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The rheological properties of pharmaceutical foam: Implications for use

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Abstract

We have evaluated various aerosol foam types having different compositions and related physico-chemical properties. The foams assessed were hydroethanolic, emulsion, and aqueous based. Composition, appearance, loss on drying, and rheological properties were analysed to characterise the macrostructure of the different aerosol foams. To confirm the validity of the vane rheological technique used, and facilitate intuitive understanding of the data, similar data were collected for a commercial shaving foam. Of the physico-chemical parameters that were evaluated, rheological properties were distinct among hydroethanolic, emulsion, and aqueous aerosol foam types. The results indicate that beyond composition differences, physico-chemical differences do exist between these aerosol foam types. The viscoelastic flow properties provided an insight of the macrostructure of materials that have been foamed.

Keywords: Aerosol foam; Hydroethanolic; Emulsion; Aqueous; Rheology; Topical drug

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1. Introduction

Aerosol foam (or mousse) is a topical dosage form, having physico-chemical properties that are both unique and shared with more conventional dosage forms, such as ointment, cream, gel, and solution. While consumers may apply a wide range of topical dosage forms, as found in both cosmetics and pharmaceuticals, their decision to use a particular dosage form may be dictated by intended use, site of application, expected performance, and expected side-effect profile.

The aerosol foams discussed in this article are those used in pharmaceutical applications and not those used in simple surfactant solutions. Therefore, the bubble stability and rheological properties of aerosol foams was investigated. While bubble stability and rheological properties are important aspects of foam properties; the ability of the foam to deliver the drug active contained within the foam is also important and has been dealt with elsewhere (Sciarra, 1996; Johnsen, 2003; Purdon et al., 2003).

Aerosol foams were first mentioned by Boe (1950) and by Spitzer (1953) in their patents for lather forming composition and the use of surface active agents as emulsifying agents for certain propellants in aqueous media, respectively. During the 1960s breakthroughs in aerosol foam technology included the development of “quick break” foams (Anon., 1960) and the theory of formulation and formation of aerosol foams (Richman and Shangraw, 1966a,b).

Ideally, from a user perspective, pharmaceutical aerosol foam, once expelled from a can will have the following properties related to foam structure:

(i) Stable on standing and no collapse or drainage will occur during an acceptable period post-expelling from an aerosol can.
(ii) Can be manipulated by the user to the extent that foam can be lifted off a surface and applied to the skin, typically by hand or using an applicator.
(iii) Persists while being manipulated.
(iv) Is easily destroyed when rubbed into the skin, i.e., low shear.
(v) Can deliver drug across the skin as effective if not better than conventional dosage form of creams and ointments.
(vi) Once sheared and spread on the skin, will typically have less residue than creams and ointments.

The properties of foam will depend largely on the composition of the base formulation, as well as the type and level of propellant. Despite limitations arising from the explanation of

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foam composition and aerosol propellant properties, the following definition of aerosol foam is being applied in this paper: "A dosage form containing one or more active ingredients, surfactants, aqueous or non-aqueous liquids, and the propellants. If the propellant is in the internal (discontinuous) phase (i.e. of the oil-in-water type), a stable foam is discharged, and if the propellant is in the external (continuous) phase (i.e. of the water-in-oil type), a spray or quick breaking foam is discharged" (FDA CDER Data Standards Manual—Dosage Form).

Aerosol foams are a unique dosage form in that the properties of the dosage form within the container are different from that expelled from the container. The properties of the container (e.g., the valve and its orifice size and/or the actuator) can also influence the foam structure itself.

The aforementioned definition of aerosol foams does not address the physico-chemical differences between foam types. The location of the propellant is of great importance to the production of the foam. Furthermore, aerosol foams are typically formed with liquefiable gases and not compressed gases such as nitrogen.

Propellants are emulsified and not solubilized (Richman and Shangraw, 1966), thus indicating that propellants are incorporated into the base formulation if compatible. A unique property of aerosol foams is that the surfactant responsible for producing the emulsion in the container also plays a role in stabilizing the film surrounding each foam bubble. There are at least three propellants (i.e., liquefied gases) that have been used in aerosol foams, each behaving slightly differently based on their properties.

Aerosol foams are typically made up of a base composition comprising typical materials that can produce simple solutions or emulsions and would also include the drug. Addition of the base composition to a can and pressurisation with a liquefiable propellant can create foam structures with different properties depending on the base composition.

The basic building blocks of a foam formulation are bubbles (Shaw, 1992). Technically, bubbles can be described as polyhedral or spherical films enveloping gaseous cores. To maintain a bubble's physical form, the surrounding film must be sufficiently cohesive to withstand the pressure exerted by the trapped gas. In aerosol foams, the surrounding film is typically comprised of the "aerosol base". The aerosol base can be a liquid, semi-solid or even a solid at room temperature and can share the physico-chemical characteristics that are typical of conventional vehicles (e.g., cream and gels). Aerosol foams can be categorized as emulsion or quick-breaking based on their physical characteristics (Abram and Tomlinson, 2001). A two-phase oil-in-water emulsion foam provides the patient with a pharmaceutical product that has characteristics of being non-drying, since it does not contain alcohol. The quick-breaking hydroethanolic foams are typically a single-phase composition and contain a significant amount of ethanol. Depending on the ratio of water to ethanol, the temperature at which the foam breaks can be controlled. A typical characteristic of the hydroethanolic foam is that it has a low viscosity inside the pressurized container.

Foams exhibit a variety of important flow characteristics, such as yield stress, elastic (solid-like) behaviour at small deformation, and a shear rate dependent viscosity when the yield stress is exceeded (Princen and Kiss, 1986). These rheological properties are critical for the functionality of the foam, and it is possible that, like for many other multi-phase systems (slurries, emulsions, etc.), changes in the basic recipe engender changes in the flow (rheological) properties of each recipe. Foams tend to have a high viscosity compared with the bulk fluid, a yield stress that enables them to maintain their structure for prolonged periods, and an elasticity that allows them to deform from, and recover to, their original configuration. We will measure these properties with a view to comparing them for the different foam compositions tested.

Rheological measurements for foams and concentrated emulsions have been problematic, because foams have a friable structure and can often be composed of large bubbles. Typical measurement geometries have a gap size of between tens of micrometers (shallow angle cone and plate geometry) to 1 or 2 mm (concentric cylinder or plate and plate geometry). These relatively small measuring gaps mean that the foam structure is compromised before it can be measured.

Multiphase materials tend to slip at the boundary of standard measuring geometries, which are most often a smooth surface fabricated from titanium or stainless steel. This has been shown to be a significant problem for foams. Princen and Kiss (1986, 1989) found that slip was so marked with their novel concentric cylinder measuring geometry that it could not be completely prevented, and consequently, new considerations had to be introduced for their experimental determination of the rheology of concentrated emulsions.

