Critical quality attributes enhance understanding of skin sensory perceptions

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Introduction

In topical drug product development, a positive sensorial experience, when applying the product on the skin, can play a vital role in patient perception and acceptance. Although it is valuable to explore and understand how dermatologic formulation compositions (quantitative differences, Q2) impact sensory feelings, human sensorial panel tests can be pricey, and have challenges associated with training human subjects, and the outcomes can be subjective in nature. In this work, we aimed to study the possibility of predicting sensory attributes of topical semi-solid gels using in vitro instrumental tests characterizing physicochemical and structural critical quality attributes (CQAs-Q3), which may relate to the sensorial behaviour of products during use.

Method

Eight topical gels products manufactured with hydroxyethyl cellulose (HEC) or carbomer homopolymer (Carbopol® 980P (CBP)) were selected from 26 gel formulations to conduct sensory panel test (shown in Table 1) by using statistical analysis of the in vitro characterization data.

Specifically, for in vitro characterization, rheological assessments were carried out on an AR-G2 rheometer using steady-state controlled shear stress sweep test mode, at 32^{o}C and 500 µm gap with a 40 mm parallel plate. Texture properties of gel samples were examined by applying the texture profile analysis performed by a TA.XTplus texture analyzer with a cylindrical probe of 38.1 mm diameter. Frictional property of gels was characterized by using a HR1 Discovery Tribometer, TA Instruments with three-ball on plate geometry. An infrared thermal imaging (IRT)-based technique was used to assess in vitro cooling potential of the topical gels. The temperature dynamics of the area of interest were recorded at specific time intervals from 0 min (immediately after sample application) to 2 min of duration using IRT.

For in vivo sensory panel test, skin biophysical properties of 46 subjects (n=46, ethics ID number: 2020/HE001995) were firstly examined using a non-invasive Courage + Khazaka (C+K) electronic GmbH instrument, equipped with multiple probes. Then, subjects were trained on the concepts and assessment criteria of the 6 different sensory attributes (spreadability, cooling sensation, shine, slipperiness, stickiness, and smoothness) classified as during and after-feel sensations. To start the panel test, at time 0, 25 µL of each gel sample was placed onto a marked forearm area (19.6 cm^2) of subject, and spread by subject's forefinger at rotational speed of 1 circle/s for 15 s. After 15 s, subjects stopped spreading, and assessed cooling sensation, shine and slipperiness. The after-feel attributes of stickiness and smoothness were evaluated after waiting for 1 and 2 min, respectively. Gel sensorial attributes were evaluated using a continuous 1-9 scale, representing from very low (1) to very high (9) intensity.

The results from the in vivo sensory panel tests were compared with the in vitro characterization data and formulation composition of the gels to understand the correlation (if any) between formulation, in vitro characterization data and sensory observations.

Table 1: (a) Formulations of hydroxyethyl cellulose (HEC) and **(b)** carbomer homopolymer (Carbopol® 980P (CBP)) gels in %w/w of compositions. Eight gels including HEC-02, HEC-07, HEC-08, HEC-10, and CBP-01, CBP-02, CBP-10, CBP-11 (red colored) were selected out of 26 formulations for the sensory panel study.

(a)

Composition (%w/w)	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

(b)

Composition (%w/w)	CBP-01	CBP-02	CBP-03	CBP-04	CBP-05	CBP-06	CBP-07	CBP-08	CBP-09	CBP-10	CBP-11	CBP-12	CBP-13	CBP-14
Carbopol 980	0.5	0.25	0.65	0.25	0.25	0.5	0.5	0.5	0.1	1.0	0.5	0.5	0.5	0.5
Ethanol	-	-	-	-	-	-	20	-	-	-	35	50	10	-
Propylene glycol	15	15	15	25	35	35	15	50	15	15	15	15	15	25
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	84.4	84.6	84.2	74.6	64.6	64.4	64.4	49.4	84.7	82.5	49.2	34.4	74.3	74.2

q.s.: quantum satis/the amount which is enough

Results

The determined skin biophysical parameters (by C+K instrument) of the 46 subjects exhibited high interindividual variability, which could represent a true sample from the general population. The recorded intensity scores of 6 sensory attributes for the 8 examined topical gels with 2 blinded replicates are depicted as spider graph (Figure 1). It can be seen that the two sets of control samples (HEC-08 and CBP-02, blinded replicates) were perceived consistently, by the subjects even though there are huge differences in skin biophysical properties among 46 subjects.

