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Stability of topical erythromycin formulations

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Summary

The stability of erythromycin, suspended in a w/o and an o/w emulsion or dissolved in an alcoholic solution and gel, was tested over a 12 week period. The influence of pH and storage temperature was evaluated. A shift in pH from 6.3 to 8.5 as well as an increase in storage temperature from 4°C to 25°C seemed to decrease the stability of erythromycin. The activity of erythromycin in emulsions with an aqueous phase of pH 8.5 had only 40% of the original activity after 1 month storage at 25°C. The alcoholic solution and gel retained more than 90% of their initial activity after 1 month storage at 25°C.

Introduction

Erythromycin is used as a topical (Hellgren and Vincent 1980, 1983; Lesher et al., 1985; Broniarczyk-Dyla and Arkuszewska 1989) and systemic (Wansker, 1961; Akers et al., 1975) agent against acne vulgaris and neonatal conjunctivitis (Bialer et al., 1987). No stability problems were reported when using fatty base ointments (Bialer et al., 1987). Stability problems of erythromycin salts were reported when used in intravenous admixture programs (Bergstrom and Fites, 1975; Pluta and Morgan 1986) and the pH seemed critical for the stability of erythromycin or its salts. Studies in vitro showed a decreasing activity when the pH was lower than 8 (Heilman and Herrell, 1952), so prescriptions often adjust the pH of the aqueous phase of semi-solid preparations to 8.5.

In this study the stability of six formulations was tested: an o/w emulsion, a w/o emulsion (both emulsions with and without a pH correction), an alcoholic solution and an alcoholic gel. The influence of storage temperature on the stability of erythromycin in the six formulations was studied.

Materials and Methods

The composition of the o/w base was as follows: cetyl alcohol, 15%; white beeswax, 1%; propylene glycol, 10%; sodium lauryl sulfate, 2%; methyl *p*-hydroxybenzoate, 0.08%, propyl *p*-hydroxybenzoate, 0.02%; deionized water, 72%. Another cream was prepared using the same formula as mentioned previously but the pH was adjusted from 6.3 to 8.5 by adding sodium hydrox-

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ide. The composition of the w/o emulsion was as follows: white beeswax, 8%; spermaceti, 10%; cetiol V, 60%; sorbitan monooleate, 2%; methyl *p*-hydroxybenzoate, 0.08%; propyl *p*-hydroxybenzoate, 0.02%; deionized water, 20%. As in the case of the first o/w emulsion, the pH of the aqueous phase was left unchanged. Another w/o cream was made with deionized water containing the same concentration of sodium hydroxide as in the o/w base. As water was the internal phase, the pH of the emulsion obtained could not be checked. 1.5% erythromycin (Certa, Brussels, Belgium) was suspended in all vehicles.

An alcoholic solution, containing ethanol, propylene glycol, deionized water (40 : 20 : 40; v/v) and 1.5% erythromycin, was prepared. The erythromycin was dissolved in the ethanol prior to mixing. An alcoholic gel was prepared by adding 2% of a hydroxyethylcellulose derivative (Idroramnosan®, Arion, Brussels, Belgium) to the alcoholic mixture mentioned above.

The four emulsions were stored in aluminum ointment tubes (Chimexport, Antwerp, Belgium) at 4° and 25 °C. The alcoholic solution and gel were stored at 25 °C in a room with continuous artificial daylight of moderate intensity and were packed in a dark brown glass bottle and an aluminum ointment tube, respectively.

A microbiological method, modified from the method described in the British Pharmacopoeia (1988), using an agar-well diffusion technique, was used to assay the erythromycin concentrations. Methanolic standard stock solutions were prepared from a powder of known potency (950

