

FIXED-COMBINATION ADAPALENE 0.1% / BENZOYL PEROXIDE 2.5% GEL PROVIDES OPTIMAL PERCUTANEOUS ABSORPTION COMPARED TO MONAD FORMULATIONS OF THESE COMPOUNDS

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INTRODUCTION

- Adapalene 0.1% / benzoyl peroxide 2.5% gel (A/BPO) is a fixed-combination topical agent for the treatment of acne.
- However, both active compounds are also available as monads, to be used in association or as monotherapy for the treatment of acne.
- The purpose of this study was to determine the effect of different treatment regimens on the percutaneous absorption of adapalene 0.1% gel and benzoyl peroxide (BPO) 2.5% gel in *ex vivo* human skin.

METHODS

- *In vitro* percutaneous absorption studies were conducted using full-thickness human skin from three donors, mounted on polycarbonate membrane inserts of 6-well culture plates. A dose of 10 mg/cm² of each formulation was applied on the skin surface (application area of 1 cm²) and 2 mL of phosphate buffer saline were added in the receptor compartment.
- Treatment regimens included: 1) A/BPO gel; 2) BPO 2.5% gel for 10 minutes followed by adapalene 0.1% gel; 3) adapalene 0.1% gel for 10 minutes followed by BPO 2.5% gel; 4) BPO 2.5% gel for 10 hours followed by adapalene 0.1% gel; and 5) adapalene 0.1% gel for 10 hours followed by BPO 2.5% gel. Skin samples were incubated (37°C and 5% CO₂) for 24 hours. Each condition was performed in triplicate for each of the three donors (i.e. n=9).
- Concentrations of adapalene and BPO equivalent (BPO-eq) (i.e. benzoic acid after chemical transformation of BPO) were measured in the epidermis (including *stratum corneum*), dermis and receptor fluid using high-performance liquid chromatography. Comparison of treatment regimens was performed using a bioequivalence criterion (estimated ratio within 0.8 and 1.25) and classical statistical testing via analysis of variance (ANOVA).

