Influence of quantitative differences in propylene glycol on the performance of diclofenac sodium 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 investigation evaluates the influence of quantitative differences in propylene glycol (PG) on the performance of diclofenac sodium topical gels.

METHODS

Diclofenac topical sodium gels (0.5% w/w), were prepared using different PG concentrations (Table 1). A small amount of sodium hydroxide was required to adjust the pH to 7.0 ± 0.5. The 40% w/w PG-containing product was considered as the hypothetical reference gel. The PG concentrations in the rest of the gels represent ± 10% and ± 25% quantitative differences compared to 40% w/w in the reference gel. Critical quality attributes (CQAs) of the gels including pH, water activity, density, and rheological properties were characterized (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 diclofenac sodium (n=3). The saturation solubility of diclofenac sodium in propylene glycol: 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, 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 after that, 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

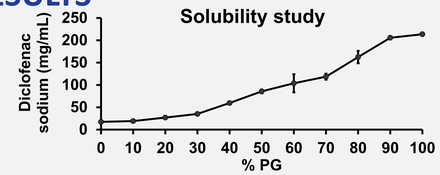

Figure 1.Solubility of drug in PG : water binary solutions

Table 1: Composition of diclofenac sodium topical gels

Ingredients (%w/w)	D.PG-F25-	D.PG-F10-	D.PG-F40.Ref	D.PG-F10+	D.PG-F25+
Diclofenac Na	0.5	0.5	0.5	0.5	0.5
PEG-400	30	36	40	44	50
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
NaOH 1N	0.7	1	1	0.7	1
Water qs	100	100	100	100	100

The saturation solubility of diclofenac sodium increased as the PG concentration increased from 0% to 100% in the PG: water binary solutions (17.35 ± 1.29 to 213.63 ± 0.98 mg/mL).

Most significant changes in saturation solubility were observed around the 40% w/w PG : water solution, which was subsequently selected as the starting PG concentration for the reference gel for the remaining studies.

Table 2: Critical quality attributes (CQAs) of diclofenac sodium topical gels

Sample ID	pH	Water activity (aW)	Density (g/mL)	Zero shear (Pa.s)
D.PG-F25-	6.98±0.01	0.89±0.01	0.99±0.01	2912.38±79.58
D.PG-F10-	6.90±0.01	0.87±0.00	0.98±0.01	4199.65±626.91
D.PG-F40.Ref	7.11±0.02	0.86±0.01	1.02±0.06	4700.04±102.17
D.PG-F10+	7.11±0.02	0.84±0.01	0.98±0.01	4721.77±36.08
D.PG-F25+	7.10±0.01	0.79±0.01	0.99±0.01	4692.63±470.03

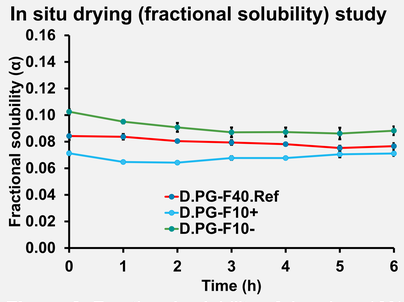

Figure 2. Fractional solubility of drug in ± 10% PG variant gels vs. reference gel

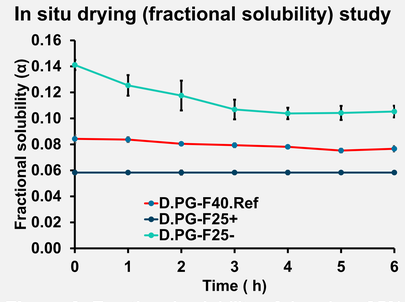

Figure 3. Fractional solubility of drug in ± 25% PG variant gels vs. reference gel

The in situ drying studies revealed that, compared to the reference gel, a greater change over time in the fractional solubility profile for diclofenac sodium was observed in the ± 25% PG variant gels compared to those observed in the ± 10% PG variant gels.

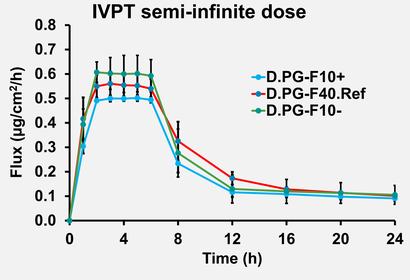

Figure 4. Flux profiles of drug from ± 10% PG variant gels vs. reference gel

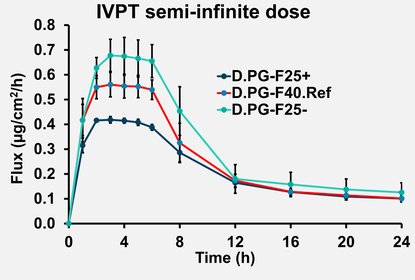

Figure 5. Flux profiles of drug from ± 25% PG variant gels vs. reference gel

In alignment with the above observation, greater differences were seen between the IVPT flux profiles of ± 25% PG variant gels and the reference gel, than between those of ± 10% PG variant gels and the reference gel.

CONCLUSIONS

The current study suggests that in the case of these specific formulations of diclofenac sodium topical gels, changing the PG concentration to greater than 10% relative to the reference gel (40% w/w PG) influences the performance of the diclofenac sodium gel. The data further suggest that product performance of topical products may primarily be driven by thermodynamic activity.

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