Impact of quantitative differences in an inactive ingredient on the performance of topical products containing lidocaine or diclofenac sodium

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S. Rangappa[1], P. Ghosh[2], Y. Jiang[2], S. G. Raney[2], S. Narasimha Murthy[1,3]

[1]Topical Products Testing, Oxford, MS 38655, USA
[2]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
[3] Institute for Drug Delivery & Biomedical Research, Bangalore, Karnataka, India

CONTACT INFORMATION: murthygroup@gmail.com, testingtopicals@gmail.com

PURPOSE

Evaporative metamorphosis of topical products can lead to significant changes in the quantitative composition of the formulation. As the solvent(s) evaporate, the concentration of solubilized drug increases in the diminishing amount of solvent(s), typically up to the saturation solubility of the active pharmaceutical ingredient (API). The dynamic change in the fractional solubility or degree of saturation (α) of the API may impact the bioavailability of the API from a topical product. α is used in the current study as a measure of the thermodynamic activity; 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. Previously, we demonstrated that it may be feasible to utilize α vs time profiles, in conjunction with in vitro permeation testing (IVPT), to evaluate the impact of quantitative differences in inactive ingredients on the performance of topical products using metronidazole topical gels as a model system. The purpose of the current study is to assess the generalizability of the phenomenon by studying additional APIs, i.e., lidocaine and diclofenac sodium, which, compared to metronidazole, are expected to have more substantial differences in the α profiles in response to changes in excipient concentration.

METHOD

For lidocaine and diclofenac sodium, topical gels (0.25% and 0.5% w/w, respectively) comprised of polyethylene glycol (PEG-200), ethylene-diamine-tetra acetic acid (EDTA), sodium benzoate, hydroxyl ethyl cellulose and water were manufactured. The concentration of PEG-200 was varied across the formulations from 1% to 20% w/w. The saturation solubility of lidocaine and diclofenac sodium in PEG-200: water binary solutions was determined (n=3). An 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 the API (n=3). Finally, a semi-infinite dose IVPT study was performed across human cadaver skin using Franz diffusion cells (n=3 skin donors, 6 skin sections 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. Correlation of the degree of saturation profile and the IVPT profile was investigated.

RESULTS

The saturation solubility of each API greatly increased as the PEG-200 concentration increased from 0% to 100% in the PEG-200: water binary solutions.

Lidocaine **Saturation solubility**

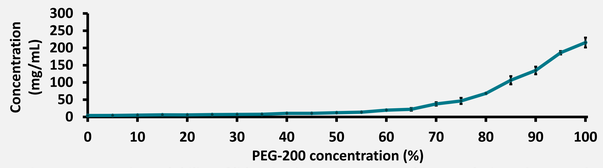

Figure 1: Saturation solubility of lidocaine in PEG-200: water binary solutions (n=3 ± SD)

Diclofenac Sodium

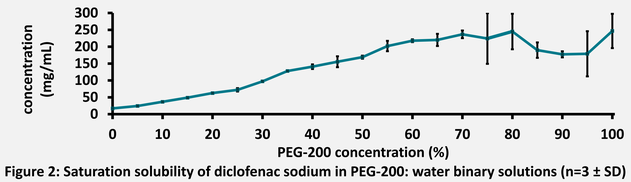

Figure 2: Saturation solubility of diclofenac sodium in PEG-200: water binary solutions (n=3 ± SD)

The in situ drying studies indicated that there was a greater change over time in the α profile for each API in the 1% PEG-200 gel compared to the 10% PEG-200 gel and 20 % PEG-200 gel. More specifically, a relatively rapid increase was observed in the degree of saturation profile for each API in the 1% PEG-200 gel compared to the other two gels.

In Situ Drying Study

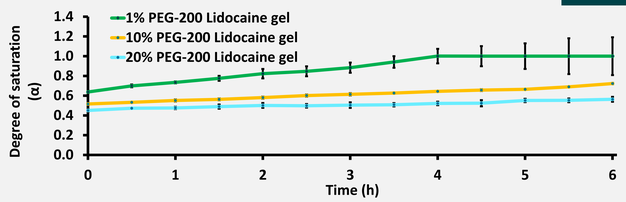

Figure 3: Degree of saturation profiles of lidocaine in the PEG-200 gels (n=3 ± SD)