RESULTS

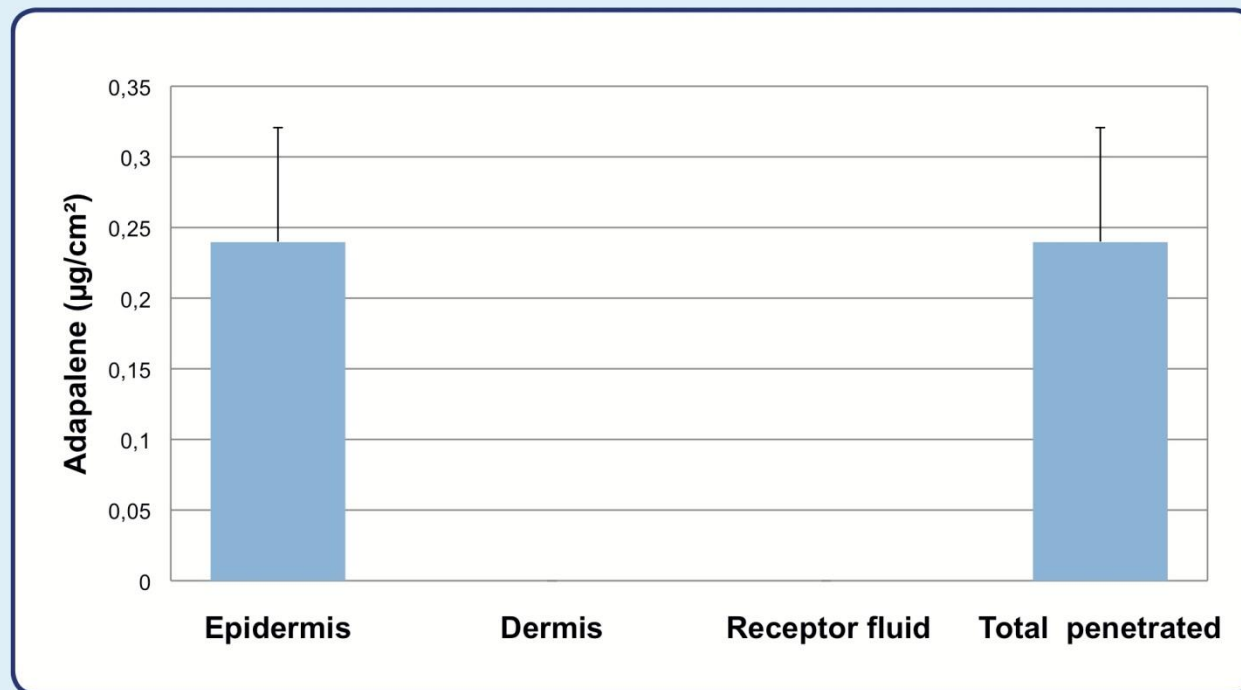
■ Skin characteristics

- Three full-thickness skin samples from three female donors, aged 56 to 79 years, were used in the study. Thickness ranged between 1.7–2.2 mm.

■ Adapalene release

- Adapalene was recovered only in the epidermis (including *stratum corneum*), regardless of treatment regimen, while the amounts recovered in the dermis and receptor fluid were below the limit of quantification (**Figure 1**).

Figure 1. Skin distribution of Adapalene ($\mu\text{g}/\text{cm}^2$) – Mean and SEM (n=9)