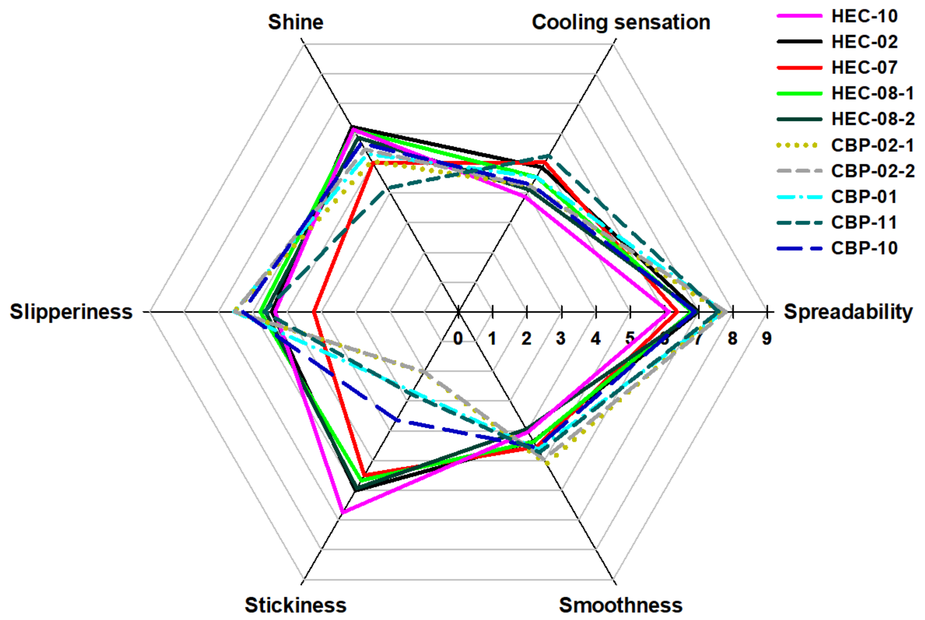

Figure 1: Spider diagram of sensory scores of spreadability, cooling sensation, shine, slipperiness, stickiness and smoothness attributes assessed at different time points using 9-point hedonic scale of examined hydroxyethyl cellulose (HEC) and carbomer homopolymer (Carbopol® 980P (CBP)) gels including HEC-02, HEC-07, HEC-08, HEC-10, CBP-01, CBP-02, CBP-10, CBP-11 (codes and formulations showed in Table 1). HEC-08 and CBP-02 were two blinded replicates named as HEC-08-1, HEC-08-2 and CBP-02-1, CBP-02-2.

Cooling sensation, shine and smoothness sensory attributes of gel formulations were perceived with only slight differences across the 8 gels. However, dissimilarities in spreadability, slipperiness and stickiness perceptions between the gels were sensed well by the subjects, which meaningfully correlates with the formulation composition and in vitro characterization data. The HEC gels, with higher coefficient of friction (CoF) values (Figure 2A), were ranked lower in intensity of spreadability as compared to CBP samples (Figure 2B). Additionally, the HEC gels were observed with lower perception scores of slipperiness than those of CBP gels overall, as shown in Figure 1. The higher ethanol content in HEC gel formulations related directly with a higher evaporation rate (Figure 2A) and could cause a remarkable impact on decreasing the feeling of slipperiness due to leaving a dried solid film on the applied skin area. Also, HEC gels were perceived stickier than CBP gels, which could be linked to higher friction and stringiness values (of tribological behaviour and texture profile) of the HEC gels (Figure 2A) compared to CBP gels (Figure 2B).