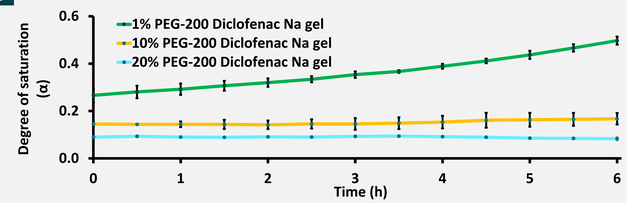

Figure 4: Degree of saturation profiles of diclofenac sodium in the PEG-200 gels (n=3 ± SD)

In alignment with the observation in the in situ drying study, the IVPT flux profiles for each API in the 1% PEG-200 gel were higher compared to compared to the other two gels.

IVPT

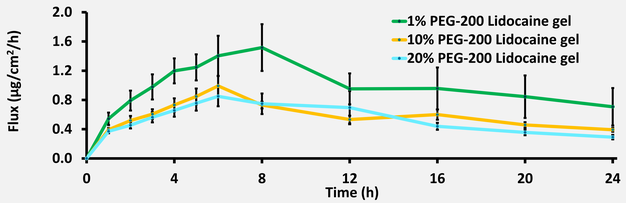

Figure 5: Flux profiles of PEG-200 Lidocaine gels using semi-infinite dose (n=6 replicates per donor; 3 donors; data presented as mean ± SEM)

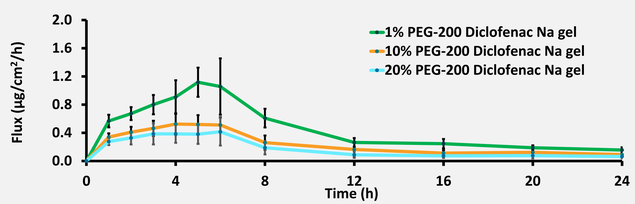

Figure 6: Flux profiles of PEG-200 diclofenac sodium gels using semi-infinite dose (n=6 replicates per donor; 3 donors; data presented as mean ± SEM)

A relatively linear correlation was observed between the $AUC_{0\text{-}6h}$ (α profile) and the $AUC_{0\text{-}6h}$ (obtained from IVPT flux profile) for lidocaine gels. For the diclofenac sodium 10% and 20% PEG-200 gels, the α was relatively constant over the 6 hours, and correlation was not observed.

Correlation Plots

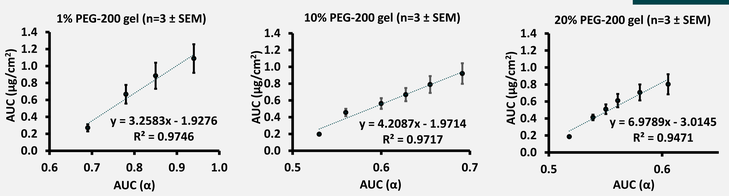

Figure 7: Correlation profiles of PEG-200 lidocaine gels (n=6 replicates per donor; 3 donors; data presented as mean ± SEM)

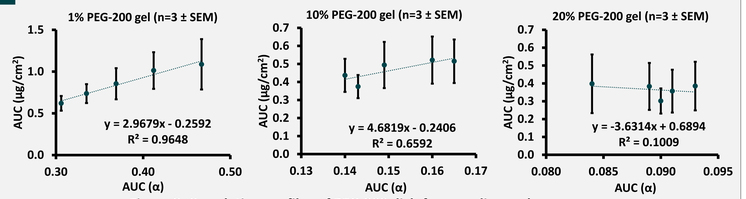

Figure 8: Correlation profiles of PEG-200 diclofenac sodium gels (n=6 replicates per donor; 3 donors; data presented as mean ± SEM)

CONCLUSIONS

The current study further supports that it may be feasible to utilize α profiles in conjunction with IVPT to evaluate the impact of quantitative differences in inactive ingredients on the performance of topical products with quantitative differences in formulation compositions, which may occur during evaporative metamorphosis. The data suggests that the time course of changes in α may be the primary determinant of formulation performance in certain topical gels. Additional research is underway to develop and generalize such methodologies for multiple inactive ingredients.

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Topical Products Testing LLC

Contact Information:
S. Narasimha Murthy Ph.D., Chief Scientific Officer, Topical Products Testing LLC, Oxford, MS
www.TopicalProductsTesting.com
Email: murthygroup@gmail.com, testingtopicals@gmail.com