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Short communication

The formulation and stability of erythromycin–benzoyl peroxide in a topical gel

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Abstract

The combination of benzoyl peroxide and erythromycin is used for the local treatment of acne and available as a commercial preparation. Because of the stability problems of erythromycin an extempore preparation is required. The influence of storage temperature and non active ingredients on the stability of benzoyl peroxide and erythromycin in topical gel preparations for extempore compounding is described. A microbiological and an HPLC method were used to determine the erythromycin and the benzoyl peroxide concentrations, respectively. For a formulation compounded with hydroxyethylcellulose no stability problems were observed. For the formulation containing Carbopol 940®, the levels of erythromycin varied over a wide range due to precipitation and aggregation of the drug during compounding.

Keywords: Benzoyl peroxide; Erythromycin; Gel; Formulation

1. Introduction

The combination of benzoyl peroxide and erythromycin is used for the local treatment of acne vulgaris. This combination shows less side effects as rash, erythema and irritation. It has a synergistic effect and diminishes the chance of resistance of Proprionibacterium acnes, an anaerobic bacterium and one of the factors responsible for the pathogenesis of acne vulgaris (Chalker et al., 1983; Harkaway et al., 1992; Eady et al., 1994).

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Because of the stability problems of erythromycin an extempore preparation is required. It is commercially available as a benzoyl peroxide gel with a separate vial containing erythromycin and ethanol.

Because of economical reasons and the flocky, unhomogeneous aspect of the commercial gel, dermatologists frequently prescribe a formulation containing benzoyl peroxide and erythromycin to be prepared extempore by the pharmacists.

This paper describes the influence of ingredients choice on the physical aspect of the extempore preparation and on the stability of benzoyl peroxide and erythromycin in a hydrophilic topical gel preparation.

2. Materials and methods

2.1. Materials

Benzamycin® (Dermik Laboratories, batch 96 I 20, Chicago IL, USA), the commercially available preparation containing erythromycin (3%) and benzoyl peroxide (5%), was purchased.

For the magistral formulation benzoyl peroxide 75% (Ludeco, batch 3147 E, Brussels, Belgium) and erythromycin (Ludeco, batch 1465, Brussels, Belgium) were used. The other ingredients in the formulation were polyacrylic acid (Carbopol 940®, Alpha-Pharma, Zwevegem, Belgium), hydroxyethylcellulose (Idroramnosan®, Federa, Brussels, Belgium), propyleneglycol (Fraver, Kontich, Belgium), disodium EDTA (Flandria, Gent, Belgium), sodium hydroxide (Acros, Geel, Belgium), ethanol absolute extra pure (Merck, Darmstadt, Germany), methylparahydroxybenzoate (Alpha-Pharma, Zwevegem, Belgium) and propylparahydroxybenzoate (Federa, Brussels, Belgium). Acetonitrile (Merck, Darmstadt, Germany), dichloromethane (Sigma–Aldrich, Steinheim, Germany), methanol (Panreac, Barcelona, Spain) and ethanol (Panreac) were of analytical grade.

3. Methods

3.1. Extempore preparation of the Benzamycin® gel

The Benzamycin® gel was handled as prescribed in the leaflet. Erythromycin was dissolved in the separate bottle containing ethanol. Next the solution was mixed with the Carbopol® gel, containing the benzoyl peroxide by using a plastic spatula provided within the packaging.

