Impact of Formulation Differences on Performance of Topical Gels

T. Ramezanli[1], S. Rangappa[2], K. Phan[3], Y. Jiang[1], S. G. Raney[1], Y. Mohammed[3], S. Narasimha Murthy[2], M.C. Luke[1], P. Ghosh[1]

1 Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD
2 Topical Products Testing, Batesville, MS 38606, USA
3 Frazer Institute, The University of Queensland, Australia

*Contact information: tannaz.ramezanli@fda.hhs.gov; ying.jiang@fda.hhs.gov

INTRODUCTION

Changes in the components and composition of a topical formulation may influence its performance by impacting the physicochemical and structural (Q3) properties of the product and the thermodynamic activity (TA) of the active pharmaceutical ingredient (API).

The aims of the presented studies were to evaluate the impact of 1) modulation in the amount of solubility modifiers in topical gel formulations on API's bioavailability in the skin and 2) quantitative (Q2) changes in inactive ingredients on sensorial properties of the formulations.

METHODS

For the first aim, diclofenac sodium gels were made with varying amounts of either propylene glycol (PG) or polyethylene glycol (PEG) 400. In an in situ drying study, the contents of water, PG, and API remaining on the human skin were assayed (n=3). Fractional solubility was calculated as the ratio of API concentration to its saturation solubility (SS) in the formulation and were used to estimate TA. An in vitro permeation test (IVPT) was performed (3 skin donors, 6 replicates) with a dose of 300 mg/cm^2.

Table 1. Formulation table of the diclofenac gels with varying amounts of solubilizing agents (PG or PEG 400), shown in %w/w of compositions.

Ingredients	+ 25%	+ 10%	Reference	- 10%	- 25%
Diclofenac sodium	0.5	0.5	0.5	0.5	0.5
PG/PEG 400	50	44	40	36	30
Hydroxyethyl cellulose	1.75	1.75	1.75	1.75	1.75
Xanthan gum	1.00	1.00	1.00	1.00	1.00
Sodium benzoate	0.02	0.02	0.02	0.02	0.02
EDTA	0.01	0.01	0.01	0.01	0.01
NaOH 0.5N	0.4	0.3	0.4	0.2	0.3
Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100

For the second objective, several gels were prepared with various amounts of PG and ethanol and their relevant Q3 properties were measured. The sensorial perceptions of selected gels were evaluated in a human subject sensory panel test.

Table 2. Formulations of hydroxyethyl cellulose (HEC)-based vehicle gels in %w/w of compositions. Four gels including HEC-02, HEC-07, HEC-08, and HEC-10 (red colored) were selected out of 12 formulations for the sensory panel study.

Composition	HEC-01	HEC-02	HEC-03	HEC-04	HEC-05	HEC-06	HEC-07	HEC-08	HEC-09	HEC-10	HEC-11	HEC-12
Hydroxyethyl cellulose	1	**2.2**	3	5	2.2	2.2	**2.2**	**2.2**	2.2	**2.2**	2.2	2.2
Ethanol	20	**20**	20	20	25	30	**45**	**50**	20	**20**	20	20
Propylene glycol	15	**15**	15	15	15	15	**15**	**15**	20	**30**	40	50
2-Phenoxyethanol	0.8	**0.8**	0.8	0.8	0.8	0.8	**0.8**	**0.8**	0.8	**0.8**	0.8	0.8
Water	63.2	**62.0**	61.2	59.2	57.0	52.0	**37.0**	**32.0**	57.0	**47.0**	37.0	27.0

CONCLUSION

The current studies suggest that it may be feasible to utilize TA profiles in conjunction with IVPT to evaluate the impact of quantitative differences in inactive ingredients on the performance of topical gels. The relevant Q3 data such as zero sheer viscosity assessed in vitro may be valuable to predict changes in sensorial perception of the gels in vivo. Additional research is underway to develop and generalize such methodologies for multiple inactive ingredients and other semisolid dosage forms.