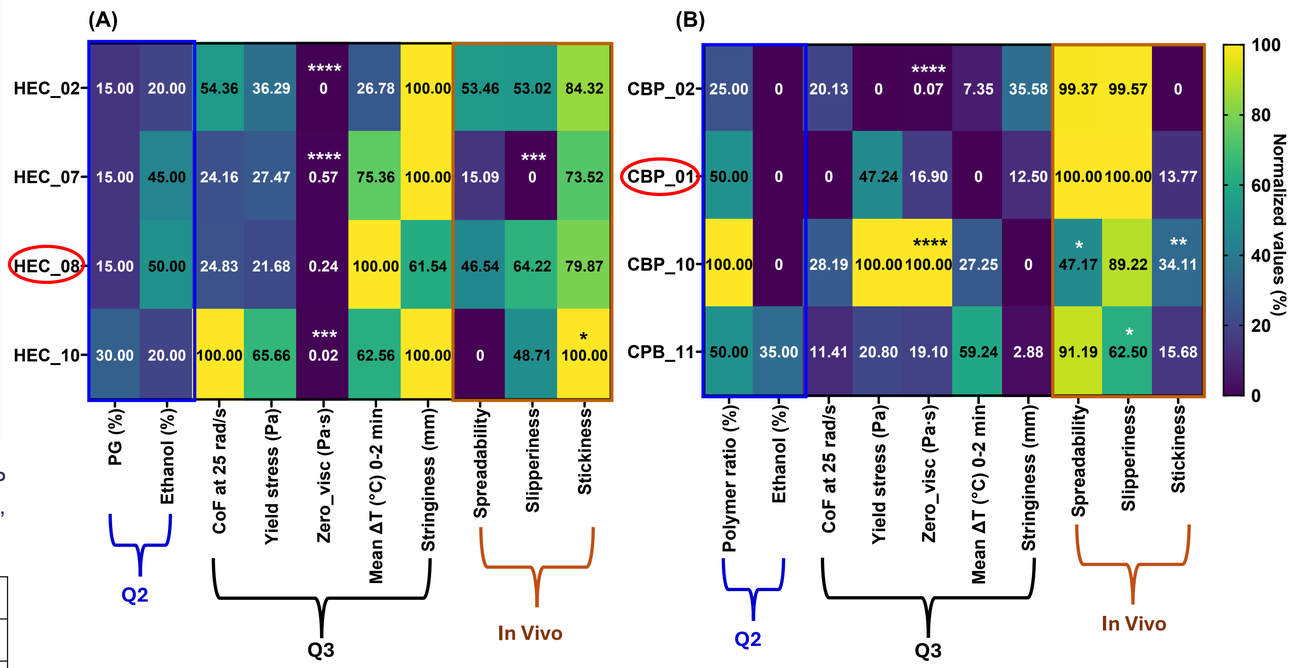

Figure 2: Ingredient concentration changes (Q2) in relation to the reference (circled in red), a subset of CQAs-Q3 normalized for different units including coefficient of friction (CoF) (tribology), zero shear viscosity (Zero_visc), yield stress (rheological property), mean temperature different from 0 to 2 min (Mean ΔT (°C) 0-2 min), stringiness (texture properties) and three sensory parameters (spreadability, slipperiness and stickiness) assessed in in vivo panel tests. Eight topical gels of hydroxyethyl cellulose (HEC) and carbomer homopolymer (Carbopol® 980P (CBP)), ethanol, propylene glycol (PG) concentration, coded as HEC-02, HEC-07, HEC-08, HEC-10 (Figure 2A), CBP-01, CBP-02, CBP-10, and CBP-11 (Figure 2B) were selected from 26 gel formulations (Table 1) by using statistical techniques to summarize characteristics according to their formulation composition (Q2) and a subset of (Q3) attributes. The number of "*" summarizes the p values/significant levels: without "*" meaning p>0.05 or no significant difference, with "*" significant difference at p<0.05, "**" significant difference at p<0.01, "***" significant difference at p<0.0005, and "****" significant difference at p<0.0001 between the gel formulations.

Conclusion

The findings show that the CQAs assessed instrumently in vitro may be valuable in understanding most of the sensorial characteristics of topical gel formulations assessed in vivo. Significant differences in instrumental attributes, such as rheological, tribological behaviour and texture properties are likely to be perceptible to human subjects. Therefore, overall, the research findings suggest that data from selected instrumental techniques to evaluate CQAs may be predictive of sensory properties of topical products.

Learning objectives

Demonstrate potential instrumental approaches to assess CQAs to describe and predict skin sensory attributes of topical gels. Evaluate the impact of various formulation changes on sensorial attributes of topical gel products.

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