Correlation Between the Quality Attributes and Performance Characteristics of Metronidazole Gels and Creams: Implications for the Evaluation of Bioequivalence

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PURPOSE AND OBJECTIVE

The objective of this study was to characterize the physicochemical properties of topical gels and creams using multiple orthogonal tests, and to evaluate the relationship between these product quality attributes and the performance of the corresponding drug products. In this study, product performance was evaluated using *In Vitro* Permeation Tests (IVPT) to characterize the cutaneous pharmacokinetics of metronidazole.

Five commercially available topical metronidazole gel and cream products were included in the study. MetroGel® 0.75% (from Prasco) , was the Reference Listed Drug (RLD) gel and two bioequivalent gels; metronidazole gel 0.75% ("Generic Gel-1" from Tolmar and "Generic Gel-2" from Taro) were evaluated in parallel, along with an RLD MetroCream® 0.75% cream (from Galderma) and one bioequivalent metronidazole cream 0.75%, generic cream (from Fougera). The gels were intended to serve as positive controls for bioequivalence relative to each other, as was each cream relative to the other. However, the gels and creams were not expected to be bioequivalent to each other, but rather, were intended to serve as negative controls for bioequivalence relative to each other.

METHODS

pH: The pH of the topical products was determined using an InLab® Micro probe.

Density: The density of the products was determined using a gas pycnometer (Accupyc II 1340, Micromeritics).

Work of Adhesion (WOA): WOA was evaluated by a TA XT2i texture analyzer using a TA-3 soft matter acrylic probe under standard set conditions.

Drug Distribution Studies: Drug distribution in aqueous and lipid phases was estimated by subjecting the products to ultra centrifugation and analyzing the drug content in the aqueous and lipid phases by HPLC.

Solvent Activity: Solvent activity was evaluated using an Aqualab water activity meter (Series 3E).

Globule Size Distribution: Bright field microscopy was used to evaluate and quantify globules in the creams using Zeiss Axiovert microscope. The median globule diameter (D_{50}) was determined by plotting globule size versus frequency

Drying Rate: Drying rates for each product were measured gravimetrically by spreading (10 mg/cm^2) of each product on an inverted polypropylene weigh boat and monitoring the weight loss at regular intervals in an incubator with a temperature of 32 ± 1^{o}C.

Rheology: Rheological studies were performed at 32^{0}C using a TA-HR2 rheometer with a solvent trap (TA instruments) equipped with a 25 mm parallel plate.

IVPT: Dermatomed posterior torso human cadaver skin (acquired from New York Fire Fighters skin bank) from 6 donors was mounted in nominal 2 cm^2 Franz diffusion cells, and 6 replicates skin sections per donor were dosed for each of the 5 metronidazole products. A finite dose (10 mg/cm^2) of each drug product (gel or cream) was used. The entire receptor volume from each of 180 diffusion cells was collected prior to dosing and at 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 hours post-dosing, and was analyzed for metronidazole using a validated HPLC method.

Statistical Analysis: Data are shown as mean ± standard deviation for quality attributes or mean ± standard error of the mean for IVPT. Differences between the products were analyzed using a student t test. p<0.05 was considered to be statistically significant.

RESULTS

Table 1: Critical Quality Attributes of Metronidazole Topical Products
(n=3 for all studies except globule size, for which n=100)

Quality Attribute	MetroCream® 0.75%, RLD Cream (Galderma)	Metronidazole cream 0.75%, Generic Cream (Fougera)	MetroGel® 0.75%, RLD Gel (Prasco)	Metronidazole gel 0.75%, Generic Gel-1 (Tolmar)	Metronidazole gel 0.75%, Generic Gel-2 (Taro)
pH	4.82 ± 0.01	5.05 ± 0.05	5.23 ± 0.01	5.02 ± 0.01	5.48 ± 0.01
Density (g/cc)	1.0238 ± 0.0004	1.0232 ± 0.0002	1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002
WOA (g.sec)	57.61 ± 0.91	63.95 ± 0.80	39.38 ± 0.30	43.93 ± 0.78	42.03 ± 0.81
Particle size (µm)	Metronidazole was observed to be completely dissolved				
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drug in Aq (mg/g)	4.20 ± 0.42	2.92 ± 0.35	---	---	---
Drug in Oil (mg/g)	2.58 ± 0.11	3.94 ± 0.18	---	---	---
Solvent Activity	0.977 ± 0.000	0.974 ± 0.002	0.992 ± 0.005	0.994 ± 0.004	1.002 ± 0.008
Drying,T_{50} (min)	43.93 ± 2.72	33.4 ± 0.61	9.12 ± 0.63	7.87 ± 0.42	11.25 ± 1.75
Rheology (G''/G')	0.6175	0.6298	0.0615	0.0660	0.0742

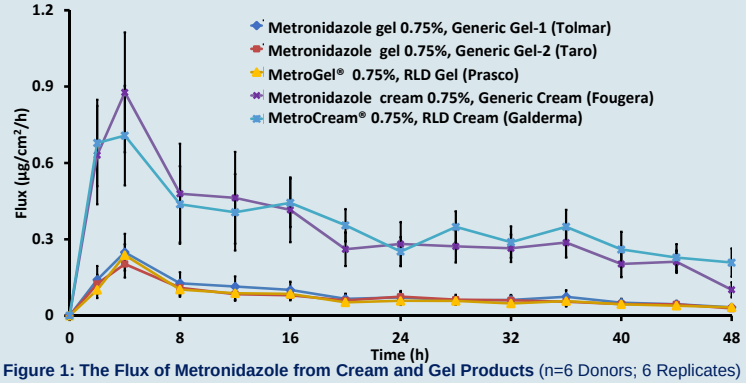

Figure 1: The Flux of Metronidazole from Cream and Gel Products (n=6 Donors; 6 Replicates)

Table 2: Cutaneous Pharmacokinetics of Metronidazole Topical Products

Product	MetroCream® 0.75%, RLD Cream (Galderma)	Metronidazole Cream 0.75%, Generic Cream (Fougera)	MetroGel® 0.75%, RLD Gel (Prasco)	Metronidazole gel 0.75%, Generic Gel-1 (Tolmar)	Metronidazole gel 0.75%, Generic Gel-2 (Taro)
AUC (µg/cm^2)	18.40 ± 4.27	17.40 ± 4.75	3.76 ± 0.60	4.18 ± 0.77	3.61 ± 0.48
J_{max} (µg/cm^2/h)	0.98 ± 0.14	0.98 ± 0.27	0.24 ± 0.02	0.27 ± 0.03	0.20 ± 0.02

NOTE: Pharmacokinetic parameters are average total cumulative permeation (area under the curve; AUC) and average maximum flux (J_{max})

CONCLUSION

The coordinated evaluation of product quality and performance illustrated that metronidazole products with comparable physical and structural attributes exhibited a similar dynamic rate (flux profile) and extent of metronidazole bioavailability. The microscopic and rheological differences in microstructure between the creams and gels were correlated with differences in product performance between the creams and the gels. The corollary was that physical and structural similarities between the two creams, and among the three gels, also correlated with similar product performance. The same correlation was observed for solvent activity and drying rate, which suggested a mechanistic basis for differences in the flux profiles for the gels compared to the creams; the creams, which dried more slowly also provided a more sustained drug delivery relative to the gels that dried more rapidly. Collectively, these results underscore the value of comprehensive product quality and performance characterizations, 1) to identify critical quality attributes for topical semisolid dosage forms, and 2) to glean insights into the mechanistic bases of topical drug delivery from such products that might relate to failure modes for therapeutic performance, and for bioequivalence.

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