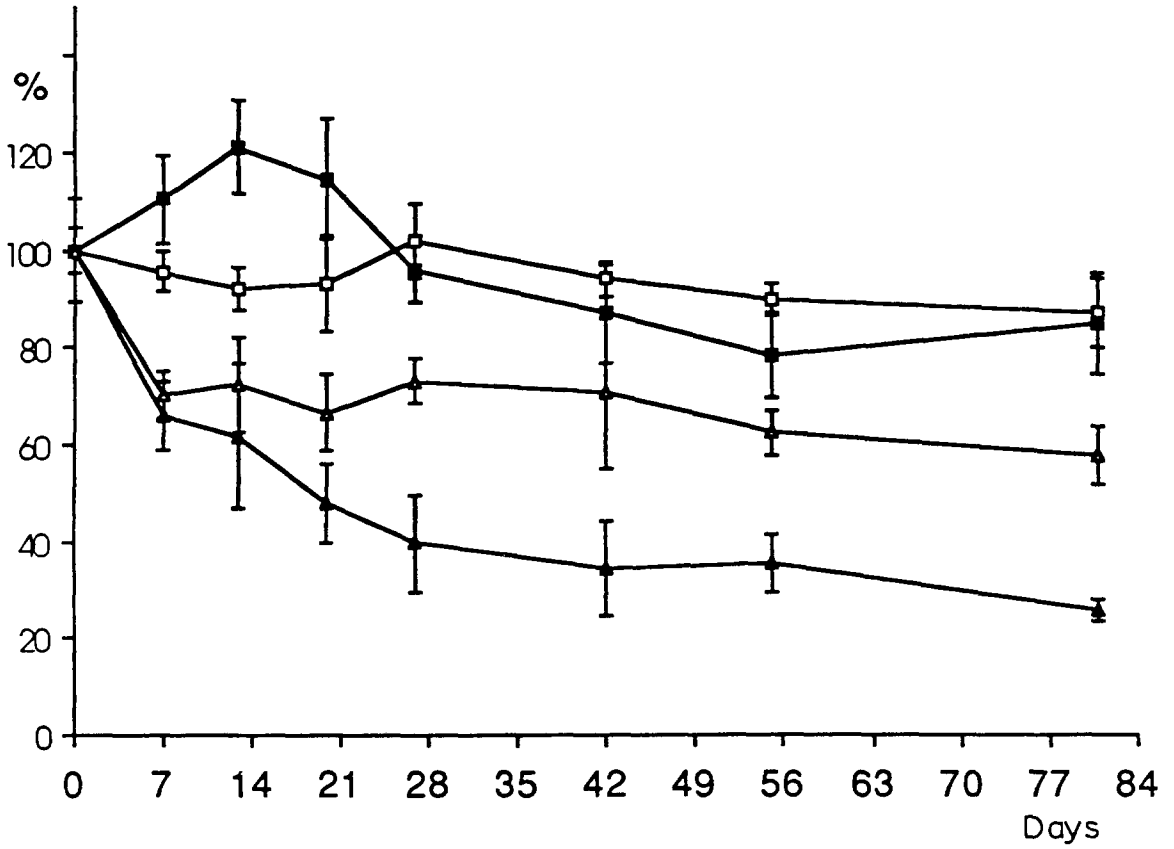

Fig. 1. Stability of erythromycin in o/w emulsions. Mean percentage of the initial activity (± SD on the measurements; $n = 12$) as a function of time, of erythromycin in o/w emulsions stored at 25 °C (△———△) and 4 °C (□———□) and with adjustment of the pH to 8.5, stored at 25 °C (▲———▲) and 4 °C (■———■).

IU/mg, WHO International Standard) and stored in liquid nitrogen. Four working standards were prepared daily in a phosphate buffer pH 8.0 (0.7 g KH_2PO_4, 12.2 g $K_2HPO_4 \cdot 2H_2O$, water to 1 l). The susceptible organism used was Micrococcus luteus (ATCC 9341, American Type Culture Collection, Rockville, MD, U.S.A.). 30 ml of antibiotic medium no. 11 (Difco no. 593, Difco, Detroit, MI, U.S.A.), were poured into standard plastic disposable petri dishes (9 cm in diameter). Wells, 6 mm in diameter, were punched in the seeded agar. Four wells were filled with 80 μl of the standard solution and two wells with the unknown solution, obtained by dissolving the sample in methanol and diluting the methanolic solution in a phosphate buffer. After growth at 25 °C for 2 days, zone sizes were measured to an accuracy of 0.001 mm with a Mitutoyo optical comparator (Mitutoyo Ltd., Tokyo, Japan). Six petri dishes were used for each unknown sample and the results were calculated by the method of least squares with the use of the individual calibrations curves.

