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Evaluation of critical microstructural and performance attributes of azelaic acid topical gels

Md Ashraf-Uz-Zaman[1], Ann-Marie Ako-Adounvo[1], Megan Kelchen[2], Priyanka Ghosh[2], Muhammad Ashraf[1], Ahmed Zidan[1]

[1]Office of Pharmaceutical Quality Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER), U.S. FDA., [2]Office of Research and Standards, Office of Generic Drugs, CDER, U.S. FDA

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PURPOSE

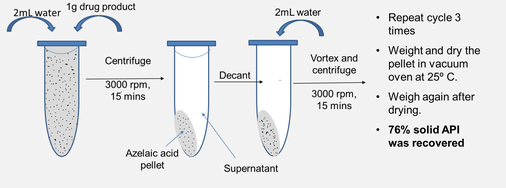
Azelaic acid topical gel (15% w/w) is a complex formulation in which azelaic acid is primarily suspended as uniformly dispersed irregularly shaped drug particles. This gel formulation may contain oily ingredients as humectants or cosolvents; however, the contribution of the oil phase to thermodynamic equilibrium and permeation of azelaic acid across skin is unclear. This study aimed at investigating the critical microstructural attributes of this gel formulation and their effects on release rate and dermal availability of azelaic acid following topical application.

METHODS

The marketed drug product (FINACEA (azelaic acid) topical gel, 15%) was mechanically separated into various phases to assess phase volumes and drug distribution of the active pharmaceutical ingredient (API). Microscopic images of azelaic acid gel were captured at multiple magnifications after staining with various oil soluble dyes to visualize the oil phase and determine its droplet size distribution. Differential scanning calorimetry (DSC) was used to evaluate the polymorphic form of the API. Morphologically directed Raman spectroscopy (MDRS) were also utilized to identify various phases of the gel and to evaluate particle size distribution (PSD) of dispersed solid phase of lab manufactured gel formulations and FINACEA. A multi-arm in vitro permeation test (IVPT) study (three donors and n=4) was designed to evaluate the contribution of the oil phase to the permeation of azelaic across human cadaver skin samples. In this IVPT study, azelaic acid permeation from gel formulations containing both oil and aqueous phase was compared with azelaic acid permeation from gel formulation containing only aqueous phase. The IVPT study also included arms to elucidate the role of solid particles on overall flux of azelaic acid permeation. The release of azelaic acid from these gel formulations (n = 4) over one hour was also investigated using an adapted in vitro release test (IVRT) method.

RESULTS AND DISCUSSION

Mass balance analysis: The results of the mass balance analysis suggests that 76% of azelaic acid is present in solid state with a wide PSD (Figure 5, Arm 5). A very small amount of azelaic acid was present in the oil phase, constituting less than 1% of the formulation, based on the phase separation process used in the current study.



Scheme 1. Phase separation process of FINACEA gel as part of the mass balance analysis

RESULTS AND DISCUSSION

Solid phase characterization: Microscopic images, Raman spectra, and DSC analysis confirmed that the sample processing steps used for the mass balance study for FINACEA does not appear to affect the polymorphic form of the API.

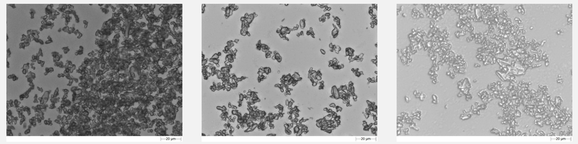


Image of gel as is | Image of diluted gel | Image of diluted gel on aluminum foil

Figure 1. Microscopic images of FINACEA

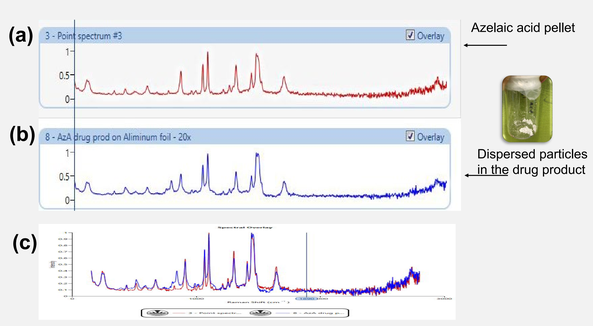


Figure 2. Raman spectra of (a) drug particles separated from FINACEA, (b) drug particles in FINACEA, and (c) overlap of (a) and (b) Raman spectra.

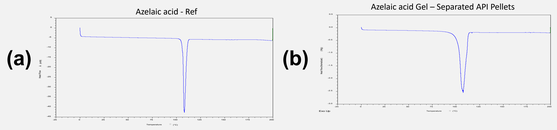


Figure 3. DSC of (a) reference azelaic acid, (b) azelaic acid particles separated from FINACEA.

Visualization of the oil globules: 8-Anilino-1-naphthalene sulfonic acid ammonium salt (ANSA) successfully stained the oil droplets for visual observation. Aggregates of oil globules were observed in FINACEA (diluted).

