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In-vitro release of diclofenac diethylammonium from lipid-based formulations

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Abstract

This article presents the preparation and topical performance of some new lipid-based formulations of diclofenac, namely (a) a diclofenac aqueous gel containing mixed micelles (sodium cholate:egg lecithin molar ratio 0.55); (b) diclofenac lotion that contains soya lecithin, ethanol and buffer; and (c) diclofenac lipogel containing egg lecithin, isopropyl myristate, propylene glycol and ethanol. Gel formulations were prepared using Carbomer 934. Release of diclofenac from all formulations was monitored via dialysis through Spectra/por membrane into phosphate buffer (0.2 M pH = 7.4) using a Franz cell. Drug release profile and diffusion coefficients were compared with brand formulation (Geigy's Vlotaren Emulgel). Statistical analysis of data show that the diffusion coefficient of the drug from these formulations rank according to the following order: Diclofenac lotion ($D = 5.308 \times 10^{-7}$ cm^2/s) > lipogel ($D = 2.102 \times 10^{-7}$ cm^2/s) > Voltaren Emulgel (1.518×10^{-7} cm^2/s) > aqueous gel mixed micelle (0.966×10^{-7} cm^2/s). These results show that diclofenac lotion and lipogel maybe more suitable formulations than the conventional topical dosage form. © 2002 Published by Elsevier Science B.V.

Keywords: Diclofenac; Topical; Lecithin; Release rate; Diffusion coefficient; Lipogel; Lipid-based

1. Introduction

Topical administration of therapeutic agents offer many advantages for oral and intravenous administrations (Guy and Hadgraft, 1985). One of the major disadvantages in percutaneous drug delivery is its low normal drug penetration rate through the skin. Several techniques have been explored to increase the penetration of drugs, including the use of enhancers, such as surfactants/solvents (Ho et al., 1994; Lopez et al., 2000), azone (Watton et al., 1985), essential oils and terpens (Vinod et al., 1993; Nagai and Takayama, 1993), lipids (Nishihata et al., 1987; Yokomiza, 1996a,b; Kirjavainen et al., 1999a), various forms of lipid vesicles such as liposomes, niosomes (Touitou et al., 1994; Vyas et al., 1995; Woyczikowski et al., 1996) and ethasomes (Touitou et al., 1994, 2000; Dayan and Touitou, 2000) and transfersomes (Cevc, 1996). In most lipid formulations, the active substance is incorporated into

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lipid aggregates or applied together with a lipid suspension in a hydrogel or more frequently, in an oil-in-water emulsion (Cevc and Blume, 1992).

Diclofenac, a phenyl acetic acid derivative, is a potent member of the non-steroidal anti-inflammatory drugs (NSAIDs), which, due to its gastrointestinal disturbances, is topically administrated in the form of a 1.16% gel (Reynolds, 1996). In recent years, there have been many in-vitro reports on lipid-based NSAIDs formulations, such as aqueous gel forms of diclofenac (Nishihata et al., 1987), indometacin gel ointment containing lipids (Natsuki and Takabatake, 1987) niosomal diclofenac (Raja-Naresh et al., 1993) and pluronic lecithin organo-gel (plo) of diclofenac (Burnham et al., 1998; Grace et al., 1999). The latter provides an affective short-term reduction in elbow pain and wrist extensor weakness associated with chronic lateral epieondylitis.

We hereby describe three new lipid-based diclofenac formulations and compare their in-vitro performance with that of a brand formulation (Voltaren Emulgel®).

2. Materials and methods

2.1. Equipment

Instruments used were ultraviolet spectrophotometer 160 A (Shimadzu, Tokyo, Japan), Franz diffusion cell (locally made) and Vortex mixer (Heidolph, Germany).

