AAPS PharmSciTech, Vol. 9, No. 1, March 2008 (© 2007)
DOI: 10.1208/s12249-007-9009-5

Brief/Technical Note

Spreadability Measurements to Assess Structural Equivalence (Q_3) of Topical Formulations—A Technical Note

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Received 20 June 2007; accepted 12 September 2007; published online 12 January 2008

KEY WORDS: Q_3 equivalence rheology; spreadability; topical formulations; vane method.

INTRODUCTION

Due to the disadvantages associated with comparative clinical trials (e.g., extensive time and cost involved), *in vitro* methods are of high interest for evaluating the bioequivalence of topical formulations (1,2). The analysis of spreadability is one such method that can help assess bioequivalence of formulations that are qualitatively (Q_1) and quantitatively (Q_2) equivalent. The FDA will usually not request additional bioequivalence testing for solution formulations that are Q_1 and Q_2 equivalent. However, semi-solid formulations that are Q_1 and Q_2 equivalent may have differences in the physical attributes and state of the product (arrangement of matter, aggregation) that reflect changes in the manufacturing method or the physical state of starting materials. Thus, structural similarity (Q_3) can be defined as a third aspect of equivalence (3). The rheology of semi-solids is sensitive to changes in the microstructure and is potentially able to detect Q_3 differences. In addition, the viscosity of a topical formulation will affect its application and delivery of the active agent to and across the skin, resulting in variance in its therapeutic performance.

Subjective spreadability has been shown to be related to rheology through a material's yield stress, the minimum shear stress required to initiate flow (σ_o). Specifically, the spreadability is inversely proportional to σ_o. (4,5) Extensive studies have been completed for the yield stress analysis of semi-solid foods that can be extended to semi-solid pharmaceutical formulations (4,6–8). In this study, the *vane method* has been employed to determine the yield stress of Q_1/Q_2 topical formulations in an attempt to determine if they were Q_3 equivalent. The vane method (Fig. 1) involves the immersion of the blades of a vane into a sample followed by slow rotation at a constant RPM until the torque exerted on the vane reaches a maximum value and the sample begins to flow. Torque *vs.* time curves are used to determine yield stress where M_o is the maximum torque exerted on the vane by the fluid.

MATERIALS AND METHODS

The materials used in these studies were four topical formulations containing the active ingredient Econazole Nitrate 1%, and these were obtained from the Food and Drug Administration. All three of the generic formulations were previously determined to be equivalent to the innovator product in clinical bioequivalence studies. In these studies, the creams were referred to as formulations A, B, C and D, where formulation C is the innovator and formulations A, B, and D are generic brands. These rheological flow tests were carried out on a Brookfield RV DV III + Digital Rheometer using a Brookfield cone (CPE 52) and plate apparatus. The rheological vane method experiments were carried out on a Brookfield RV DV III + Digital Rheometer using a vane spindle attachment.

Flow Curves Procedure

Flow curves for these formulations were constructed by discharging 0.5 mL of each formulation onto the center of the plate. The gap was then set for the cone and plate apparatus so that the cone was at an appropriate and consistent distance from the plate for each trial. The rheometer was then

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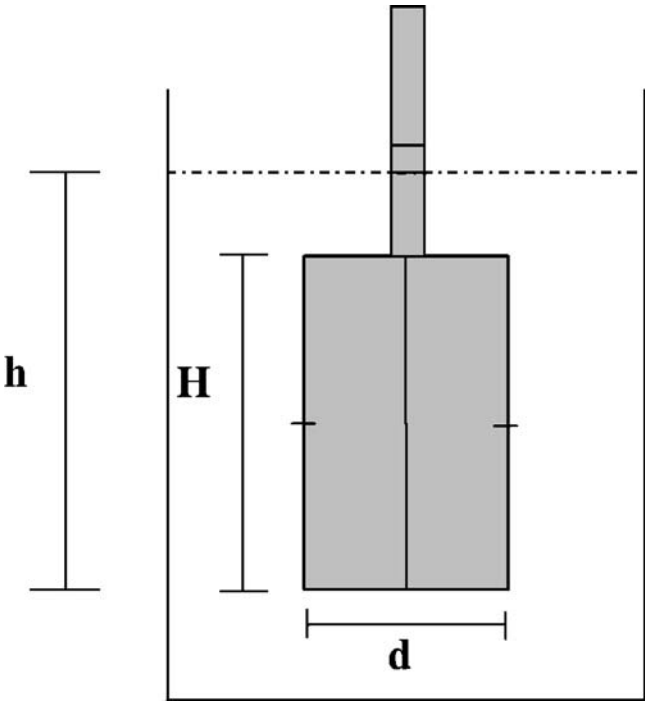