3.2. Preparation of the compounded formulations

A quantity of 50 g Carbopol® gel was prepared separately and contained the following excipients: Carbopol 940® 1 g, propyleneglycol 7.5 g, disodium EDTA 25 mg, sodium hydroxide solution (1 N) for pH adjustment to a value of 7 and water for preservation. Water for preservation was made by 1% (g/g) dilution in distilled water of a propyleneglycol solution containing 8% (g/g) methyl- and 2% (g/g) propylparahydroxybenzoate. Erythromycin (1.5 g) was dissolved in 4.4 g ethanol 90° (prepared by dilution of absolute ethanol extra pure in distilled water). Next the ethanolic erythromycin solution was mixed with the Carbopol® gel. Finally, the benzoyl peroxide was incorporated in 1/4 of the erythromycin–Carbopol® gel mixture, brought through an ointment mill and mixed with the remaining part of the erythromycin–Carbopol® gel mixture. A formulation based on Carbopol 940® and containing a four times higher ethanol 90° concentration (17.7 g) was also prepared. An amount of 50 g gel based on hydroxyethylcellulose was also made by dispersion of 1 g hydroxyethylcellulose in 17.7 g water for preservation. Erythromycin (1.5 g) was dissolved in 17.7 g ethanol 90° and then 8.8 g propyleneglycol was added. The amount of ethanol 90° used in this formulation was four times higher than for the first Carbopol® gel formulation. Next the erythromycin–propyleneglycol–ethanol 90° solution was incorporated in the hydroxyethylcellulose gel. Finally the ben-

zoyl peroxide was added to 1/4 of the mixture and brought through an ointment mill and next mixed with the remaining part of the gel.

3.3. Microbiological determination of the erythromycin levels

A microbiological method, modified from the method described in the British Pharmacopoeia (1988), was used to assay the erythromycin within the different formulations (Arret et al., 1971). Standard erythromycin solutions were prepared by dissolving a known concentration of erythromycin in ethanol 90° and then dilute it to 50 ml in a phosphate buffer pH 8 (0.523g KH_2PO_4 and 16.73 g K_2HPO_4, distilled water to 1 l) (Vandenbossche et al., 1991). Working solutions of 1 and 2 μg ml^{-1} were prepared in a phosphate buffer pH 8. The susceptible organism used was *Micrococccus luteus* (ATCC 9341, LMC, Gent, Belgium). 400 ml of antibiotic medium no. 11 (Difco No 593, Difco, Detroit, MI, USA) was prepared and cooled to 48° C before adding to the organism. Then the antibiotic medium was poured onto a glass plate. After solidification, the plate was dried for 30–45 min. at room temperature. Next wells, 8 mm in diameter, were punched in the medium in a 6×6 design. On each row, one well was filled with 150 μl of the low concentration standard solution (1 μg ml^{-1}), one well with 150 μl of the high concentration standard solution (2 μg ml^{-1}) and the four other wells were filled with low and high concentrations of the unknown solutions. After growth at 37° C for 1 night (Incubator: Termaks 4000, Termaks, Norway), the zone sizes were measured with a microbiological assay system (STS, Newmark, Suffolk, UK). With the help of a weighted average and a statistical average, the concentrations of erythromycin were calculated.

3.4. HPLC determination of the content of benzoyl peroxide

3.4.1. Apparatus and chromatographic conditions

The HPLC apparatus consisted of a SP 8700 pump (Spectra Physics, Darmstadt, Germany), a Lichrocart® 125-4 (Merck, Darmstadt, Germany) analytical column (with guard column 4-4) packed with Lichrospher® 100 RP-18 (Merck).

Both the analytical column and the guard column were operated at ambient temperature. For the detection, a Vari-Chrom UV-detector (Varian, Zurich, Switzerland) set at 254 nm was used. The mobile phase composed of acetonitrile–water (60:40, v/v) was pumped at a flow rate of 1.0 ml min^{-1}.

3.4.2. Standard solutions and unknown solutions

A benzoyl peroxide stock solution (2 mg ml^{-1}) was prepared in acetonitrile. Then dilutions in acetonitrile were prepared in order to reach a final concentration of 16, 24, 32 and 40 μg ml^{-1}. Valerophenone (Sigma, St Louis, USA) was the internal standard and used in a final concentration of 4 μg ml^{-1}.The solution (1 ml) was diluted with acetonitrile to 25 ml and 20 μl of this solution was injected into the chromatograph.

For the determination of benzoyl peroxide in the formulation with Carbopol 940® gel, 0.6 g gel was dissolved in 45 ml acetonitrile and 5 ml internal standard solution was added. This mixture was stirred for 20 min and filtered through a PTFE Yellow, 0.45 μm, 25 mm filter (Chromacol, UK). After filtration 1 ml was diluted with acetonitrile to 25 ml and 20 μl was injected into the chromatograph.

