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# Effect of formulation wipe-off time on topical bioavailability of metronidazole using dermal microdialysis


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## BACKGROUND

- Metronidazole (MTZ) applied topically to the skin exhibits a slow absorption into the dermis and the entire pharmacokinetic profile was not captured over a 48 hr sampling schedule in Yucatan Mini-pigs (n=2)[1].
- The assessment of Bioequivalence requires that both the rate and the extent at which a drug reaches the dermis be characterized in order to establish bioequivalence of two formulations.
- It would be difficult to translate such a long experiment into a clinical setting and even more difficult planning for longer experiments
- It is also unrealistic that a topical formulation remains on the skin of the patient untouched for such a long time.

## PURPOSE

1. To study the effect of formulation removal on dermis exposure resulting from the application of 10 mg/cm$^2$ of two MTZ topical dermatological formulations compared to non-removal.
2. To characterize the dermal absorption and elimination processes of MTZ from both formulations and independently with a "retrodialysis" approach.

## METHODS

- Figure 1 shows the dosage sites and probes location on the dorsum of an animal (n=3). Two dMD probes were inserted under each site. Probes were perfused with 0.04 µg/ml solution of D3-MTZ in Lactated Ringer solution as an internal standard (IS) to calculate the correction factor. Dialysate samples were collected every hour and analyzed with a validated UPLC-MS-MS method (LLOQ 0.4 ng/mL)[2]. Formulations studied were 0.75% Metronidazole Cream (Fougera, Melville, NY) and 0.75 % Metronidazole Gel (Tolmar, Fort Collins, CO). The 10 mg/cm2 dose was accurately measured with a Distriman Positive displacement pipette1 and applied for 10 seconds with a circular motion to the 4.9 cm2 area. Formulations were wiped off (W.O.) at predetermined times (6hr, 12hr, and no wipe off) by using 3 cotton pads with the following scheme: dry, wet (100µl water), dry. Two probes, per study, were perfused with MTZ (0.02 µg/ml ) for a predetermined time and then switched to LR solution with 0.04 µg/ml of D3-MTZ in Lactated Ringer. Trans-epidermal Water Loss (TEWL) was measured prior to formulation application. Probe depth was measured using GE LOGIC*e7 (22 MHz-probe)

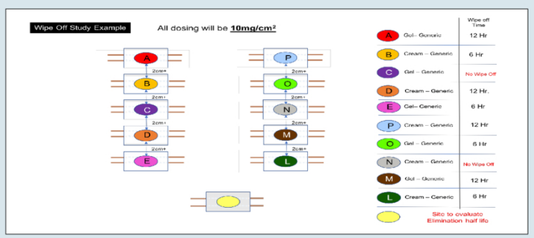


**Figure 1:** Example scheme for formulation removal times.

## RESULTS

**Effect of Probe Depth**

- Figure 2 shows that the higher AUCs were detected at locations where probes were more superficial than 0.2 cm. When data from these probes were excluded from analysis, resulted in a reduction of variability (Figures 3, 4, and 5).

**Impact of Formulation Removal (Figure 3)**

- **GEL**: There is no significant difference in AUCs between the 6hr wipe off scheme with the 12hr wipe off (p=0.978) and 48 hr wipe off (p=0.992) for the **gel** product.
- **CREAM:** There is a significant difference between the 6hr wipe off scheme with the 12hr wipe off (P=0.026) and 48 hr wipe off (P=0.006) for the **cream** product. The AUC from the 12-hour wipe-off was not statistically different from the no-wipe AUC.

**Dermis Elimination**

- The terminal phase, as well as Cmax, is clearly detectable in 42 of the 68 probes within 36 hours.
- After 36 hours the dermis concentrations tend to plateau.
- The median half life for the gel product was 10.6 hr (n= 20) and for the cream product was 9.5 hr (n=19).
- The median half life for the retrodialysis was 1.4 hr (n=6).

**Bioavailability**

- Regardless of the W.O. time, the gel vs. the cream products had clearly different bioavailability.
- The point estimate for the 90% CI for the $C_{max}$ plots were outside the 80-125% acceptable values for the gel vs. cream (Figure 4).
- The point estimates were also outside the 90% CI for the AUC plots for the acceptable 80%-125% ratio (Figure 5).

