Comparing the Performance of Metronidazole Topical Gels with Variant Concentrations of Polyethylene Glycol (PEG)-400 in the Formulation

ID # 1850195

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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. The current poster focuses on evaluating the influence of quantitative differences in PEG-400 on the performance of metronidazole topical gels.

METHODS

Five metronidazole topical gels, 0.5% w/w, which contains 22.5%, 27%, 30%, 33%, and 37.5% w/w PEG-400 were prepared according to the formulation compositions shown in Table 1. The 30% w/w PEG-400-containing gel was considered as the hypothetical reference gel. The PEG concentrations in the rest of the gels represent ± 10% and ± 25% quantitative differences compared to 30% w/w of PEG-400 in the reference gel. Solubility of metronidazole in PEG-400 and water systems were evaluated (n=3). An assessment of critical quality attributes (CQAs) of the gels including water activity, density, pH, and rheological characteristics (n=3) were carried out. 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, PEG-400, and metronidazole (n=3). The saturation solubility of metronidazole in PEG-400: water binary solutions was determined (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 and 6 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 thereafter, every 4h up to 24h. Data were presented as mean ± SD, except for IVPT data from three skin donors, which are presented as mean ± SEM.

RESULTS

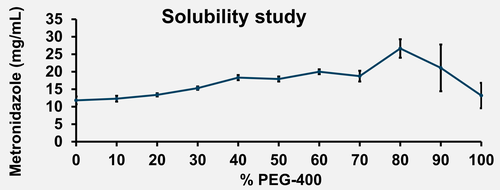

Figure 1.Solubility of drug in PEG-400:water binary solutions

The saturation solubility of metronidazole in the PEG-400: water binary solutions increased from 11.82 ± 1.08 to 18.32 ± 0.73 mg/mL as the PEG-400 concentration increased from 0% to 40%.

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

Table 1: Composition of metronidazole topical gels

Ingredients (%w/w)	M.PEG-400 F25-	M.PEG-400 F10-	M.PEG-400 F30.Ref	M.PEG-F10+	M.PEG-400 F25+
Metronidazole	0.5	0.5	0.5	0.5	0.5
PEG-400	22.5	27	30	33	37.5
Hydroxy ethyl 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 rate viscosity (Pa.S)
M.PEG-400 F25-	5.72±0.01	0.99±0.01	1.03±0.01	1705.53±40.66
M.PEG-400 F10-	5.76±0.02	0.97±0.01	1.05±0.01	1578.72±155.31
M.PEG-400 F30.Ref	5.41±0.01	0.97±0.01	1.05±0.01	1413.82±74.41
M.PEG-400 F10+	5.81±0.01	0.96±0.01	1.01±0.01	1685.07±26.68
M.PEG-400 F25+	5.88±0.01	0.96±0.01	1.06±0.02	1446.97±79.07

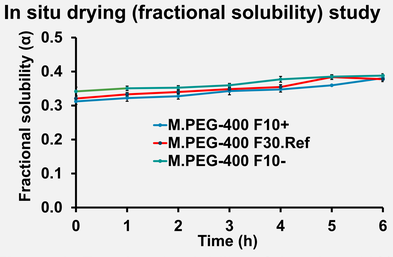

Figure 2. Fractional solubility of drug in ± 10% PEG-400 variant gels vs. reference gel

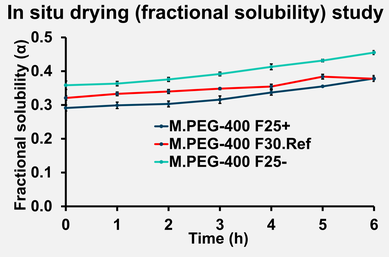

Figure 3. Fractional solubility of drug in ± 25% PEG-400 variant gels vs. reference gel

The in situ drying studies revealed modest differences in the magnitude of the fractional solubility profile vs time profiles of metronidazole between the ± 10% PEG-400 variant gels and the reference gel. The ± 25% PEG-400 variant gels had greater differences and more rapid increase in fractional solubility profiles of metronidazole than the reference gel.

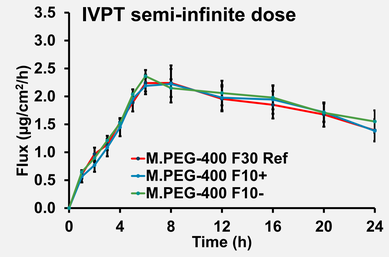

Figure 4. Flux profiles of drug from ± 10% PEG-400 variant gels vs. reference gel

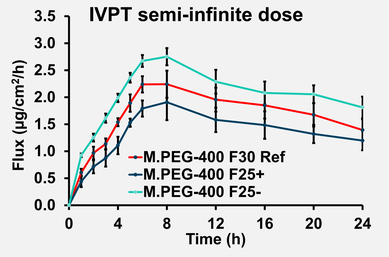

Figure 5. Flux profiles of drug from ± 25% PEG-400 variant gels vs. reference gel

In alignment with the above observation, the IVPT flux profiles of the ± 10% PEG-400 variant gels were similar to that of the reference gel, while the IVPT flux profiles of the ± 25% PEG-400 variant gels were different from that of the reference gel.

CONCLUSIONS

The current study suggests that a ± 10% change in PEG-400 concentration relative to the reference gel (30% w/w PEG-400) did not appear to impact the bioavailability of the API from these formulations. However, a ± 25% change in the concentration of PEG-400 may impact the rate of permeation of metronidazole gels due to changes in the fractional solubility vs. time profile, and thereby the thermodynamic activity. The data further support that product performance of topical products may primarily be driven by thermodynamic activity of the API in the formulation.

FUNDING

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of two grants, U01FD006507 totaling $1,069,876 and U01FD006496 totaling $1,075,000, each with 100 percent funded by FDA/HHS. The views are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

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