Fig. 1. A vane, used in the vane method, with blade height of H and blade diameter of d with the height (h) of vane immersed in a fluid. This geometry is used along with the maximum torque value obtained with the vane method to obtain the yield stress of the fluid

programmed with increasing RPM (shear rate) over a range of 1 to 24 s^{-1} at constant temperature (25°C).

Vane Method Procedure

Glass vials (~60 mL) were filled with the formulations and allowed to settle for three days before running trials. A vane spindle of known geometry was attached to the rheometer and the samples were centered with respect to the vane spindle and elevated to full immersion. The % torque over time was recorded and the average for each formulation (n=3) was converted to torque using a constant value given for the specific spring in the rheometer. A plot of torque *versus* time was constructed for each formulation that gave M_o which was converted to yield stress using the following equation (4,8):

$$\sigma_0 = \frac{2M_o}{\pi d^3}\left(\frac{h}{d}+\frac{1}{3}\right)^{-1} \quad (1)$$

where h and d are the height of the vane immersed and diameter of the vane, respectively.

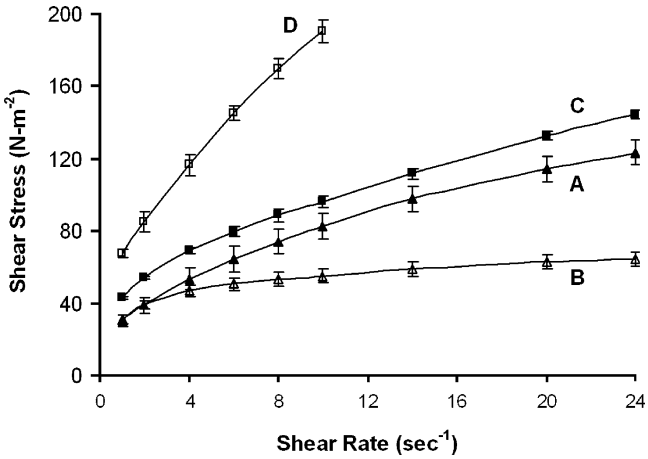

Fig. 2. Plot of shear stress (N m^{-2}) *vs* shear rate (s^{-1}), flow curves, of all four formulations at T=25°C (Error=±1 SD, n=3). This slope of the curves gives the viscosity of the fluid at each shear rate. In this figure, formulation C is the innovator, while formulations A, B and D are generic topicals

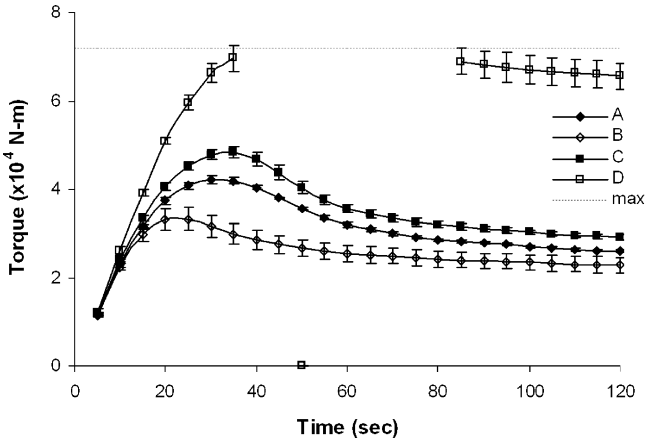

Fig. 3. Torque (N m) *vs* time (s) data from vane method for all formulations (Error=±1 SD, n=3). In this figure, formulation C is the innovator, while formulations A, B and D are generic topicals. The maximum torque value of the spring used in the RV DV III + rheometer is 7,187 N m and is included in the plot (*dotted line*)