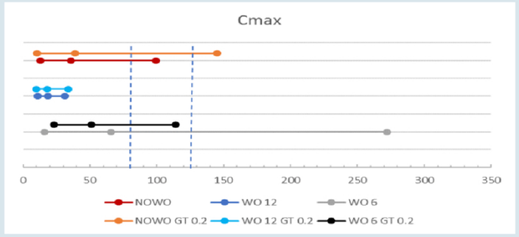


**Figure 4:** 90% confidence intervals for the ratios of ln transformed **Cmax**. The dashed lines indicate the bioequivalence limits 80-125% CI. The number next to WO indicates the Wipe Off time (ie. WO 6 indicates wipe off at 6hrs, etc). GT 0.2 indicates probes that were more superficial than 0.2cm were excluded from this analysis**. Cream is the reference while gel is the test.**

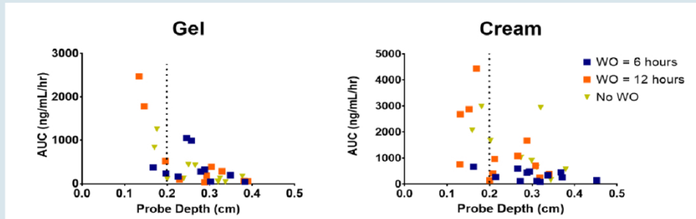


**Figure 2:** Plots of AUC versus probe depth for each probe

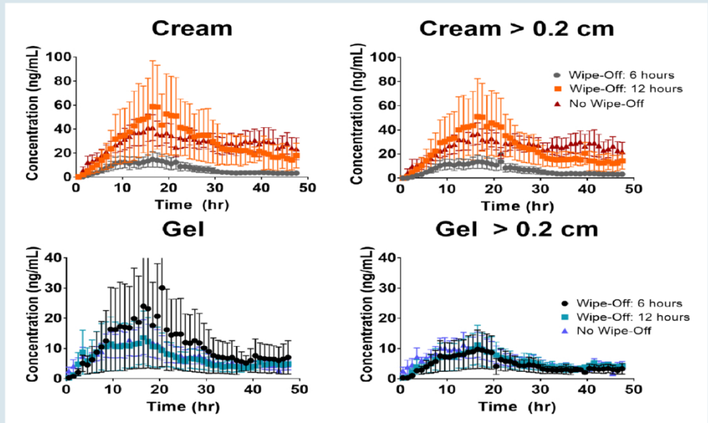


**Figure 3:** Average skin-concentration profiles (mean ± SEM) sorted by formulation and WO scheme (left) and the average dermis concentrations for probes at depth greater than 0.2 cm (right).

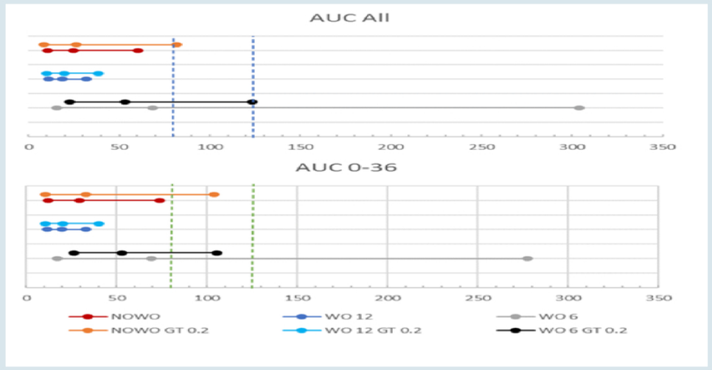


**Figure 5:** 90% confidence intervals for the ratios of ln transformed **AUC**. The dashed lines indicate the bioequivalence limits 80-125% CI. The number next to WO indicates the Wipe Off time (ie. WO 6 indicates wipe off at 6hrs, etc). GT 0.2 indicates probes that were more superficial than 0.2cm were excluded from this analysis. **Cream is the reference while gel is the test**.

## CONCLUSIONS

- Wipe-off of the formulation to truncate delivery may provide a useful strategy to shorten the length of a clinical study investigating dermis pharmacokinetics of topically applied formulations.
- The gel and cream products evaluated were discriminated as having a **different bioavailability**.
- Dermis exposure from the **gel** is independent of this W.O. scheme, suggesting that the drug delivery from the gel is complete **within 6 hours**.
- Drug delivery to the dermis from the **cream** is slower than the gel, and it is completed **within 12 hours**.
- More superficial probes appeared to measure higher dermal concentrations.
- Data collected after 36 hours may be affected by the potential development of peripheral edema due to prolonged immobility and anesthesia.
- The "formulation independent" elimination half-life is much shorter than the one observed at the formulation sites suggesting a residual amount of release from the products even after the $T_{max}$.

## REFERENCES


1. Benjamin Kuzma, Sharareh Senemar, Tannaz Ramezanli, Priyanka Ghosh, Sam G Raney, Grazia Stagni. Evaluation of local bioavailability of metronidazole from topical formulations using dermal microdialysis: preliminary studies in Yucatan mini-pig, AAPS Annual Meeting 2018, Washington D.C., November 2018.
2. Benjamin Kuzma, Sharareh Senemar, Richard DePinto, Grazia Stagni. LC/MS/MS method for the quantification of Metronidazole in skin dialysate, AAPS Annual Meeting 2018, Washington D.C., November 2018. (Poster# 508892)


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