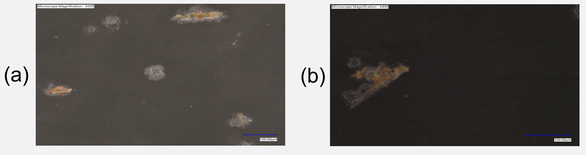
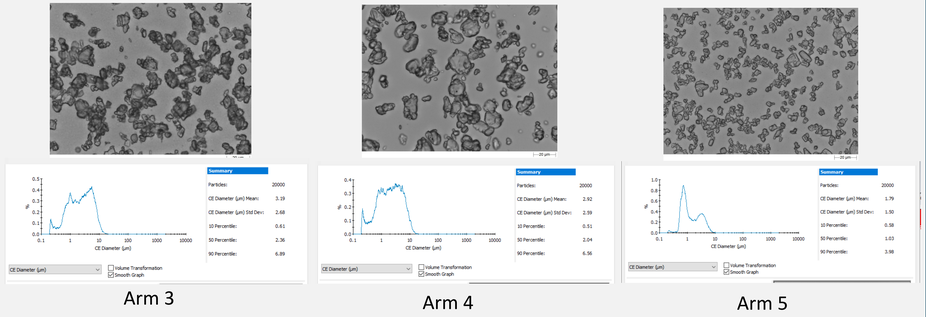


Figure 4. Microscopic images of continuous phase of FINACEA when stained with ANSA (a) 300X, (b) 400X

Particle size distribution of solid azelaic acid formulations: In-house azelaic acid gel formulations, along with FINACEA, were evaluated for PSD of the dispersed solid API. Particle size distribution of FINACEA (Arm 5) was found to be substantially smaller than that of the in-house formulations (Arm 3 and 4).



Arm 3 | Arm 4 | Arm 5

	Arm 3	Arm 4	Arm 5
D10 (µm)	0.61	0.51	0.58
D50 (µm)	2.36	2.04	1.03
D90 (µm)	6.89	6.56	3.98

Figure 5. Microscopic images and PSD of in-house formulations (Arm 3 and Arm 4) and the marketed drug product (Arm 5); Arm 3: In-house formulation that includes an aqueous phase, oil phase, and 15% (w/w) solid azelaic acid dispersed in formulation; Arm 4: In-house formulation that includes an aqueous phase and 15% (w/w) solid azelaic acid dispersed in formulation; Arm 5: FINACEA

Multi-arm IVPT study: An IVPT study evaluating the permeation of azelaic acid from various formulations (Arms 1-5 described in Figure legends)) was performed. Representative graphs of cumulative amounts and flux of azelaic acid over time are presented in Figure 6a and 6b, respectively.

The cumulative amounts versus time curve exhibited a biphasic permeation pattern for Arms 3, 4, and 5, characterized by an initial rapid permeation phase followed by a relatively slower phase, alike to a linear trajectory after 24 hours. However, for Arm 1 and Arm 2 (formulation fractions that lack suspended solid particles), the rapid initial permeation phase was minimal and brief.

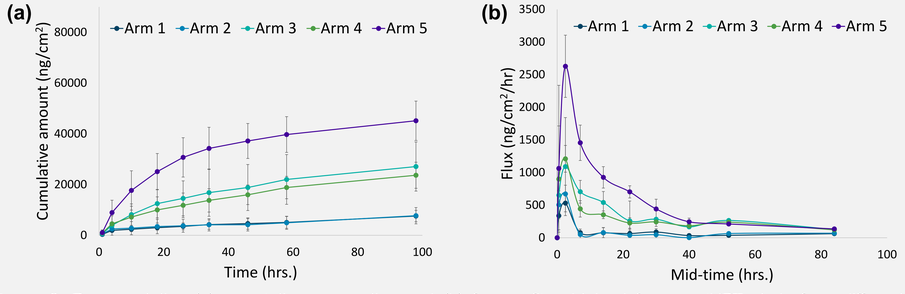


Figure 6. Representative (a) cumulative permeation and (b) flux profile obtained from an IVPT study from different formulations using static diffusion cells with aliquot sampling technique using three donors (n=4 replicates, Data are presented mean± SD). Arm 1: In-house formulation that includes an aqueous and oil phase saturated with dissolved azelaic acid; Arm 2: In-house formulation that includes an aqueous phase saturated with dissolved azelaic acid; Arms 3, 4 and 5: please see Figure 5.

RESULTS AND DISCUSSION

IVRT study: Typically, an IVRT study serves as a sensitive and discriminating tool for comparing the impact of variations in the inactive ingredients and manufacturing process on the release of the API from a given formulation

Preliminary IVRT studies conducted to evaluate the influence of differences in PSD on drug release (between Arm 3 and Arm 5) indicate that differences in PSD may influence drug release, which could in turn influence bioavailability as observed in the IVPT studies. However, additional studies would be necessary to confirm this observation.

CONCLUSIONS

Critical microstructure attributes, namely phase status, PSD, drug release and permeation, may be useful along with other formulation attributes in comparing the performance of gel formulations of azelaic acid for topical application. This evaluation scheme and results enhanced our understanding of the performance of azelaic acid gel upon topical application.

ACKNOWLEDGEMENT & DISCLAIMER

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