2.2. Materials

All chemicals used were of either analytical or pharmaceutical grade. Soya lecithin (LipoidS75 containing: phosphatidylcholine 70.3%, phosphatidylethanolamine 9.5%, lysophosphatidylcholine 2.5%; Lipoid GmbH, Ludwigshafen, Switzerland), diclofenac diethylammonium (Unique Chemicals), egg lecithin, sodium cholate, propylene glycol, isopropyl myristate, absolute ethanol, potassium dihydrogen phosphate (all from Merck Darmstadt, Germany). Carbomer 934, regenerated cellulose acetate membrane, molecular weight cut-off 1000 (Spectra/por®-Spectrum Labs. Inc., Rancho Domingues, CA).

2.3. Methods

2.3.1. Sample preparation

Gel samples—in all formulations described below, the concentration of diclofenac diethylammonium was 1.16%.

(a) A 1.16% lipogel diclofenac: egg lecithin was dissolved in a mixture of isopropyl myristate and propylene glycol (2.5:20 v/w) to which 34% v/w of an ethanolic solution of diclofenac was added. The isotropic solution obtained was mixed with an equal weight of 2% Carbomer 934 gel by tituration. The final concentration of egg lecithin was 0.25%.

(b) An aqueous gel containing mixed micelles was prepared as follows: sodium cholate and lecithin (molar ratio 0.55, total lipid concentration 100 mg/ml) were dissolved in methanol:chloroform (1:1 v/v) and dried in a rotary evaporator and stored under vacuum for 3 days to reach a constant weight. The dried film was then reconstituted with purified water, the resultant suspension was flushed with N_2, sealed and allowed to equilibrate for 2 days at room temperature to obtain a mixed micellar solution (Alkan-onyuksel and Son, 1992). Diclofenac was then added to this solution and left to equilibrate. The time required to reach the new micellar equilibrium state was 24 h, as evidenced by its isotropy and the absence of precipitation upon centrifugation. The isotropic solution was then incorporated into an equal weight of 2% Carbomer 934 by tituration.

(c) A diclofenac lotion containing soya lecithin: diclofenac was dissolved in warm absolute ethanol and soya lecithin was then dissolved in the mixture thus obtained. Sufficient quantity of 0.2 M phosphate buffer pH = 7.4, was then added dropwise (while stirring vigorously) to reach a final concentration of 1% soya lecithin and 34% ethanol.

2.3.2. In-vitro release studies

Our essential goal was to compare the in-vitro release profiles of our formulations with that of a known commercial product using an inert membrane that is commonly used for such purposes.

These membranes usually have a porous substructure made of a mixed hydrophobic/hydrophilic matrix and are thus considered simple models of the human skin. Although the permeabilities of such membranes against drugs are, in absolute terms, higher than the human skin, the data obtained are nonetheless instructive as they merely reflect the relative permeability of the various formulations.

Pieces of synthetic membrane (Spectra/por) were soaked in 0.2 M potassium dihydrogen phosphate buffer pH = 7.4, for 24 h before mounting in a Franz-type diffusion cell, (receiving side: 50 ml degassed 0.2 M phosphate buffer, effective diffusional area 12.56 cm^2). About 4 g of sample was placed on the donor side, fully covering the membrane. The whole assembly was placed in a water bath, maintained at 32 ± 1 °C and continuously well stirred. Care was exercised to remove any air bubble from the under side of the membrane and the receiving solution.

At specified time intervals (15, 30, 45, 60, 90, 150, 180 min) 2 ml samples were removed from the receiver compartment, i.e. partial sampling and refilled with an equal volume fresh buffer (Shah, 1999). All samples were analyzed for diclofenac content spectrophotometrically using a wavelength of 276 nm.

2.3.3. Statistical analysis

Nonparametric tests of comparisons amongst different formulation were performed using Kruskal–Wallis and Mann–Whitney test. The former was used to test the significant effect of formulation on the diffusion coefficient and the latter allowed the pair-wise comparison of any two formulations. The significant level was set at $a = 0.05$.