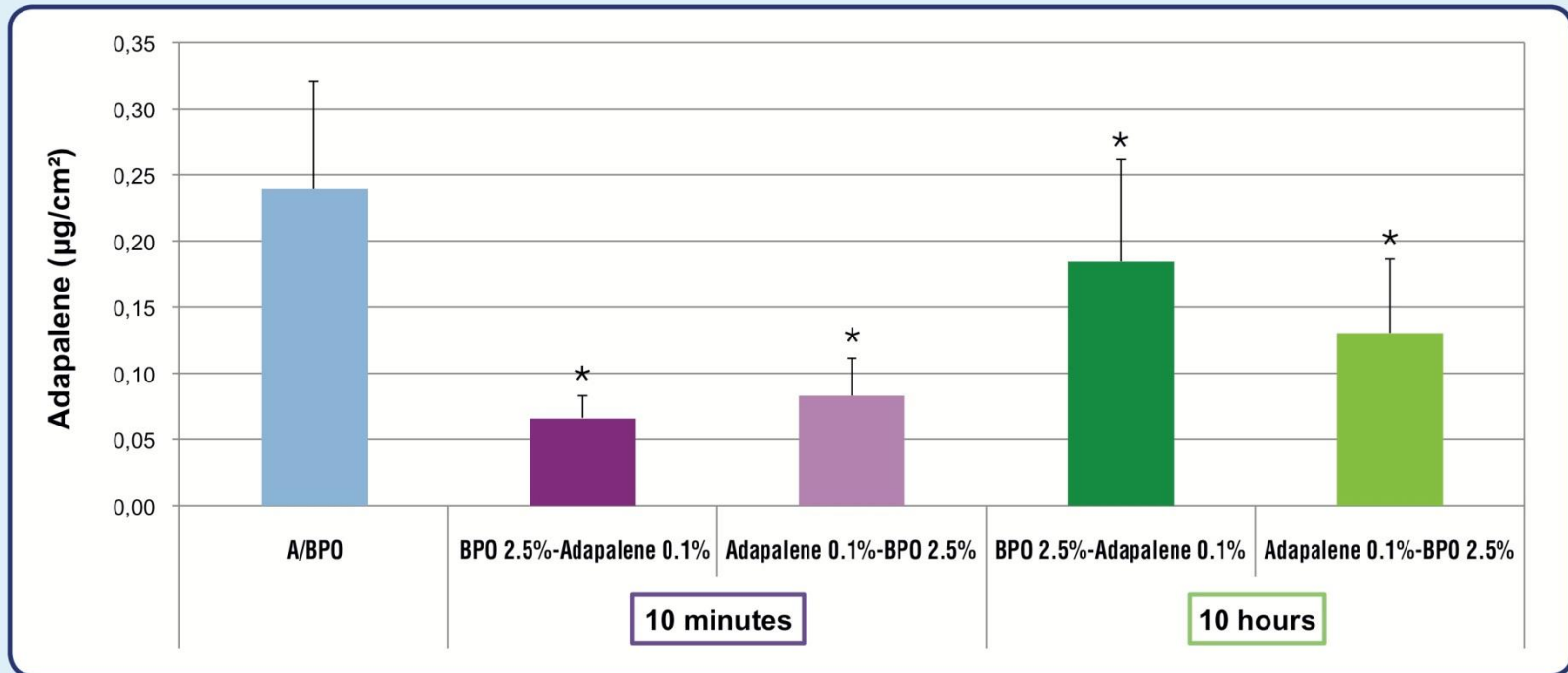


SEM; Standard error of the mean

RESULTS

- Based on bioequivalence acceptance criteria, results showed that all association regimens were different from A/BPO gel. Analysis of variance showed that all association regimens were statistically significantly different from A/BPO gel ($p < 0.05$), except BPO 2.5% gel for 10 hours followed by adapalene 0.1% ($p > 0.05$). A/BPO gel showed higher adapalene release compared to all monad formulations (**Figure 2**).

Figure 2. Adapalene: Total penetrated into skin ($\mu\text{g}/\text{cm}^2$) – Mean and SEM (n=9 or 8)



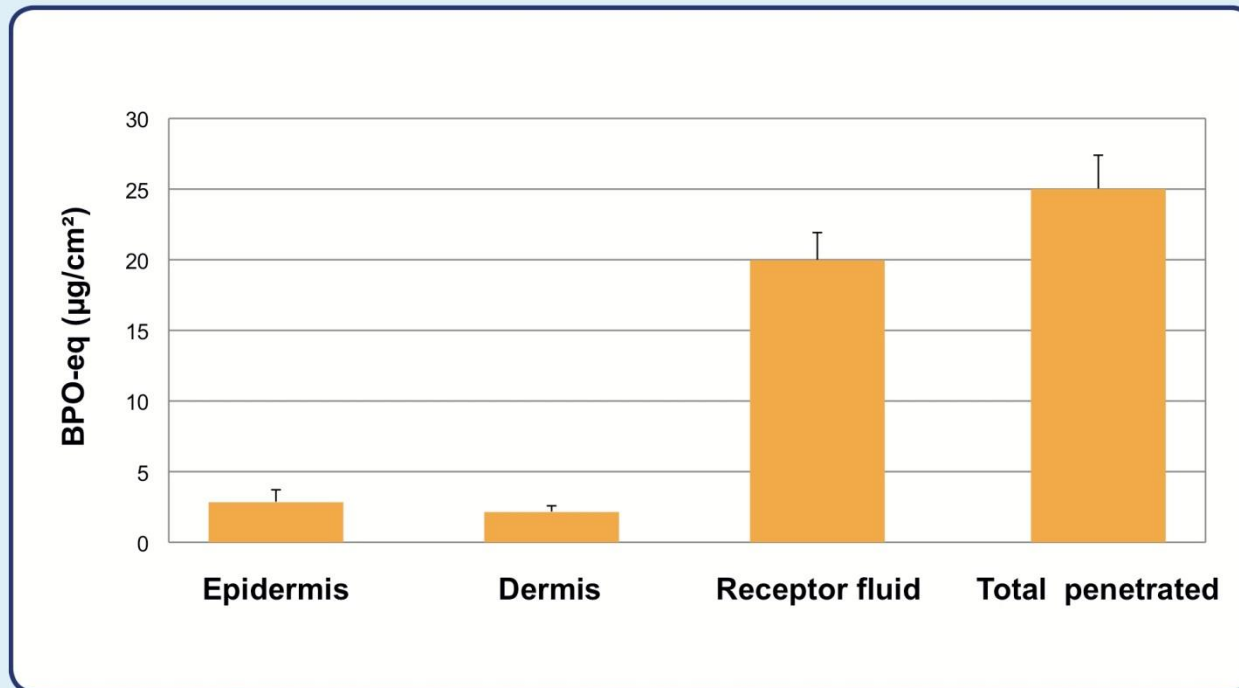
*Outside the acceptance interval of [80% -125%] ($< 80\%$)
SEM; Standard error of the mean

RESULTS

■ BPO-eq release

- BPO-eq was mainly recovered in the receptor fluid and to a very lesser extent in the epidermis and the dermis (**Figure 3**), regardless of treatment regimen. Moreover, the results showed that the association regimens with application of adapalene 0.1% gel prior to BPO 2.5% gel were different from A/BPO gel treatment. A/BPO gel showed higher BPO-eq release compared to monad formulations (**Figure 4**).