Results and Discussion

As Fig. 1 indicates, the activity of erythromycin decreased to 70% of the original activity within the first week when the o/w emulsion was stored at 25 °C. The o/w emulsion stored at 4 °C retained more than 90% of the original activity during the first month. A faster decrease in activity was noted for the o/w emulsion with a pH adjusted to 8.5 and stored at 25 °C in comparison to the original

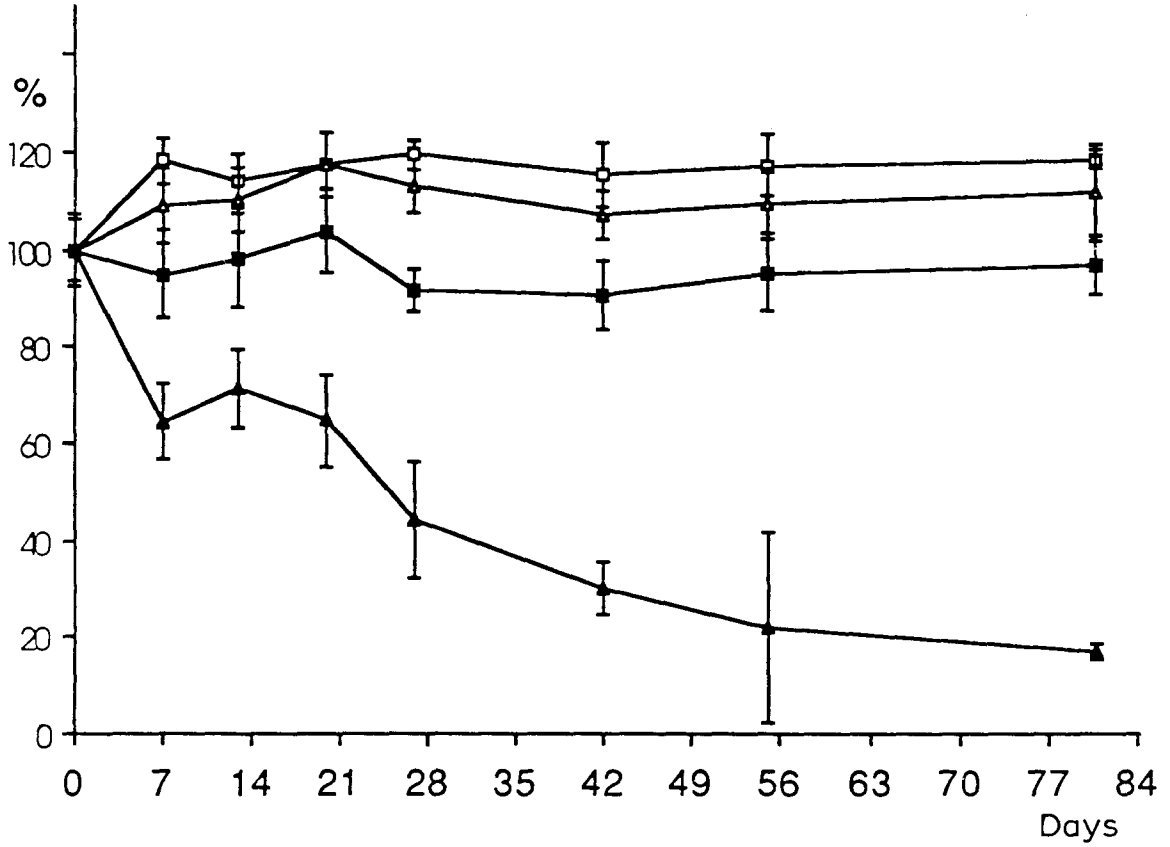

Fig. 2. Stability of erythromycin in w/o emulsions. Mean percentage of the initial activity (± SD on the measurements; $n = 12$) as a function of time, of erythromycin in w/o emulsions stored at 25 °C (△——△) and 4 °C (□——□) and with adjustment of the pH to 8.5, stored at 25 °C (▲——▲) and 4 °C (■——■).

o/w emulsion. After 1 and 2 months the activity of the emulsion with a pH adjusted to 8.5, stored at 25 °C decreased to about 40 and 30% of the original activity, respectively.

As Fig. 2 indicates, the activity of the w/o emulsions retained more than 90% of the original activity during the 12 week test period except for the emulsion adjusted to pH 8.5, stored at 25 °C. This emulsion lost about 35% of the original activity after 1 week and more than 65% after 2 months.

The activity of the alcoholic solution and the gel decreased to 90% during the first 3 weeks (Fig. 3). More than 80% of the activity remained 2 months after preparation, when stored at 25 °C.