3. Results and discussion

The drug release profiles of diclofenac across the Spectra/por membrane from the three lipid-based formulations as well as brand formulation (Voltaren Emulgel) and their corresponding diffusion coefficients were calculated via Higuchi's procedure (Higuchi, 1967) Figs. 1 and 2. Each data point represents the statistical average of independent determinations. Different formulation significantly affected the diffusion coefficient (Kruskal–Wallis test, $H = 16.89$, $P = 0.001$). Based on the paired comparison of formulations using Mann–Whitney tests, the following ranking of diffusion coefficients is concluded: Diclofenac lotion > Lipogel > Voltaren Emulgel > Mixed micelle gel. The results show that diclofenac lotion

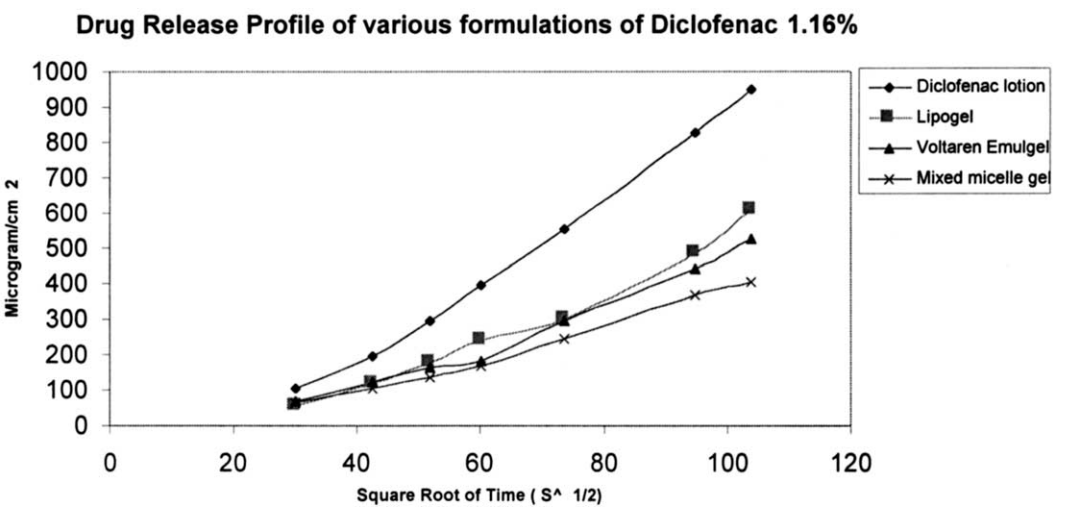

Fig. 1. Drug release profiles of various formulations of Diclofenac 1.16% and brand sample according to the Higuchi equation. Each point represents the mean of five independent experiments, $P < 0.05$.

