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Influence of varying amount of an inactive ingredient on the microstructure and performance of metronidazole topical gels

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PURPOSE

Evaporative metamorphosis of topical products could lead to significant change in the degree of saturation of the active pharmaceutical ingredient (API) in the formulation over time. The dynamic change in the degree of saturation of the API may impact the bioavailability of the API from a topical product. The objective of this study was to investigate the influence of quantitative changes in an inactive ingredient on the microstructure and the performance of topical gels containing metronidazole as the API.

METHODS

Five metronidazole topical gels (0.5% w/w) comprising of polyethylene glycol (PEG-200), ethylenediamine tetra acetic acid (EDTA), sodium benzoate, hydroxylethylcellulose, and water were manufactured. The concentration of PEG-200 was varied across the formulations from 1% to 25%. The drying profile of selected formulations (F1-F3 in Table 1) were evaluated using a gravimetric method, water activity was measured using Aqualab-3, and pH was determined using a Toledo pH meter with a microprobe (n=3). An additional in situ drying study was performed on human cadaver skin in Franz diffusion cells for selected formulations. The gels were sampled from the donor compartment periodically for up to 6h. The samples were subjected to content assays for water, PEG-200, and metronidazole (n=3). The saturation solubility of metronidazole in PEG-200: water compositions was also determined. Fractional solubility (α) is used in the current study as a measure of the degree of saturation; the parameter is defined 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. Finally, a semi-finite dose in vitro permeation testing (IVPT) study was also performed across human cadaver skin using Franz diffusion cells (n=3 skin donors, 6 replicates per skin donor) using 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. An infinite dose IVPT study was also performed using formulations with varying concentrations of metronidazole (F1, F4 and F5 in Table 1), as a control to demonstrate the sensitivity of the IVPT method. The IVPT data are presented as mean ± SEM. Correlation of the fractional solubility profile and the in vitro permeation profile was investigated.

Table 1. Formulation compositions of metronidazole topical gels

Composition	F1	F2	F3	F4	F5
Metronidazole	**0.5**	**0.5**	**0.5**	**0.25**	**0.75**
PEG 200	**1**	**10**	**20**	**1**	**1**
EDTA	0.01	0.01	0.01	0.01	0.01
Sodium benzoate	0.02	0.02	0.02	0.02	0.02
Hydroxy ethyl cellulose	5	5	5	5	5
Water qs	100	100	100	100	100

RESULTS

The pH and water activity were similar across the selected formulations F1-F3 (Table 2). Although the gravimetric drying profiles demonstrated slight differences across gels (Figure 1), the fractional solubility vs. time profiles were relatively stable and comparable across the three selected gels (Figure 2). There were no significant differences in the observed permeation profiles for the three gels in the semi-infinite dose IVPT study (Figure 3), and the data were in alignment with the fractional solubility profiles. The infinite dose study (Figures 4 and 5) suggested that the IVPT method used in the study is sensitive and suitable for detection differences in permeation, when such differences exist.

Table 2. pH and water activity of selected metronidazole gels (n=3, mean ± SD)

Metronidazole gels	pH	Water activity
Metronidazole-1% PEG 200 gel (F1)	**7.036 ± 0.025**	**0.998 ± 0.003**
Metronidazole-10% PEG 200 gel (F2)	**7.045 ± 0.021**	**0.994 ± 0.006**
Metronidazole-20% PEG 200 gel (F3)	**7.057 ± 0.022**	**0.997 ± 0.001**

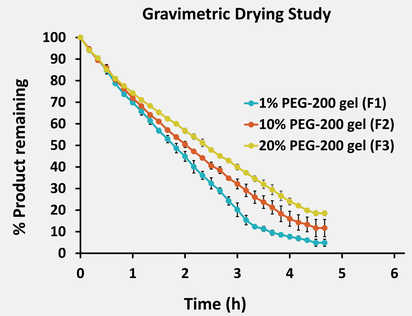

Figure 1: Drying profiles of metronidazole gels (n=3, mean ± SD)

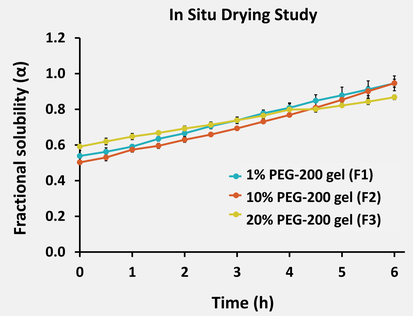

Figure 2: Fractional solubility of metronidazole gels (n=3, mean ± SD)

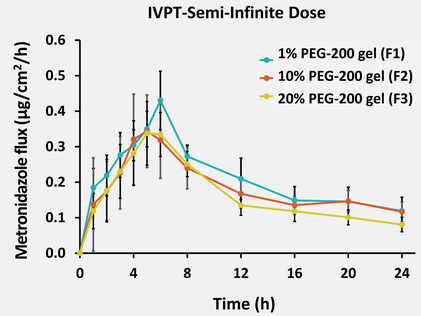

Figure 3: Flux profiles of metronidazole gels using a semi-infinite dose (n=6 replicates per skin donor; 3 skin donors; data presented as mean of 3 donor data ± SEM)

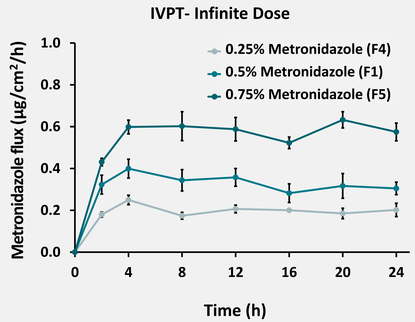

Figure 4: Flux profiles of metronidazole gels using an infinite dose (n=6 replicates per skin donor; 3 skin donors; data presented as mean of 3 donor data ± SEM)

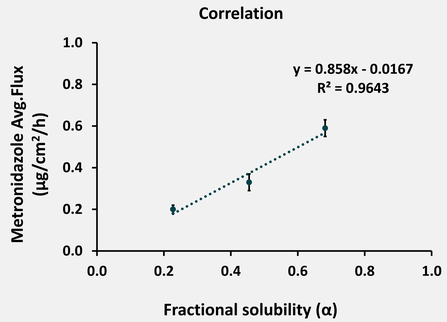

Figure 5: Correlation of flux vs. fractional solubility of metronidazole gels (n=3, mean ± SEM)

CONCLUSIONS

The current study suggests that it may be feasible to utilize fractional solubility profiles in conjunction with IVPT to evaluate the impact of quantitative differences in inactive ingredients on performance of topical products during evaporative metamorphosis.

However, additional research with multiple active and inactive ingredients is necessary to develop and generalize such methodologies.

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