Assessing the Influence of Quantitative Differences in Propylene Glycol on the Performance of Metronidazole Topical Gels

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PURPOSE

Evaporative metamorphosis of topical products can result in significant quantitative changes in the formulation composition and a dynamic change in the degree of saturation of the active pharmaceutical ingredient (API) as solvents in the formulation evaporate. Topical products having differences in the degree of saturation-time profiles of the API may have differences in bioavailability. Previously, we demonstrated that it may be feasible to utilize fractional solubility as a measure of degree of saturation, in conjunction with in vitro permeation testing (IVPT), to evaluate the influence of quantitative differences in inactive ingredients (i.e., polyethylene glycol (PEG)-200) on the performance of topical gels containing various APIs (i.e., metronidazole, diclofenac sodium, lidocaine). To assess the generalizability of the phenomenon, additional drugs and inactive ingredients were investigated and are being presented separately. This poster focuses on evaluating the influence of quantitative differences in propylene glycol (PG) on the performance of metronidazole topical gels.

METHODS

Metronidazole topical gel, 0.5% w/w, with 30% w/w propylene glycol (PG) was prepared and considered as the hypothetical reference gel. Gel variants containing ± 10% and ± 25% difference in PG concentration compared to the reference gel were also prepared (Table 1). The saturation solubility of metronidazole in PG: water binary solutions was determined (n=3). Physicochemical and structural (Q3) characterization of the gels was also performed (n=3). An in situ drying study was performed on human cadaver skin in Franz diffusion cells for all the formulations. The gels were sampled from the donor compartment periodically for up to 6h. The samples were subjected to content assays for water, PG, and metronidazole (n=3). Fractional solubility is calculated as the ratio of the concentration of API in the formulation to the saturation solubility of the API in the same formulation at any given time. A semi-infinite dose IVPT study was performed on human cadaver skin (3 skin donors, 6 replicate skin sections per skin donor) using Franz diffusion cells and a dose of 300 mg/cm^2. The receptor solution was sampled every hour for the first 6h, and after that, every 4h up to 24h. Data are presented as mean ± SD, except for IVPT data from three skin donors, which are presented as mean ± SEM.

RESULTS

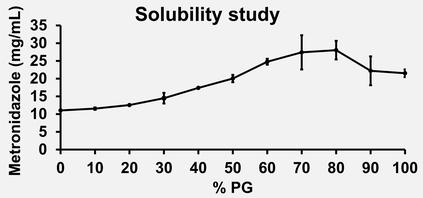

Figure 1.Solubility of drug in PG:water binary solutions

The saturation solubility of metronidazole increased as the PG concentration increased from 0% to 80% in the PG: water binary solutions (11.04 ± 0.09 to 28.03 ± 2.62 mg/mL) and then decreased at 90% PG concentration (21.53 ± 1.09 mg/mL).

Most significant changes in concentration were observed around the 30% w/w PG:water solution, which was subsequently selected as the starting PG concentration for the reference gel for the remaining studies.

Table 1.Composition of metronidazole topical gels

Ingredients (%w/w)	M.PG-F25-	M.PG-F10-	M.PG-F30.Ref	M.PG-F10+	M.PG-F25+
Metronidazole	0.5	0.5	0.5	0.5	0.5
Propylene glycol	22.5	27	30	33	37.5
Hydroxyethyl cellulose	1.75	1.75	1.75	1.75	1.75
Xanthan gum	1.0	1.0	1.0	1.0	1.0
Sodium benzoate	0.02	0.02	0.02	0.02	0.02
Edetate disodium	0.01	0.01	0.01	0.01	0.01
Water q.s	100	100	100	100	100

Table 2.Critical quality attributes (CQAs) of metronidazole topical gels

Sample ID	pH	Water activity (aw)	Density (g/mL)	Zero shear viscosity (Pa.s)
M.PG-F25-	6.33±0.02	0.94±0.01	1.01±0.02	2063.14±37.30
M.PG-F10-	6.18±0.01	0.92±0.01	0.98±0.01	2270.13±244.98
M.PG-F30.Ref	6.09±0.01	0.91±0.01	1.02±0.02	2744.01±388.43
M.PG-F10+	6.19±0.01	0.90±0.01	1.03±0.00	3130.12±312.12
M.PG-F25+	6.75±0.03	0.87±0.01	1.02±0.01	1989.96±47.05

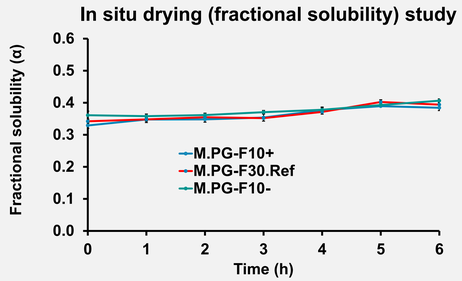

Figure 2. Fractional solubility of drug in ± 10% PG variant gels vs. reference gel

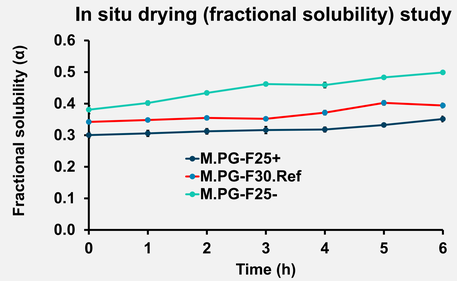

Figure 3. Fractional solubility of drug in ± 25% PG variant gels vs. reference gel

The in situ drying studies revealed that no obvious differences were observed in the fractional solubility vs. time profile of metronidazole between the ± 10% PG variant gels and the reference gel. The ± 25% PG variant gels had greater differences in the fractional solubility vs time profiles of metronidazole compared to the reference gel.

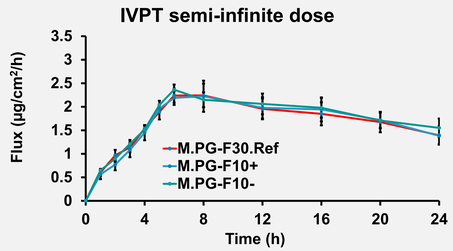

Figure 4. Flux profiles of drug from ± 10% PG variant gels vs. reference gel

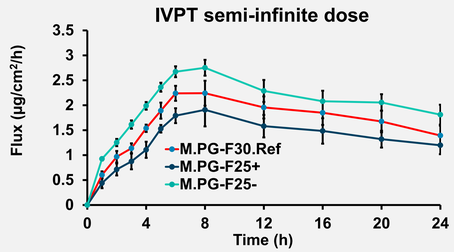

Figure 5. Flux profiles of drug in ± 25% PG variant gels vs. reference gel

In alignment with the observation above, the IVPT flux profiles of ± 25% PG variant gels were different relative to the reference gel. However, such differences were not observed in ± 10% PG variant gels.

CONCLUSIONS

The current study suggests that a ± 10% change in PG concentration relative to the reference gel (30% w/w PG) did not appear to alter/influence the performance of the metronidazole gels that were evaluated in the current study. However, a ± 25% change in the concentration of PG compared to the reference gel influenced the rate of permeation of the API from the metronidazole gels, potentially due to changes in fractional solubility, and thereby thermodynamic activity. The data further suggest that product performance of topical products may primarily be driven by thermodynamic activity of the API in the drug product.

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