This study showed the influence of the choice of vehicule and pH on the stability of topical preparations containing erythromycin. In conclusion, although erythromycin is more active at an alkaline pH (Heilman and Herrell, 1952), the pH adjustment to 8.5 has a deleterious influence on the stability of the active compound. The confusion concerning the stability of erythromycin in ointments might have its origin in the data published by Sheinaus and Lee (1955) where the authors stated that erythromycin in an o/w emulsion was most stable at a pH of 8.6. It should be emphasized that this former study did not include controls for the microbiological dosage of erythromycin while the absence of a calibration curve made the interpretation of the results doubtful.

All tested emulsions, stored at 4 °C, the w/o emulsion without pH adjustment, the alcoholic

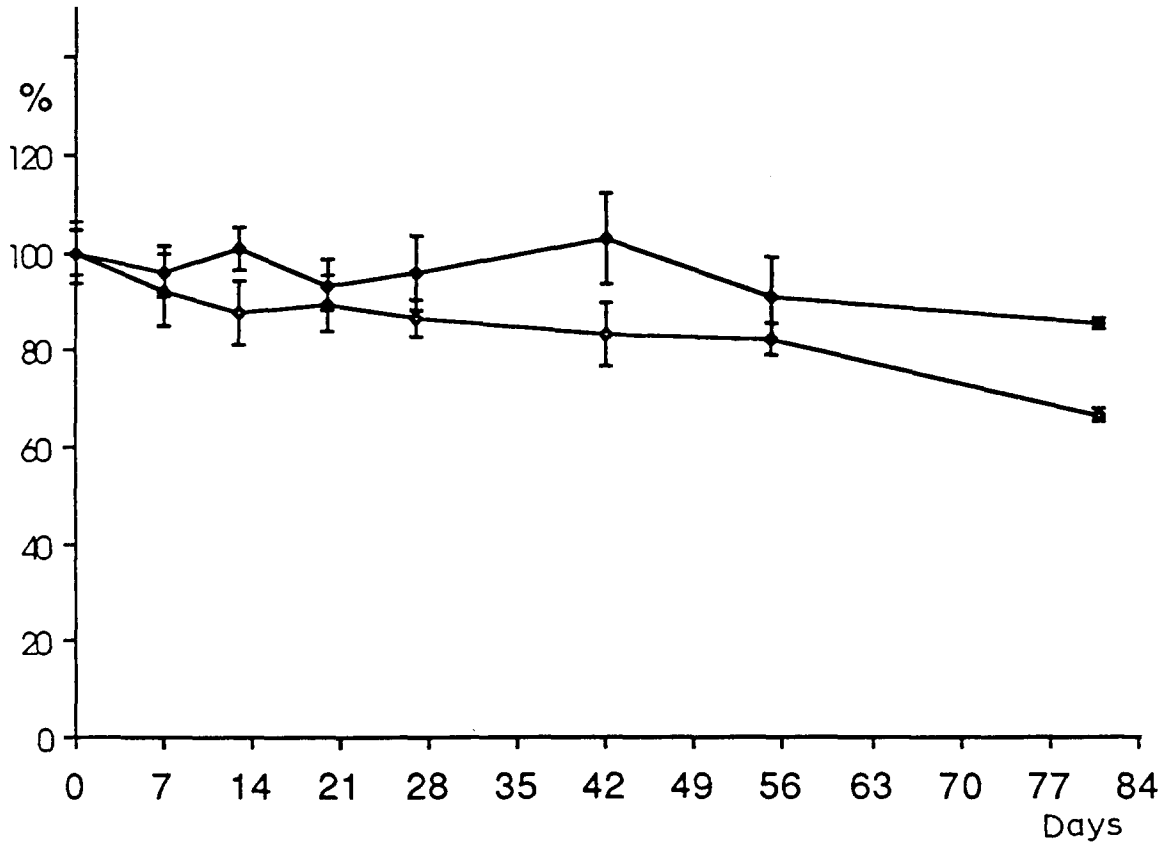

Fig. 3. Stability of erythromycin in solution or gel. Mean percentage of the initial activity (±SD on the measurements; $n = 12$) as a function of time, of an erythromycin alcoholic solution (◇——◇) and gel (◆——◆) stored at 25 °C.

solution and the gel, stored at 25 °C, showed an acceptable stability (> 90% activity) during 1 month after preparation.

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