Moreover, the steady shear viscosity of foams has been difficult to measure because the bubble structure tends to be easily destroyed at low shear rates, once the yield stress has been overcome. For this reason, the only successful steady shear investigations have been theoretical and relied on computer modelling. Knowing the viscosity of a foam system at elevated shear rates, however, may have no real benefit, since these systems cannot generally exist at those shear rates.

The yield stress of foams arises above a critical gas fraction, surface tension, and bubble size (Khan et al., 1998). Two conflicting effects influence yield stress in foam: increases in gas fraction due to drainage tends to raise yield stress, whereas increases in bubble size tends to reduce yield stress. Furthermore, the changing properties of foams on standing make it difficult to determine yield stress. A pendulum device was used to observe the change in yield stress as the gas fraction and bubble size increased in aqueous foams (Gardiner et al., 1998). A true yield stress was observed at the dry foam limit, i.e., following cessation of liquid drainage and stabilization of gas bubble size. Much of the previous work was in concentrated emulsions and then was extended to foam. This was because emulsions are easier to work with in terms of their temporal stability and the relative ease with which model emulsion systems can be made. Princen and Kiss (1986) used a modified concentric cylinder apparatus and Lee (2004) measured microcellular foams (unit size > 10 μm), probably using a parallel plate with

Table 1
Products assessed

Product	Source	Identification
OluxE™	Stiefel Laboratories Inc.	UFC-1C
Verdeso™	Stiefel Laboratories Inc.	UEBD-1C
Emulsion Placebo (o/w)	Stiefel Laboratories Inc.	XEE-C
Evoclin™	Stiefel Laboratories Inc.	D46043-2
Luxiq®	Stiefel Laboratories Inc.	D6F103
Olux®	Stiefel Laboratories Inc.	D6F104
Solux™	Stiefel Laboratories Inc.	F148/65/2 E522/38/1
5% benzoyl peroxide (BPO)/1% Clindamycin	Stiefel Laboratories Inc.	F535/28/03 E594/10/01
PEG 400 Placebo[a]	Steifel Research Australia	F522/6/3 E522/6/3
Aqueous Placebo[a]	Steifel Research Australia	F564/05/02 E594/10/02
Ovace® (20% sodium sulfacetamide)	Coria Laboratories Ltd.	XDCP-1, E 09/07
Salicylic acid (2%)	Stiefel Laboratories Inc.	F55-62-02 Lot 614-11-01
Utralytic™2 (20% urea)	Ivax Dermatologicals	Lot UL001, E 07/2007
Gillette® pure and sensitive shaving foam with aloe and vitamin E	Procter and Gamble	11124X

[a] Non-commercial product.

small measuring gap. These methods would be unsuitable for most foams because of the small measurement gap compared with the unit bubble size.

The existence of a linear viscoelastic regime has been observed by Hohler and Cohen-Addad (2005), who commented that foam structures are in many respects similar to those of other disordered, closely packed, small soft units, such as concentrated emulsions and soft pastes.

Buhse et al. (2005) presented an updated classification of topical dosage forms comparing the physico-chemical properties of ointments, creams, gels, and lotions. The classification included rheology, loss on drying, specific gravity, surface tension, thermogravimetric analysis, water absorption, dilution properties, microscopic evaluation, transmittance of visible light, appearance, and composition. They found that rheology was the most discriminating property separating creams and lotions. Loss on drying, composition, and thermal behaviour were able to separate creams and ointments and composition and thermal behaviour separated gels from other dosage forms. The Buhse study did not focus on delivery of drug from the topical dosage forms, rather the inherent properties of the dosage form. Drug is unlikely to play a major role unless at a sufficient concentration that it may affect some of these physical properties and delivery across the skin.

In this study various pharmaceutical aerosol foams were evaluated based on their composition and related physico-chemical properties. The foams assessed were hydroethanolic (HF), emulsion (EF), or aqueous (AF) based. Composition, appearance, loss on drying, location of the propellant, and rheological properties were analysed as an indicator of the macrostructure of the different aerosol foams.

To facilitate more intuitive understanding and validation of the data, the same rheological tests were conducted using a common shaving foam; ‘Gillette® Pure and Sensitive’. Rheological data (yield stress, viscoelastic moduli, and complex viscosity) from the shaving foam were obtained using both a traditional rheological technique (serrated plate and plate geometry) and vane geometry, adapted here for dynamic measurements on foam systems. It was necessary to adapt existing rheological measurement techniques in a novel way to produce relevant data, details of these methods are included here for the first time.

2. Materials and methods

2.1. Materials

The materials were tested from the can, as supplied either from production or wholesalers, and were used within their expiry date (Table 1).

2.2. Rheological equipment

The experimental apparatus used in this work was a Thermo Electron HAAKE RS150 Controlled Stress Rheometer (RS150), used in controlled deformation (CD) mode for the viscoelastic measurements and in controlled stress (CS) mode for the yield point measurements. The vane sensor used (Nguyen and Boger, 1983, 1985), shown schematically in Fig. 1a, was the FL20 (4 blades, diameter 21 mm, and height 16 mm). For verification of the vane results and for the temperature-sweep tests, a serrated parallel plate sensor, 35 mm diameter was used (Fig. 1b). The serrations on both the sensor plate and the bottom plate allowed the test material to adhere to the surface of the test geometry, without slipping.

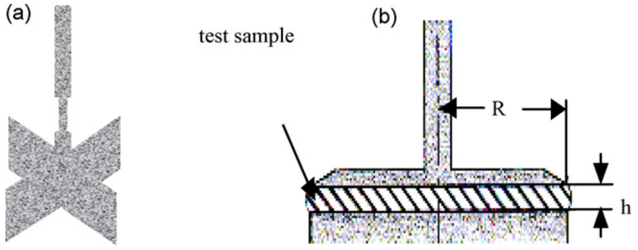


Fig. 1. (a) Vane sensor and (b) parallel plate sensor.

2.3. Rheological properties

The yield stress data were collected using a shear stress sweep, whereby the response of each material was measured under steady shear (rotation of the sensor) with respect to gradually increasing shear stress, at constant temperature.

Determination of the viscoelastic properties was through stress sweeps (to isolate the linear viscoelastic envelope [LVE]) and frequency sweeps (which measure the viscoelastic moduli, G' and G'', and the complex viscosity, η^*). The response of each material was measured in oscillation with respect to either increasing stress, using stress sweeps to isolate the LVE at a constant frequency of oscillation, or increasing frequency, using frequency sweeps to measure the response of the material to increasing frequency of oscillation whilst keeping the strain constant. This data can be used to compare the macrostructure of the various materials. Temperature was maintained constant for these tests at 20 ± 2 °C.

