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In vitro release of diclofenac diethylamine from caprylocaproyl macrogolglycerides based microemulsions

Ljiljana Djordjevic*, Marija Primorac, Mirjana Stupar

Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, Vojvode Stepe 450, P.O. Box 146, 11221 Belgrade, Serbia and Montenegro

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Abstract

The purpose of the present study was to determine the influence of both formulation parameters and vehicle structure on in vitro release rate of amphiphilic drug diclofenac diethylamine (DDA) from microemulsion vehicles containing PEG-8 caprylic/capric glycerides (surfactant), polyglyceryl-6 dioleate (cosurfactant), isopropyl myristate and water. From the constructed pseudo-ternary phase diagram at surfactant–cosurfactant mass ratio (K_m 1:1), the optimum oil-to-surfactant–cosurfactant mass ratio values (O/SC 0.67–1.64) for formulation of microemulsions with similar concentrations of hydrophilic, lipophilic and amphiphilic phases (balanced microemulsions) were found. The results of characterization experiments indicated bicontinuous or nonspherical water-continuous internal structure of the selected microemulsion vehicles. Low water/isopropyl myristate apparent partition coefficient for DDA as well as elevated electrical conductivity and apparent viscosity values for the investigated microemulsion formulations containing 1.16% (w/w) of DDA, suggested that the drug molecules was predominantly partitioned in the water phase and most likely selfaggregate and interact with interfacial film. Release of DDA from the selected water-continuous (W/O), oil-continuous (O/W) and balanced microemulsions was investigated using rotating paddle dissolution apparatus modified by addition of enhancer cell. A linear diffusion of DDA through regenerated cellulose membrane was observed for the W/O and O/W formulations with the low content of dispersed phase. Non-linearity of the drug release profile in the case of bicontinuous formulations was related to the more complex distribution of DDA including interactions between the drug and vehicle. The membrane flux value increases from 25.02 $\mu g\,cm^{-2}\,h^{-1}$ (W/O microemulsion) to 117.94 $\mu g\,cm^{-2}\,h^{-1}$ (O/W microemulsion) as the water phase concentration increases. Moreover, the obtained flux values for balanced microemulsions (29.38–63.70 $\mu g\,cm^{-2}\,h^{-1}$) suggested that bicontinuous microstructure hampers the release of the amphiphilic drug.

Keywords: Microemulsion; Caprylocaproyl macrogolglycerides; Release rate; Diclofenac diethylamine

* Corresponding author. Tel.: +381 11 397 0379; fax: +381 11 397 2840.
E-mail address: girasole@ptt.yu (L. Djordjevic).

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1. Introduction

During the recent decades various colloidal systems have been investigated as suitable pharmaceutical vehicles for successful dermal and transdermal delivery of active substance. Microemulsion systems, owing to their thermodynamic stability, ease of preparation, transparency, low viscosity, and considerable potential for solubilising variety of drugs, often have been the object of investigations in relation to drug delivery (Kumar and Mital, 1999). The results of numerous studies (Bonina et al., 1995; Schmalfuß et al., 1997; Delgado-Charro et al., 1997; Trotta et al., 1997; Bolzinger et al., 1998; Kreilgaard et al., 2000, 2001; Baroli et al., 2000; Lehmann et al., 2001; Spiclin et al., 2003) have suggested that microemulsion vehicles have a significant potential to increase penetration of hydrophilic, lipophilic, and amphiphilic substances into and through the skin compared to conventional vehicles. Depending on physico-chemical properties of components, microemulsion internal structure (usually water in oil (W/O), oil in water (O/W) or bicontinuous), and interactions between drug and vehicle, these microemulsions display a rich behaviour regarding the release of solubilized material (Kumar and Mital, 1999). Also, the results of several transdermal drug delivery studies have suggested that microemulsions with similar amount of water, oil and tensides (so called balanced microemulsions) have the most favourable properties as skin penetration enhancers (Delgado-Charro et al., 1997; Bolzinger et al., 1998). Anyhow, still there are no general conclusions about correlation between composition, structure and drug delivery potential of the system. The addition of active substance in the pharmaceutical microemulsions may affect significantly the stability and structure of the system (Kumar and Mital, 1999). Also, the incorporated drug participates in the microstructure of the system and may influenced it, especially if the drug posesses amphiphilic and/or mesogenic properties and such interactions may strongly influence drug release (Müeller-Goymann et al., 1995; Kriwet and Müeller-Goymann, 1995). Diclofenac diethylamine (DDA) (Fig. 1) is a nonsteroidal anti-inflammatory drug which have been used for dermal application more often than other diclofenac salts, due to its amphiphilic nature. It has been observed that DDA molecules form micelles and lyotropic liquid crystals in water (Kriwet and Müeller-Goymann, 1993). Furthermore, the interactions of this drug with phospholipids have been reported (Engehausen and Müeller-Goymann, 1992), and the fluidizing effect of DDA on the human stratum corneum lipids has been detected (Kriwet and Müeller-Goymann, 1995). The main goal of the present paper was to investigate both the influence of DDA on physico-chemical properties of a microemulsion vehicle and the correlation between structure and composition of the vehicle and in vitro drug release.

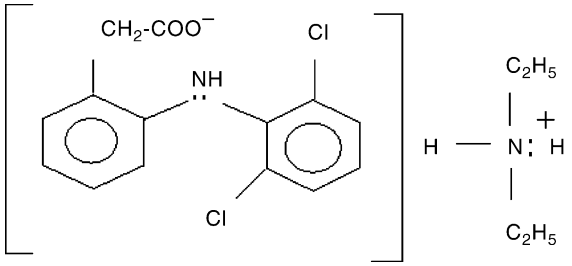

Fig. 1. Structural formula of diclofenac diethylamine.

The important disadvantage of the microemulsion vehicles is that the microemulsion state usually forms within specific concentration ranges of components and often requires a high content of surfactants inducing significant alterations to the skin barrier function (Kumar and Mital, 1999; Lawrence and Rees, 2000). Good biological acceptance of non-ionic surfactants (Kibbe, 2000) as well as ability to form microemulsions that are insensitive to pH and electrolyte concentration are the main motives for their extensive use (Kumar and Mital, 1999; Lawrence and Rees, 2000). There have been several studies involving microemulsion drug delivery vehicles for topical application based on low-irritant caprylocaproyl macrogolglycerides as surfactant, and polyglycerol fatty acid esters as cosurfactant (Gašperlin and Špiclin, 2001; Delgado-Charro et al., 1997; Kreilgaard et al., 2001; Djordjevic et al., 2004). However, there were no attempts to establish a surfactant–cosurfactant mass ratio (K_m) that is adequate for formulation of microemulsions containing relatively high and similar percentages of both water and oil phases. Thus, the second goal of this study was to optimise the mass ratios between the surfactant (PEG-8 caprylic/capric glycerides), cosurfactant (polyglyceryl-6 dioleate) and oil (isopropyl myristate) in order to formulate balanced microemulsions.