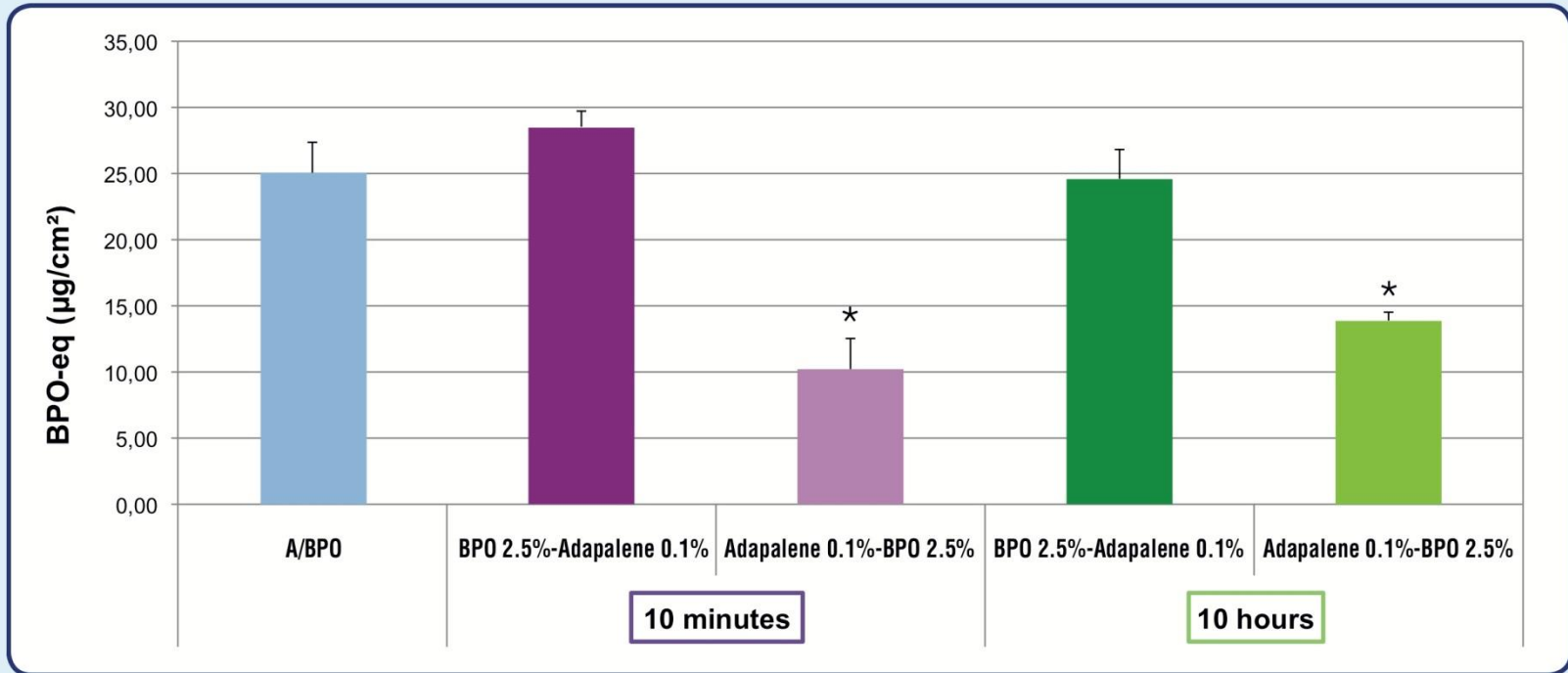
Figure 3. Skin distribution of BPO-eq ($\mu\text{g}/\text{cm}^2$) – Mean and SEM (n=9)



SEM; Standard error of the mean

RESULTS

Figure 4. BPO-eq: Total penetrated into skin ($\mu\text{g}/\text{cm}^2$) – Mean and SEM (n=9 or 8)



*Outside the acceptance interval of [80% -125%] (< 80%)
SEM; Standard error of the mean

CONCLUSION

This study demonstrated that fixed-combination A/BPO gel provides optimal percutaneous absorption of the active compounds compared to association of monad formulations of adapalene 0.1% and BPO 2.5%.