Following the work of Zhang et al. (1998), the validity of the vane measurements was assessed using a conventional serrated plate and plate measuring geometry with a variety of measurement gaps. Changing the gap allowed finding a technique that accurately determined the rheology of the shaving foam without disrupting the structure of the material during the measurement.

A similar oscillatory technique, but with fixed strain (within the LVE) and fixed frequency was used to monitor temperature dependence of the different materials. In this study the temperature was gradually increased, and the resultant changes in the moduli monitored.

2.4. Sample handling and experimental set-up

The materials were kept in a refrigerator (4 °C) before testing and then placed on the bench in a temperature-controlled laboratory (20 °C) for 2 h immediately before testing to allow for temperature equilibration.

After calibrating the system, the cup was filled (for vane measurements) or sample was carefully placed at the centre of the lower fixture on the rheometer (plate/plate measurements). The sensor was lowered slowly into the sample at controlled speed, 2.5 mm/min. This feature allows minimal (and repeatable) disruption to the sample structure during set-up. Where possible (foam stability permitting), the material was allowed to rest and physically and thermally stabilise for 5 min before testing commenced.

2.4.1. Yield stress

The yield stress was determined by linearly increasing the shear stress from 0.01 to 500 Pa in a time of 500 s and observing the response of the material. The location of the change in response from creep (no flow, the structure stretches) to flow was found. This is the yield point of the foam.

2.4.2. Linear viscoelastic envelope isolation

The linear viscoelastic envelope (LVE) region – the range of amplitudes of oscillation for which the structure of the sample remains intact – was found by imposing increasingly high amplitudes of oscillation on the sample at constant frequency and observing the response at 20 °C for each sample. Thus, it was possible to later quantify and compare frequency-dependent viscoelastic properties of the samples without influencing their at-rest structures.

2.4.3. Frequency sweep

Testing was in the LVE for an angular velocity, ω, of 0.683–683 rad/s. The data collected for these tests included the elastic modulus, G' (a measure of the contribution of elastic forces to flow), the viscous modulus, G''(a measure of the contribution of viscous forces to flow) and the complex viscosity, η^*.

2.4.4. Temperature sweep

A constant strain amplitude (within the LVE at 20 °C for each material) and frequency (1 Hz) were selected, and the temperature was increased from 20 to 80 °C at a preset rate of 3.6 °C/min. The viscoelastic response of the material was measured and the temperature–structure relationship was then inferred.

2.5. Appearance and foam quality

Foam quality was assessed using an in-house ranking of 1–5, with “1” representing fine bubble foams and “5” representing coarse large bubble foams.

2.6. Loss on drying

Approximately 3–5 g of foam was expelled into a preweighed beaker and the foam quantity determined. The beaker was placed in a 65 °C oven and weighed at intervals until constant weight was achieved, typically after 5–7 days.

3. Results

3.1. Composition

The composition of the aerosol foam base for each product is described in Table 2. A comparison of the typical composition appearance in a glass aerosol bottle is shown in Fig. 2.

3.2. Appearance

A typical foam dollop is shown in Fig. 3. The appearance of the contained foam, depending on sample composition, ranged from colourless and clear to opaque, but the appearance of the released foam for each sample was white to off white.

3.3. Foam quality

When expelling the sample from the aerosol container, a white foam structure was observed, with fine bubbles on the surface. The change in appearance of the foam typically resulted in some foam drainage over a period of 30 min, with some coarsening or partial softening of the foams over 30 min (Fig. 4).

Table 2
Foam products formulation description and composition

Product	Formulation type	Key components		
OluxE™	Emulsion	Water	Oil	Surfactant
Verdeso™	Emulsion	Water	Oil	Surfactant
Emulsion Placebo (o/w)	Emulsion	Water	Oil	Surfactant
Evoclin™	Solution: hydroethanolic	Water	Ethanol	Waxes
Luxiq®	Solution: hydroethanolic	Water	Ethanol	Waxes
Olux®	Solution: hydroethanolic	Water	Ethanol	Waxes
Solux™	Emulsion (with ethanol present)	Water	Ethanol	Waxes
5% Benzoyl peroxide/1% Clindamycin	Aqueous: suspension	Water	Thickener	
PEG 400 Placebo	Solution: anhydrous	Oil		
Aqueous Placebo	Solution	Water	Thickener	
Ovace® (20% sodium sulfacetamide)	Aqueous: suspension	Water		
Salicylic acid (2%)	Emulsion: hydroethanolic	Water	Ethanol	Waxes
Utralytic™2	Emulsion	Water	Oil	
Gillette® pure and sensitive shaving foam with aloe and vitamin E				

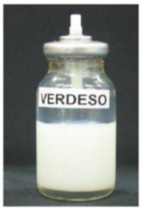
Product	**OLUX®**	**Verdeso®**	**Ovace**
Aerosol Base	Solution	Emulsion	Suspension
Key Excipients	Water Ethanol Waxes	Water Oils Surfactants	Water Polymer Surfactants
Appearance			

Fig. 2. Typical appearance of foam compositions for three different formulations: hydroethanolic, oil and water emulsion, and aqueous suspension.

3.4. Loss on drying

Loss on drying represents residue remaining after all volatiles have evaporated from the dried down formulation. Results for different vehicle bases are shown in Table 3.

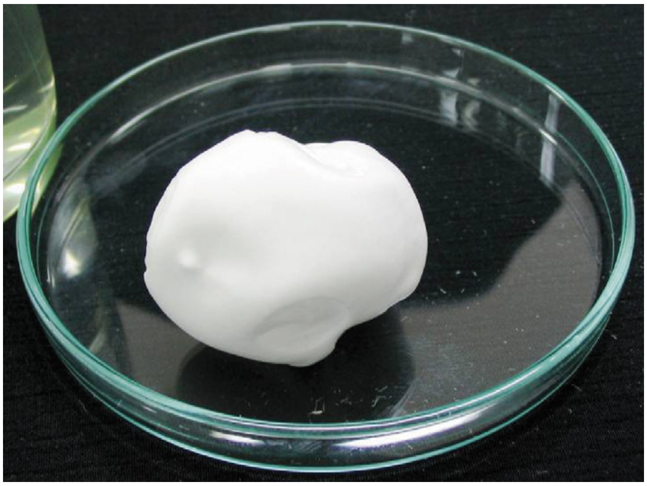


Fig. 3. Aerosol foam dollop.

3.5. Addition of propellant

The quality of foam produced is dependent in part on the type of propellant. A hydroethanolic base and foam is shown in Fig. 5 and an emulsion base and foam is shown in Fig. 6. The foams were produced using a liquefiable propellant (e.g., hydrocarbon mixture AP70) or compressed gas nitrogen.