For the determination of benzoyl peroxide in the formulation made with hydroxyethylcellulose, 0.6 g gel was dissolved in 45 ml of a solution containing 10% (v/v) dichloromethane in methanol–ethanol (1:1, v/v). Next 5 ml of the internal standard solution was added. This mixture was stirred for 20 min. and filtered through a PTFE Yellow, 0.45 μm, 25 mm filter. After filtration 1 ml was diluted with acetonitrile to 25 ml and 20 μl was injected into the chromatograph.

4. Results and discussion

Because of availability, economical and clinical reasons, physicians sometimes prescribe preparations that must be extempore compounded. Two gel formulations containing erythromycin and benzoyl peroxide based on neutralised polyacrylic acid

Table 1
The levels of erythromycin and benzoyl peroxide in Benzamycin® and the compounded formulations during storage at 6° C[a]

Time (weeks)	Benzamycin®		Carbopol 940® gel		Hydroxyethylcellulose gel	
	E	BP	E	*E*	BP	
0	142.6	–	100.3	97.8	100.9	114.3
1	139.1	–	74.3	106.5	96.1	112.8
2	121.7	–	84.0	118.9	93.5	109.9
3	117.4	–	78.6	–	98.6	111.4

[a] The concentrations are expressed in percent of the theoretical level (E, erythromycin; BP, benzoyl peroxide).

and on hydroxyethylcellulose, respectively were prepared and their stability was compared with the commercially available Benzamycin®.

When preparing the formulation with Carbopol 940® by adding the ethanolic erythromycin solution to the gel, the preparation showed a flocky aspect caused by the precipitation of erythromycin. Besides, a formulation with four times higher ethanol 90° concentration was prepared and also showed a precipitation. A formulation with hydroxyethylcellulose containing the same ethanol 90° concentration as the second Carbopol® formulation was compounded and no precipitation of erythromycin was observed.

The influence of benzoyl peroxide on the stability of erythromycin was studied at room temperature and at 6°C. Table 1 shows the erythromycin and benzoyl peroxide levels expressed in percentage of the original concentration both for the extempore prepared gels (the preparation based on Carbopol® gel with the low ethanol 90° concentration and the formulation prepared with hydroxyethylcellulose) and Benzamycin® stored at 6° C. The gel formulation containing hydroxyethylcellulose and stored at 6°C for 3 weeks showed an average erythromycin level of 97.3% (range between 93.5 and 100.9%) of the theoretical content, indicating no stability problems for the antibiotic compound. On the contrary, the formulation prepared with Carbopol 940® showed an average value of 84.3% (range from 74.3 to 100.3%) of the theoretical content. This large variation could be due to a poor homogeneity of the drug because of precipitation that occurred during the dilution of the ethanolic erythromycin solution when compounding. In the formulation containing hydroxyethylcellulose, a four times higher ethanol concentration was used in order to dissolve the erythromycin and seemed sufficient to avoid any precipitation.

Table 1 clearly shows that an overdose of erythromycin was used in Benzamycin®. A value of 140% compared to the theoretical content was noticed just after preparation. The extempore prepared gel formulation made with Carbopol 940® and stored at 6°C for 3 weeks had a mean benzoyl peroxide level of 107.7% (range between 97.8 and 118.9%) of the theoretical content. The formulation made with hydroxyethylcellulose indicated a mean value of 112.1% (range between 109.9 and 114.3%). The larger variability observed in the benzoyl peroxide concentration within the Carbopol® gel formulation was due to the agglomeration of the drug during compounding and consequently an unhomogeneous drug distribution in the gel. The flocky aspect of the Benzamycin® gel during the extempore preparation was confirmed with the extempore prepared Carbopol® gel formulation.

In conclusion it can be said that the formulation containing erythromycin and benzoyl peroxide and made with hydroxyethylcellulose as the gel forming agent showed a more homogeneous aspect than the gel formulation based on Carbopol 940® with the absence of erythromycin precipitation and of benzoyl peroxide agglomeration.

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