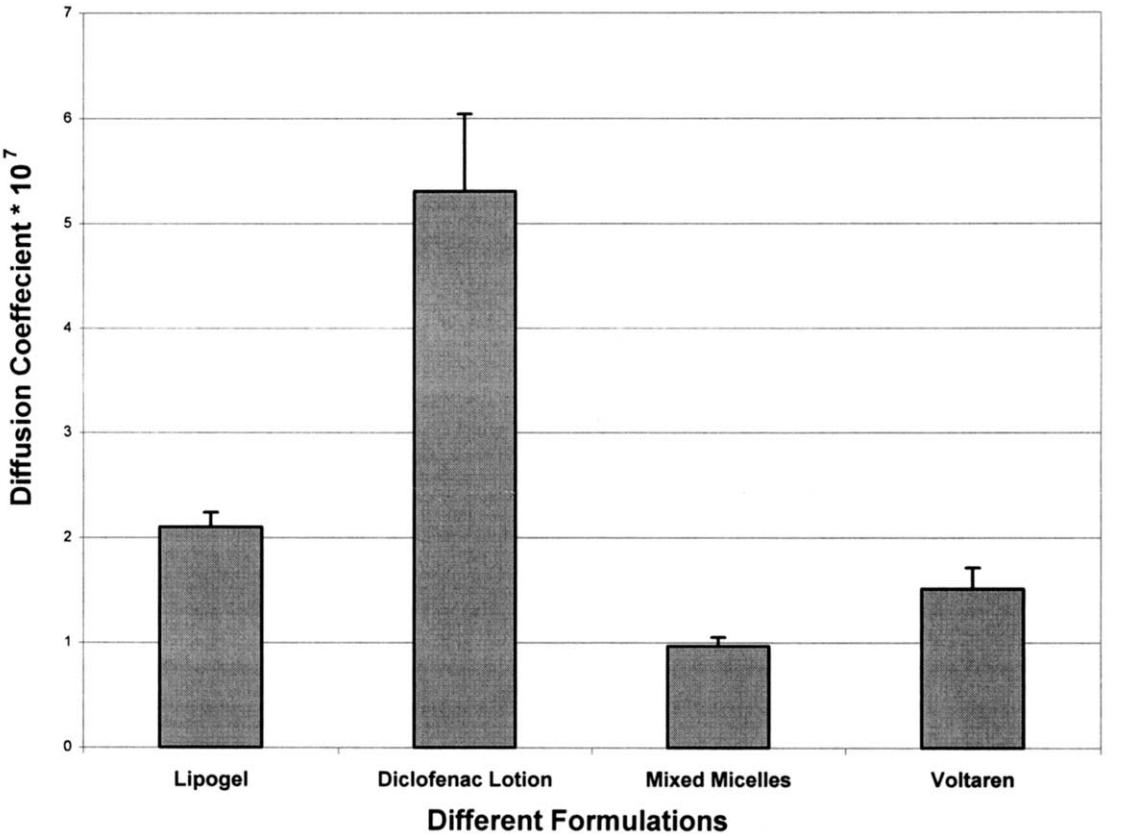

Fig. 2. Comparing the diffusion coefficient of various formulations of diclofenac, $n = 5$ independent experiments ($P < 0.05$).

(probably ethasomal form) shows the highest value of drug diffusion coefficient ($D = 5.308 \times 10^{-7}$ cm^2/s) $P < 0.05$. Thus, it is likely that the formulation is similar to ethasomes recently introduced for delivery of trihexylphenidyl to the skin (Touitou et al., 1994, 2000). Diclofenac lotion may contain small vesicles that withstand high concentrations of ethanol (34% v/v) (Kirjavainen et al., 1999b). The drug diffusion coefficient corresponding to the aqueous gel containing mixed micelles ($D = 0.966 \times 10^{-7}$ cm^2/s) is the lowest compared to brand formulation (Voltaren Emulgel®) and other formulations studied here ($P < 0.05$), This may be due to a decrease in the availability of free drug as a result of micellar complexation, i.e. the tendency of the drug to leave the vehicle is strongly dependent on its microstructure. The mixed micellar solution is yellowish, clear and isotropic and upon tituration with carbopole, produce clear yellowish gel. The drug diffusion coefficient corresponding to that of lipogel formulation ($D = 2.102 \times 10^{-7}$ cm^2/s) is superior to the brand formulation, Voltaren Emulgel ($D = 1.518 \times 10^{-7}$ cm^2/s) and all other formulations. The drug diffusion coefficient corresponding to the lipogel formulation ($D = 2.102 \times 10^{-7}$ cm^2/s) is superior to that of Voltaren Emulgel ($D = 1.518 \times 10^{-7}$ cm^2/s).

In the case of lipogel formulation, propylene glycol and ethanol were added as cosolvents to selectively increase the solubility of diclofenac in the aqueous media (rather than in micellar portion of the gel). Ethanol, along with lecithin, act as a permeability enhancer (Nishihata et al., 1987; Ho et al., 1994; Kirjavainen et al., 1999a). Isopropyl myristate which comprise the oil phase also

acts as an enhancer (Arellano et al., 1999). Another effect of adding lecithin into the lipogel formulation is to improve the emulsifying power of the medium, thereby enhancing the drug release profile.

4. Conclusions

The results presented clearly show that diclofenac lotion and lipogel have superior release rates and diffusion coefficients. In contrast, the lowest release rate is found for the mixed micellar aqueous gel that may be attributed to its lower free drug concentration as a consequence of its interaction with the excipient molecules.

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