3.6. Rheological properties

3.6.1. Measurements and validation with shaving foam

The yield stress of the Gillette® shaving foam was evaluated with the vane sensor using the rheometer in CS mode, by gradually increasing the imposed shear stress and monitoring

Table 3
Residue levels for different formulations

Formulation	Identification	Loss on drying (%)	Residue (%)
Foam hydroethanolic	F621/01/01	97.9	2.1
Foam emulsion	F274/02/01	76.5	23.5
Temovate® E cream	J7390	78.9	21.1
Temovate® ointment	8ZP0439	3.2	96.8

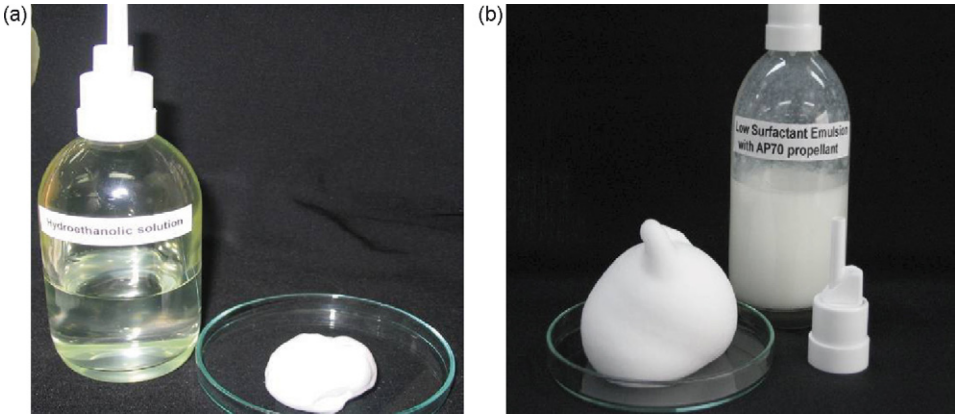


Fig. 4. (a) Foam produced from hydroethanolic base (left) and (b) foam produced from oil and water emulsion base (right).

the deformation of the foam. Initially, at low stresses, the foam deformed elastically, i.e., the structure was stretched but not broken.

During this time the deformation was quite small. Later, the yield stress was overcome and the material began to flow, with the structure deforming plastically and irreversibly. The deformation was large. Plotting the deformation (γ) and the applied stress (τ) on logarithmic scales revealed a linear region for each of these flow regimes. The point at which the flow regime changes from elastic deformation to plastic deformation is the yield stress (τ_y, Pa). Fig. 7 shows the yield stress data collected for Gillette® shaving foam at 20 °C.

The viscoelastic moduli were measured in the same apparatus, but with the rheometer operating in CD mode. The moduli were measured for their response to increasing frequencies of deformation in the LVE. In this way the internal structure of the material could be directly measured whilst it was intact, and compared with other materials. In addition to measurements with the vane technique, measurements were carried out using a conventional plate and plate geometry. The measurement gap

Fig. 5. (a) Hydroethanolic aerosol base with hydrocarbon propellant (left) and nitrogen (right). (b) Foam produced from hydroethanolic aerosol base with hydrocarbon propellant (left) and nitrogen (right).

Fig. 6. (a) Emulsion aerosol base with hydrocarbonAP70 (left) or nitrogen (right). (b) Foams produced using hydrocarbon AP70 (left) or nitrogen (right).

for this geometry was varied in order to understand the impact of the gap size on the structure of the foam before and during the measurement. The point at which the influence of the gap size was not noticeable was used to assess the quantitative validity of the vane measurements.

The LVE ranges for each foam are summarised in Table 5. The frequency sweep test was used to characterise the structure of the material by it’s response to changing frequencies. By convention, the frequency (cycles/s) was plotted as angular velocity, ω (rad/s). This is analogous to a shear rate sweep (smoothly changing the rate of rotation) for rotational viscometry.

The complex viscosity, η^* (Pa s) is the total resistance of the material to flow—it is analogous to the more familiar steady shear viscosity, measured by rotational rheometers and viscometers.

Fig. 8 depicts the data collected using the serrated plate and plate measuring geometry with different gap settings. It shows a

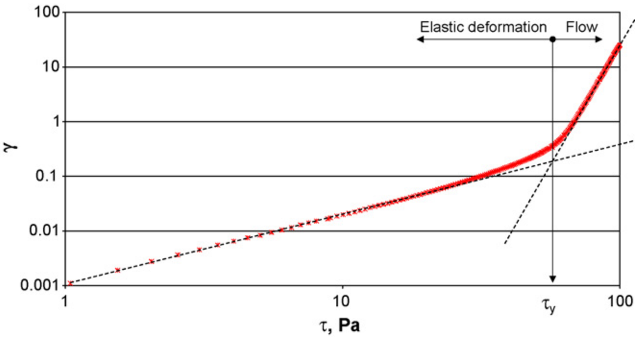


Fig. 7. Yield stress data for Gillette® shaving foam.

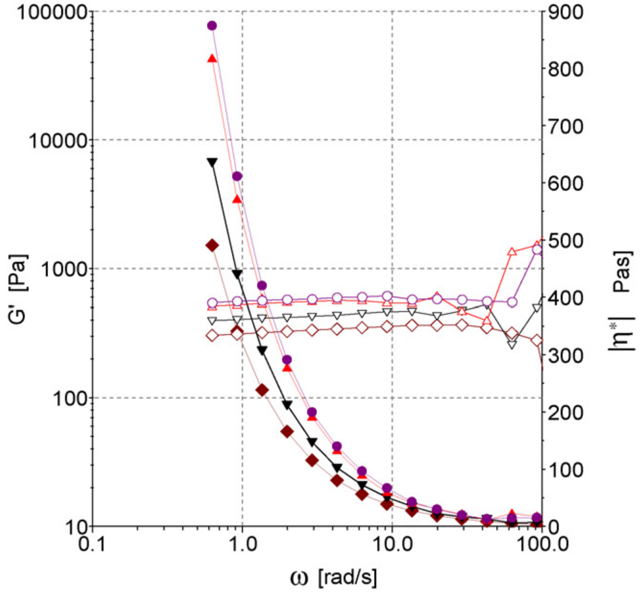


Fig. 8. The effect of gap size on η^* (filled symbols, dashed lines) and G' (open symbols, solid lines) measurements for shaving foam at 20 °C. Gap sizes: 1 mm (◊), 5 mm (▼), 10 mm (◯), 15 mm (▲).