RESULTS AND DISCUSSION

Shear stress was plotted against shear rate as shown for all four formulations in Fig. 2. This plot shows that all of formulations are pseudoplastic (viscosity decreases with increasing shear). Formulation D had the greatest resistance to flow while formulation B was the least viscous. Figure 3 shows the torque-time plots of all formulations at 0.5 RPM. The average M_o value of Formulation D exceeded the maximum torque of the rheometer (7.19×10^{-4} N m; dotted line); this formulation had the greatest yield stress (lowest spreadability). Conversely, Formulation B had the lowest M_o and yield stress, thus the highest spreadability.

Table I. Summary of the experimental results for maximum torque (M_o), yield stress (σ_o) and viscosity (μ) from flow curves and vane method (mean±1 SD; n=3)

Formulation	M_o (x10^4 N m)	σ_o (N/m^2)	μ (N s/m^2)
A	4.23+0.09	56.3+1.2	8.29+0.71
B	3.32+0.27	44.3+3.6	5.51+0.37
C	4.83+0.13	64.4+1.7	9.61+0.29
D	>7.19	>95.7	19.07+0.64

The maximum torque, yield stress (spreadability), and viscosity values of the four formulations are shown in Table I. The maximum torque values (M_o) were obtained from the peak of the torque-time data for each formulation (Fig. 3) and converted to yield stress values (σ_o). The apparent viscosity values (μ) were taken from the slope of the flow curves (Fig. 2) at a shear rate of 10 s^{-1}. The differences in the values for these Q_1 and Q_2 equivalent topical formulations may have resulted from differences in their method of manufacture as well as differences in their excipients and storage conditions.

Q3 Equivalence Analysis

Using 20% of the innovator's mean as the definition of Q_3 equivalence,(in bioequivalence studies, 20% is often chosen; 9) the average values for each generic formulation were compared to the corresponding innovator's values. Based on this, the acceptable equivalence ranges are between 3.86×10^{-4} and 5.79×10^{-4} N m for yield stress and between 51.5 and 77.3 N/m^2 for viscosity. Using this definition, only formulation A's viscosity and yield stress are equivalent to that of the innovator (C). Therefore, the data supports the Q_3 (structural) equivalence between only formulations A and C.

SUMMARY AND CONCLUSIONS

If waivers of clinical bioequivalence studies between formulations that are Q_1 and Q_2 equivalent were to be considered in the future, then evaluation of Q_3 equivalence would be needed to support a request for a waiver. The vane method is a useful technique to assess the spreadability of topical formulations and to assess structural differences (Q_3) among formulations that are Q_1 and Q_2 equivalent. The vane method has been shown to be a sensitive measure of structural differences of topical formulations. With 20% of the innovators mean as the definition of equivalence, only formulation A was determined to be Q_3 (structural) equivalent. However, all three of the generic formulations were previously determined to be equivalent to the innovator product in clinical bioequivalence studies. Thus in these studies, equivalence in spreadability to within 20% as determined via the vane method was shown not to be necessary for products to be bioequivalent. The correlation of these spreadability differences with *in vivo* performance, may be used to help establish reasonable acceptance limits for the use of the vane method as part of the evaluation of Q_3 equivalence of generic topical products.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support of the National Science Foundation/Research Experience for Undergraduates (Grant DMR-0097692) and the University of Kentucky, College of Pharmacy Summer Undergraduate Research Program.

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