yet reported.
The selection of a self-assembly entrapping matrix is often very difficult because the drug photostability is affected by the carrier stability itself, which in turn depends on the vesicle bilayer composition. Currently,