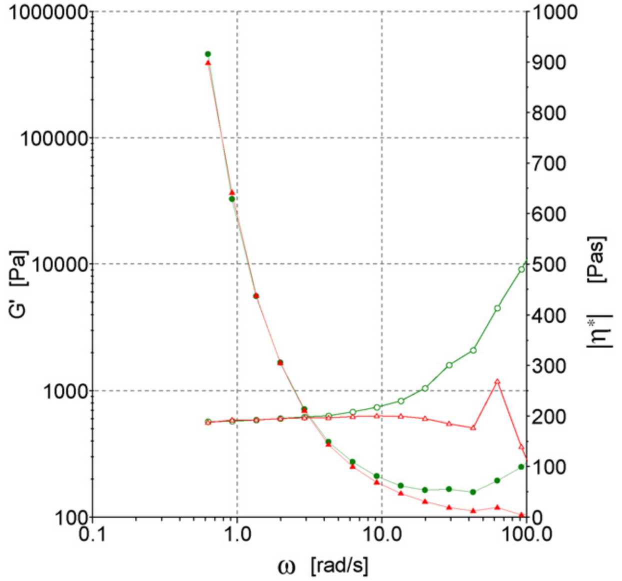


Fig. 9. Comparison of G' (filled symbols) and η^* (open symbols) for 10 mm gap serrated plate/plate (Δ symbols) and vane (● symbols) techniques for shaving foam at 20 °C.

clear pattern of increasing G' and η^* as the gap size goes from 1 to 5 mm to 10 mm. The 10 and 15 mm gaps show similar results (difference <10% for all angular velocities), with the 15 mm gap being slightly lower.

Based on the data in Fig. 8, the 10 mm gap measurement served as the basis (no slip, natural development of the foam, without restriction from the measuring geometry) against which the vane technique for foams could be compared. The results of the comparison are shown in Fig. 9. There is excellent agreement between the vane and 10 mm gap, serrated parallel plate measurement, in particular when $\omega < 4$ rad/s. Above 4 rad/s, the curves diverge.

3.6.2. Yield stress

The yield stress values for different foams are shown in Table 4. In general the emulsion foams (EF) had lower yield stresses than the hydroethanolic foams (HF). Solux$^{\text{TM}}$ is an emulsion with ethanol present and as such bridges the HF and EF groups; its yield stress reflected this. The aqueous foams (AF) had a higher yield stress than Solux$^{\text{TM}}$, but less than the HF group. Shaving foam had a yield stress slightly less than the HF group. To summarise the yield stress measurements: EF < AF < HF. Interestingly, Ultralytic$^{\text{TM}}$2 foam collapsed almost immediately when expelled from the can.

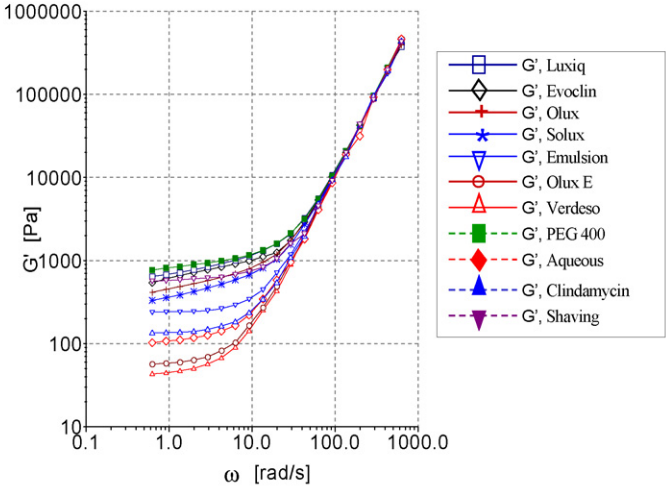


Fig. 10. Elastic modulus, G', for foam products at 20 °C.

3.6.3. Dynamic (LVE and frequency sweep) measurements

The LVE was used to isolate the region of testing for the frequency sweeps, following where the structure of the test material remained reversible (independent of the displacement). Frequency sweeps were conducted at strain, $\gamma = 0.001$ for Luxiq$^{\circledR}$, Olux$^{\circledR}$, and Solux$^{\text{TM}}$, and at $\gamma = 0.01$ for the remaining materials. Table 5 lists the extent of the LVE measured for the different foams.

The elastic modulus describes the amount of energy stored in the structure of the material during the oscillatory testing; it has been plotted in Fig. 10 as a function of the angular velocity, ω. The ranking of the elastic modulus from highest to lowest was PEG400 > Luxiq$^{\circledR}$ > Evoclin$^{\text{TM}}$ > Olux$^{\circledR}$ > Solux$^{\text{TM}}$ > Emulsion > Benzoyl peroxide (BPO)/Clindamycin > Aqueous > OluxE$^{\text{TM}}$ > Verdeso$^{\text{TM}}$. Here, the three emulsion foams had the lowest G',

Table 4
Yield stress values of foams at 20 °C

Product name	Formulation type	Identification	Yield stress (Pa)	Strain at yield
Verdeso$^{\text{TM}}$	Emulsion	UEBD-1C	8.8	0.18
Ovace$^{\circledR}$	Aqueous: suspension	XDCP-1	10.0	0.36
OluxE$^{\text{TM}}$	Emulsion	UFC-1C	11.5	0.29
Ultralytic$^{\text{TM}}$ 2 (20% urea)	Emulsion	UL001	13.9	0.30
Emulsion Placebo (o/w)	Emulsion	XEE-C	28.8	0.18
Solux$^{\text{TM}}$	Emulsion (with ethanol present)	F148/65/2 E522/38/1	29.2	0.17
5% Benzoyl peroxide/1% Clindamycin	Aqueous: suspension	F535/28/03 E594/10/01	31.2	0.40
Aqueous Placebo	Aqueous	F564/05/02 E594/10/02	36.1	0.51
Salicylic acid (2%)	Emulsion hydroethanolic	F55/62/02 Lot 614/11/01	48.6	0.17
Evoclin$^{\text{TM}}$	Solution: hydroethanolic	D46043-2	69.7	0.30
Olux$^{\circledR}$	Solution: hydroethanolic	D6F104	76.4	0.28
PEG 400 Placebo	Solution: anhydrous	F522/6/3 E522/6/3	79.8	0.24
Luxiq$^{\circledR}$	Solution: hydroethanolic	D6F103	88.7	0.25
Gillette$^{\circledR}$ shaving foam		11124X	56.0	0.17

