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Clinical Relevance of Rheological Characteristics of Topical Creams: Relationship Between Yield Stress and Dose Spreading Area

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PURPOSE

The rheological behavior of a semisolid topical product is an important quality attribute that has the potential to influence the spreading characteristics of the product, and thus its performance. The rheological properties of semisolids are known to be dictated by their microstructure and composition. The yield stress of the products is known to determine the minimum shear stress that needs to be applied on the product to render it flowing or spreadable (i.e. spreadability). During application on the skin, the rheology of the product as it is reduced to a thin film would determine its spreading area. However, there is dearth of information in the literature describing the relationship between these rheological properties and the spreading characteristics of topical drug products. The purpose of the present research was to assess the clinical relevance of rheological characterizations for topical cream products, particularly in relation to spreadability.

METHOD

In the first group, the rheological studies were performed at 32° C using a TA HR2 rheometer (TA instruments, DE) equipped with 25 mm parallel plate. The studies involved three acyclovir cream 5% (Zovirax®) Reference Products (marketed in the U.S., U.K. and Austria) and two acyclovir cream 5% Test Products marketed in Austria (Aciclostad and Aciclovir 1A). There were known differences between the Reference and Test Creams in terms of physicochemical and microstructural product quality (Q3) attributes, and none of these five creams were qualitatively (Q1) and quantitatively (Q2) the same. In the second group, a set of, Q1 and Q2 identical oil-in-water creams were prepared by implementing different manufacturing protocols to induce differences in (Q3) attributes. The spreading area for all the creams in both groups was measured on five human volunteers using 30 mg of formulation/site.

RESULTS

First study on Commercially available non Q1/Q2 acyclovir 5% cream formulations

Product	Yield Stress, Pa
Zovirax (USA)	50
Zovirax (UK)	300
Zovirax (Austria)	300
Aciclostad	100
Aciclovir-1A	100

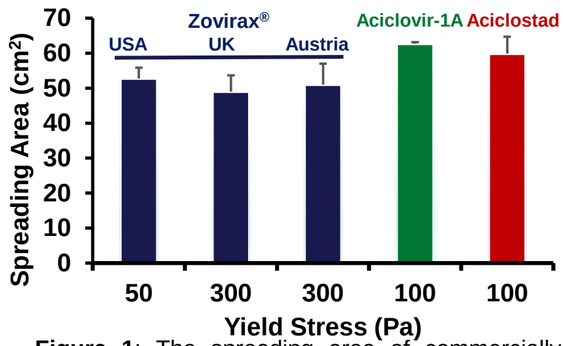

Figure 1: The spreading area of commercially available 5% w/w acyclovir creams (n=18 ± SEM)

The yield stress values for acyclovir cream 5% products varied from 50-300 Pa. The spreading area of the acyclovir products from the first group ranged between 49 - 62 cm^2 showing no significant correlation with yield stress. Notably, the spreading area was relatively consistent among the Reference Creams (~ 50 cm^2) and among the Test Creams (~ 60 cm^2). In the second study, the yield stress of the oil-in-water creams varied from 20-200 Pa and the spreading areas were in the range of 36 - 43 cm^2. The spreading area in these creams showed a correlation between the yield stress value and the spreading area, with a shallow slope of -0.04.

Second study on manufactured Q1/Q2 acyclovir 1% cream formulations

Ingredients (O/W)	Quantity (%)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69

Formulation	Globule Size (µm)	Yield Stress (Pa)
F1	11.37 ±7.03	20
F2	7.41 ±2.19	100
F3	2.98 ±1.25	90
F4	1.71±0.41	100
F5	4.30±1.33	60
F6	4.36±0.88	200
F7	4.25±0.99	120

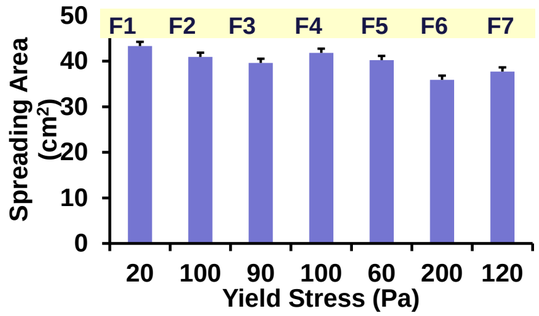

Figure 2: The spreading area of manufactured Q1/Q2 creams (n=18 ± SEM)

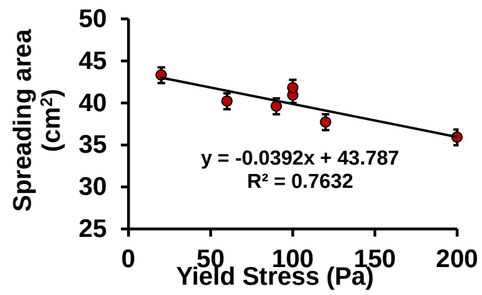

Figure 3: The relationship between yield stress and spreading area (n=18 ± SEM)

CONCLUSION

Compositional (Q1/Q2) differences between the products could significantly influence the relationship between the yield stress and spreading area of the product. When the products are of identical composition (Q1/Q2 the same), the Q3 attributes appear to dictate the rheological characteristics. Although the yield stress is thought to be one of the major determinants of spreadabilty for a semisolid, and of the corresponding area of spreading of the product, these results illustrate that even an order of magnitude difference in the yield stress may not result in a significant difference in the spreading area, suggesting that while yield stress may be an important quality attribute, it may not be predictive of the spreadability of a cream in clinical use.

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