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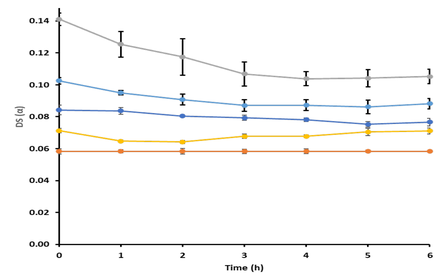
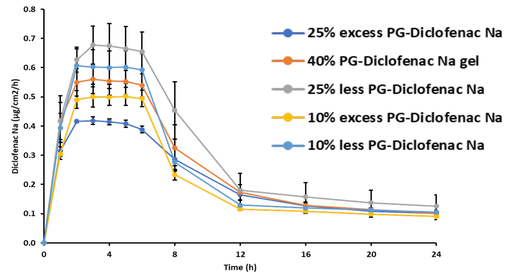
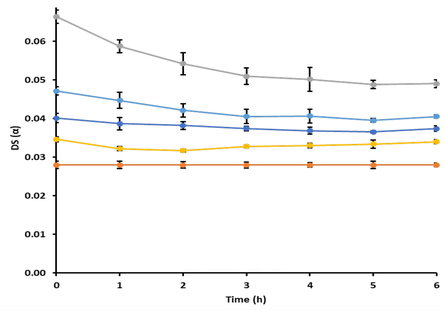
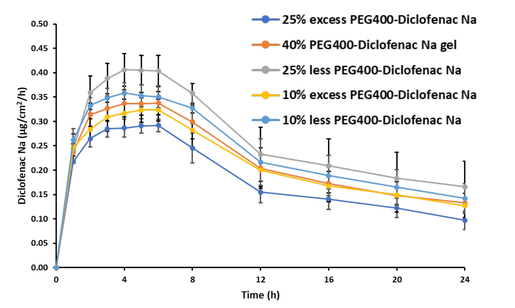
RESULTS

The saturation solubility of diclofenac sodium increased as the concentration of solubilizing agents increased from 0% to 80% in the PG: water and PEG 400:water binary solutions. The in situ drying studies revealed that the ±25% variations in PG or PEG 400, as opposed to ±10%, resulted in discriminated fractional solubility profiles for diclofenac sodium, compared to the reference gel. Subsequently, greater differences in bioavailability of diclofenac (as measured by the obtained IVPT studies) were observed from the ±25% PG or PEG 400 variant formulations (Table 3).

Table 3. Fractional solubility (thermodynamic activity) and flux permeation profiles of diclofenac sodium in the gels with PG or PEG 400 variants. Data are presented for thermodynamic activity as mean±SD (n=3), and for permeation flux as mean±SE (3 donors, 6 replicates).

Solubilizing agent	Thermodynamic activity data	IVPT Data
PG		
PEG 400		

The assessment of Q3 and in vivo sensory properties of HEC-based vehicle gels, suggests that overall, with increase in ethanol content in the gels, the evaporation rate of the formulations increased, and the gels were perceived to be less slippery by the subjects. A subset of the formulations that were found to be significantly different across numerous Q3 properties were selected for in vivo evaluation. For the formulations that were tested in vivo, the variations in both PG and ethanol content that were more than 25% compared to the reference gel, resulted in significant change in zero sheer viscosity and subsequently significant change in perception of stickiness (Figure 1).

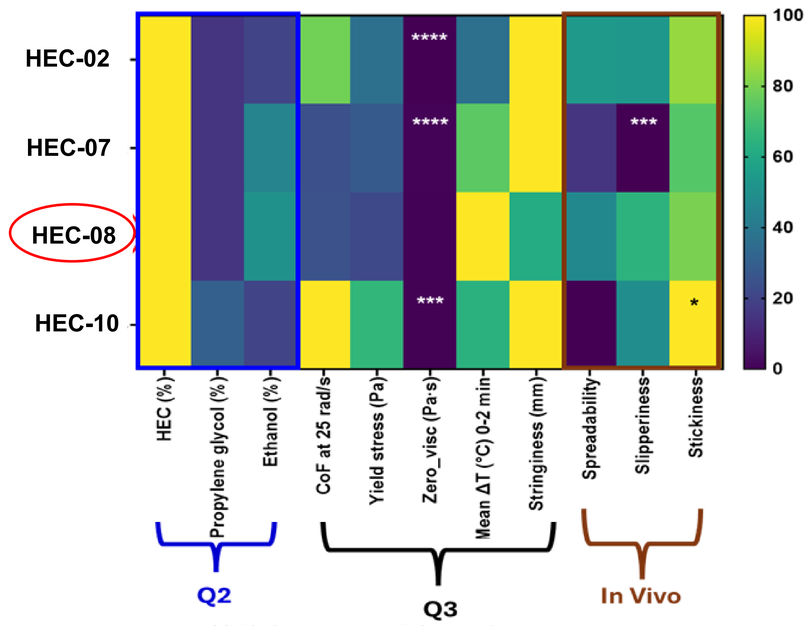


Figure 1. Changes in composition (Q2) for three HEC gel formulations in relation to the reference formulation, HEC-08 (circled in red); a subset of Q3 data normalized (in the range of 0 to 100) for different units including coefficient of friction (CoF), zero shear viscosity (Zero_visc), yield stress (rheological property), mean temperature different from 0 to 2 min (Mean ΔT (°C) 0-2 min), stringiness (texture properties); and three sensory parameters (spreadability, slipperiness and stickiness) assessed in sensory panel test. The number of "*" summarizes the p values/significant levels with "*" significant difference at p<0.05, "***" significant difference at p<0.0005, and "****" significant difference at p<0.0001 between the gels.