Table 5
LVE ranges of foams at 20 °C

Product name	Formulation type	Identification	LVE range, γ
OluxE™	Emulsion	UFC-1C	0.0 to 4.4 × 10^{-2}
Verdeso™	Emulsion	UEBD-1C	0.0 to 5.7 × 10^{-2}
Emulsion Placebo	Emulsion	XEE-C	0.0 to 5.5 × 10^{-2}
Evoclin™	Solution: hydroethanolic	D46043-2	0.0 to 3.9 × 10^{-2}
Luxiq®	Solution: hydroethanolic	D6F103	0.0 to 1.9 × 10^{-3}
Olux®	Solution: hydroethanolic	D6F104	0.0 to 5.9 × 10^{-3}
Solux™	Emulsion (with ethanol present)	F148/65/2 E522/38/1	0.0 to 4.7 × 10^{-3}
5% Benzoyl peroxide/1% Clindamycin	Aqueous suspension	F535/28/03 E594/10/01	0.0 to 1.5 × 10^{-2}
Aqueous Placebo	Aqueous	F564/05/02 E594/10/02	0.0 to 1.9 × 10^{-2}
PEG 400 Placebo	Solution: anhydrous	F522/6/3 E522/6/3	0.0 to 1.2 × 10^{-2}
Salicylic acid (2%)	Emulsion: hydroethanolic	F55/62/02 Lot 614/11/01	0.0 to 5 × 10^{-3}
Ovace®	Aqueous: suspension	XDCP-1	0.0 to 1.5 × 10^{-3}
Ultralytic™ 2	Emulsion	UL001	0.0 to 1.5 × 10^{-3}
Gillette® shaving foam		11124X	0.0 to 1.9 × 10^{-3}

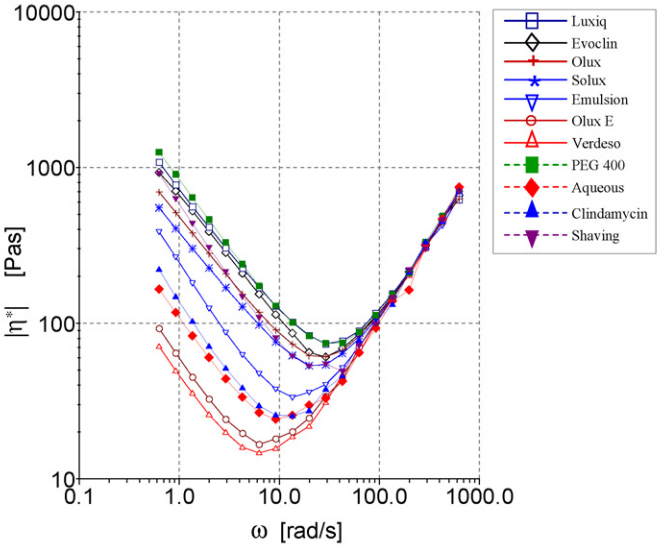


Fig. 11. Complex viscosity, η^*, for foam products at 20 °C.

indicating that the flexibility of their networks was the weakest. OluxE™ and Verdeso™ had very similar properties. On the other side, Luxiq® and Evoclin™ also were similar in the magnitude of their elastic moduli and compared with the other foams they were highly elastic. The aqueous-based foams were more elastic than the emulsion foams, and were comparable to the hydroethanolic foams.

Table 6 lists comparative values of the storage modulus, G', measured for the different foams at 1 rad/s. It should be emphasised that, like complex viscosity and many other rheological properties, G' is not a single point, but is a function of ω, the angular velocity. Table 5 serves therefore as an indication only of the relative behaviours, and not a complete definition.

In this case, the elastic modulus is useful for differentiating the materials because it provides a map of the behaviour of the macrostructure of each material, which can be compared. Another way of conceptualising G' is to consider it a measure of the solidity of the material, where high G' implies the material deforms more like a solid (immediate deformation on the application of a force, and a greater ability to return to it's original physical orientation when the force is removed—e.g., a spring or an elastic band). At $\omega = 1$ rad/s, there is a notable difference of approximately 190% between the most elastic emulsion (Emulsion Placebo, 237.1 Pa) and the least elastic hydroethanolic foam (Olux®, 448.6 Pa). The G' value could be used to help differentiate between these foams. The mixed foam, Solux (362.7 Pa),

Table 6
G' at $\omega = 1$ rad/s of foams at 20 °C

Product name	Formulation type	Identification	G' ($\omega = 1$ rad/s) (Pa)
Ovace®	Aqueous: suspension	XDCP-1	35.9
OluxE™	Emulsion	UFC-1C	56.5
Verdeso™	Emulsion	UEBD-1C	43.3
Aqueous Placebo	Aqueous	F564/05/02 E594/10/02	104.0
5% Benzoyl peroxide/1% Clindamycin	Aqueous: suspension	F535/28/03 E594/10/01	135.7
UltraLytic™2	Emulsion	UL001	150.9
Emulsion Placebo	Emulsion	XEE-C	237.1
Solux™	Emulsion (with ethanol present)	F148/65/2 E522/38/1	362.7
Olux®	Solution: hydroethanolic	D6F104	448.6
Salicylic acid (2%)	Solution: hydroethanolic	F55/62/02 Lot No. 614/11/01	448.6
Evoclin™	Solution: hydroethanolic	D46043-2	617.1
Luxiq®	Solution: hydroethanolic	D6F103	686.3
PEG 400 Placebo	Solution: anhydrous	F522/6/3 E522/6/3	804.9
Gillette® shaving foam		11124X	554.8

Table 7
η^* at $\omega = 1$ rad/s of foams at 20 °C

Product name	Formulation type	Identification	η^* ($\omega = 1$ rad/s) (Pa s)
Ovace®	Aqueous: suspension	XDCP-1	37.1
Verdeso™	Emulsion	UEBD-1C	44.8
OluxE™	Emulsion	UFC-1C	58.8
5% Benzoyl peroxide/1% Clindamycin	Aqueous: suspension	F535/28/03 E594/10/01	132.6
UltraLytic™2	Emulsion	UL001	163.2
Emulsion Placebo	Emulsion	XEE-C	235.5
Solux™	Emulsion (with ethanol present)	F148/65/2 E522/38/1	367.9
Salicylic acid (2%)	Emulsion: hydroethanolic	F55/62/02 Lot No. 614/11/01	448.6
Aqueous Placebo	Aqueous	F564/05/02 E594/10/02	452.7
Olux®	Solution: hydroethanolic	D6F104	467.3
Evoclin™	Solution: hydroethanolic	D46043-2	642.8
Luxiq®	Solution: hydroethanolic	D6F103	696.2
PEG 400 Placebo	Solution: anhydrous	F522/6/3 E522/6/3	816.5
Gillette® shaving foam		11124X	575.0

lies between the emulsion and hydroethanolic with about 150% higher G' than that measured for Emulsion Placebo. Aqueous foams are comparable in magnitude to the emulsion foams. The measurement at 1 rad/s is an arbitrary point of comparison. From Fig. 9, the curve for shaving foam exhibits similar behaviour to that of the other materials.

Complex viscosity, η^*, is a function of the viscoelastic moduli. The trend for decreasing viscosity with increasing ω is typical for many materials, and indicates a shear thinning material. At higher ω, however, this trend is reversed (Fig. 11). The ranking of the complex viscosity from highest to lowest is as follows: PEG400 > Luxiq® > Evoclin™ > Olux® > BPO/Clindamycin > Aqueous > Solux™ > Emulsion > OluxE™ > Verdeso™. Data for shaving foam shows a similar trend compared with the others.

The emulsion foams clearly tend to have lower viscosity than the hydroethanolic foams. As in the case of the yield stress measurements, the viscoelastic properties of Solux™ placed it between the hydroethanolic and emulsion foam groups. Aqueous foams were comparable with the emulsion foams. Table 7 lists comparative values of the complex viscosity measured for the different foams. The hydroethanolic foams had higher viscosity than the emulsion foams, and Solux™, the 'mixed' product, lies between the 2 more common types of hydroethanolic and emulsion foams. Aqueous foams were comparable to emulsion foams.

3.6.4. *Temperature sweep tests*

The changing elastic modulus of the different foam products with respect to the temperature is shown in Figs. 12 (hydroethanolic and emulsion foams) and 13 (other foams). The difficulties in controlling the temperature either in a large gap plate/plate geometry, or for the vane were noted earlier, and from the earlier data presented in Fig. 8, G' data in Figs. 12 and 13 should be treated as relative (not absolute), because the geometry used was with a 1 mm gap. One would expect that the key test parameter, the temperatures at which the key changes occurred, is independent of the absolute value of G' and is accurate.

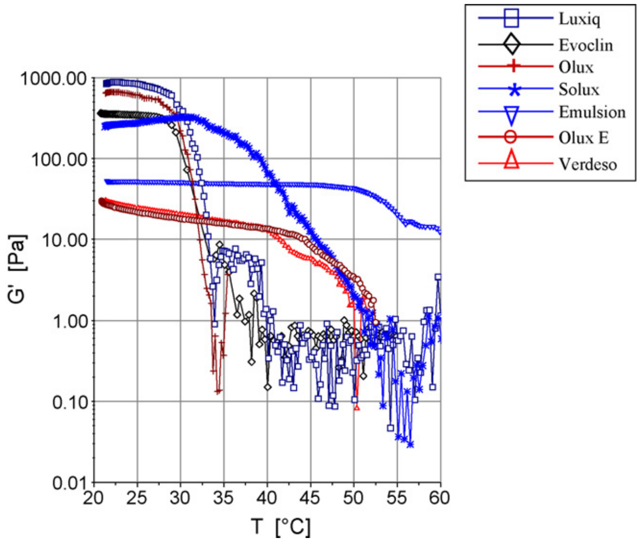


Fig. 12. Elastic modulus, G', for the hydroethanolic and emulsion foams with respect to changing temperature.

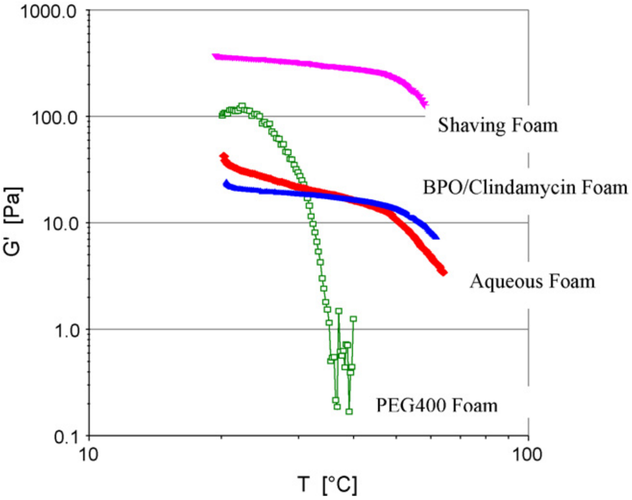


Fig. 13. Elastic modulus, G', for the Aqueous, BPO/Clindamycin, PEG400 and shaving foam products with respect to changing temperature.

Table 8
Temperature of decomposition of foams

Product name	Formulation type	Identification	Initial temperature of decomposition (°C)	Final temperature of decomposition (°C)
OluxE™	Emulsion	UFC-1C	43.4	52.0
Verdeso™	Emulsion	UEBD-1C	39.7	50.0
Emulsion Placebo	Emulsion	XEE-C	47.5	65.0
Evoclin™	Solution: hydroethanolic	D46043-2	27.5	33.8
Luxiq®	Solution: hydroethanolic	D6F103	25.0	33.9
Olux®	Solution: hydroethanolic	D6F104	24.0	33.0
Solux™	Emulsion (with ethanol present)	F148/65/2 E522/38/1	31.5	51.0
5% Benzoyl peroxide/1% Clindamycin	Aqueous: suspension	F535/28/03 E594/10/01	48.4	None achieved
Aqueous Placebo	Aqueous	F564/05/02 E594/10/02	49.0	None achieved
PEG 400 Placebo	Solution: anhydrous	F522/6/3 E522/6/3	24.0	35.1
Salicylic acid (2%)	Emulsion: hydroethanolic	F55/62/02 Lot 614/11/01	39.6	None achieved
Ovace®	Aqueous: suspension	XDCP-1	30.6	35.0
UltraLytic™ 2	Emulsion	UL001	35.1	56.0
Gillette® shaving foam		11124X	43.1	None achieved

Table 8 summarises the key temperatures from Figs. 12 and 13, the temperature at which the direction of each G' curve began to change (initial temperature of decomposition) and the temperature at which the G' signal became unstable (final temperature of decomposition).

As shown in Table 8, the hydroethanolic foams began to decompose at lower temperatures than the emulsion foams, and Solux bridged the gap between these two groups. The aqueous foams showed high temperature stability, as did the Gillette shaving foam. In terms of thermal stability, hydroethanolic foams are less stable than emulsion foams, which are less stable than aqueous based foams.

4. Discussion

4.1. *Physico-chemical properties*

4.1.1. *Composition*

Three foam types (hydroethanolic, emulsion, and aqueous) were investigated with regard to their physical properties and interaction with propellant. The hydrocarbon propellant used was water immiscible and was either dissolved or dispersed within the aerosol base or formed a separate layer above the base in a pressurized can. The dimethyl ether propellant was water miscible and dispersed differently than the hydrocarbon propellant. Sanders (1973a,b) stated that there is a definite relationship between the properties of aerosol emulsions and those of foams; this relationship was influenced by surfactants (Sanders, 1963) and foam structuring agents (Abram and Tomlinson, 2001).

4.1.2. *Appearance*

The foam as dispensed from a can was typically white to off white in appearance. The composition of the foam base and the level and type of propellant typically governed how coarse the foam appeared, with respect to fine or large bubbles. The objective for the formulation chemist would be to formulate a stable foam product with fine bubble structure, whereas to the consumer, the foam quality, appearance, and ease of manipulation are important.

4.1.3. *Foam quality*

Foam quality is a measure of the foam's physical appearance. An in-house ranking of 1–5 was used, with "1" and "2" being classified as acceptable foams that were stable, had fine bubbles, and did not lose structure over a period of 1 min. Viscosity and composition are important components of the ranking system, as the foam dollop must be manipulated on the skin. However, due to the way the foams' structure and appearance have been optimised one would not expect to see short term destabilizing effects unless impacted by temperature or shear. Although the valve and actuator may play a role in foam quality, they will not be discussed here. It should be noted that in developing foams one of the criteria for an acceptable foaming composition is the foam quality.

4.1.4. *Loss on drying*

The typical residue levels of the two different foam types were much lower than the levels typically found in conventional vehicles such as creams and ointments. Low viscosity dosage forms typically have low residue, while high viscosity dosage forms have high residue.

4.1.5. *Incorporation of propellant*

The type and level of propellant can impact the quality of the foam (Bartlett, 1986). Hydrocarbon propellant gives foam in part its structure as it boils off. A compressed gas such as nitrogen is not suitable due a very low boiling point, and flashes off too quickly, destroying the foam structure. The stiffness of the hydroethanolic foam is more due to the waxes that precipitate out as the propellant flashes off, whereas the emulsion foam is softer due the level of solubility of the propellant in the foam base.

4.2. Rheological properties

In the past, measurements on the rheological properties of foams have been difficult due to the fragility and volume of material required, which has restricted the use of traditional rheological measurement techniques (e.g., concentric cylinder, cone and plate). Using the vane rather than traditional measurement geometries resulted in a powerful new technique for reliable measurements of foam structure and flow properties.

The RS150 and vane sensor combination allows minimal disruption to the sample as the sensor system can be lowered into the sample with far less disturbance to its structure than could be achieved with a cup and bob (concentric cylinder) or cone and plate system. The shape of the vane is important because the material is not squashed between two proximate surfaces, but instead can maintain its original structure during testing. A relatively large volume of material is needed for these measurements and so there is a large mechanical and thermal inertia in the system, therefore it is unsuitable for measurements involving rapid changes in the direction or rate of deformation or for monitoring temperature changes.

Using a serrated plate and plate measuring geometry with different gap settings with increasing G' and η^* as the gap size increases from 1 to 10 mm although these decrease slightly at 15 mm. While there is an excellent agreement between the vane and the 10 mm gap serrated parallel plate measurement below $\omega < 4$ rad/s, above there is a divergence. The difference between the 10 and 15 mm gap settings may in part be due to the difficulty in filling properly a column 15 mm high, the gap may not have been completely full, and some slumping may have occurred. In addition (although care was taken to avoid it), air movement in the environment may also have had some impact on the measurement, and one would intuitively expect this impact to grow with the length of the column.

In addition to avoiding slip and allowing the natural development of the material structure, this is a good illustration of the comparative benefits of the vane sensor. The vane technique allows containing walls to be used, and so slumping is not a problem, additionally the material is protected from any environmental changes. It is also considerably easier to control the temperature of a material contained in this manner. We speculate that this divergence is an artefact of the vane technique. Compared with the plate sensor, the vane is quite heavy, and combined with the large volume of material included between the blades, this would create high levels of inertia. The effect of inertia is that secondary flow occurs when the speed of deformation (frequency) and the direction of oscillation change. Effectively, the momentum of the vane with included foam is too large to change velocity or direction quickly and so viscoelastic properties appear to increase as the frequency increases.

4.2.1. Yield stress

It was expected that the yield stress of foams could be successfully measured with the vane technique, because the vane was developed specifically for yield stress measurement. Data showing the results for foams, however, is sparse in the literature, and there is some debate as to which technique and geometry should be used, e.g., Princen and Kiss (1986) and Lee (2004). This previous research showed that the yield stress is an important factor in the characterisation of foams. Our data agrees with these findings, and further shows that the yield stress may be used as a tool to differentiate between emulsion foams (EF), aqueous foams (AF) and hydroethanolic foams (HF), and that the general trend for yield stress is EF < AF < HF.

The strain at yield is an indication of the elasticity of the structure; more elastic structures will deform more before yielding. All types of foam exhibit a variety of strains for the yield point; in general (but not in every case) those of the emulsion foams are lowest, followed by the hydroethanolic foams, followed by the aqueous foams. Shaving foam compared with emulsion foams in terms of the deformation possible before yield. For strain at yield, the following summary is pertinent (least elastic to most elastic) EF < HF < AF.

4.2.2. Dynamic (LVE and frequency sweep) measurements

Viscoelastic data – both the LVE and frequency-dependent flow properties – were measured with the vane technique. This was shown to be a reliable technique, comparable with data from a wide gap serrated plate/plate measurement. The vane technique has several advantages over plate/plate geometry, within the constraints imposed by thermal and mechanical inertia. Data confirmed the existence of the LVE, as seen previously by Hohler and Cohen-Addad (2005). Therefore, viscoelastic data could be a useful technique for differentiating between the various foam types. Similar to yield stress, the trend for viscoelastic data for the materials tested, particularly G' and η^*, was EF < AF < HF.

For the temperature sweeps, a serrated plate/plate combination allows minimal disruption to the sample as the sensor system can be lowered into it with far less disruption than could be achieved with a cup and bob (concentric cylinder) system (but more than for a vane system). The measuring gap is quite large (1 mm) compared with a cone and plate geometry, and so the disturbance to the macrostructure of the material in the measuring gap is less.

In addition, because of the small gap for cone and plate geometries, the surfaces cannot be serrated. The serrations in the plate/plate geometry allow the foams to properly adhere to the surface of the geometry and so all of the actions and reactions are transmitted directly to and from the material in the gap. A gap of this magnitude was not shown to be useful for absolute stress measurements. The relative trend, however, is thought to be correct, and the temperature variations are thought to be accurate. For thermal stability, the trend was found to be HF < EF < AF.

The difference between this and the other (room temperature) measurements appears to be the thermal instability of the HF. The solvent base in this material was able to solvate the foam structuring ingredients more effectively than the oil or water based materials.

Like the G' analysis, η^* may be a powerful tool for analysis of the differences between the hydroethanolic foams and the emulsion foams, and η^* is a term which includes both G' and G''. The hydroethanolic foams had higher viscosity than the emulsion foams, and as before, Solux$^{\text{TM}}$, the 'mixed' product, lies between the 2 more common types of formulation. Aqueous foams were comparable to emulsion foams.

The trend for decreasing viscosity with increasing ω is typical for many materials, and indicates a shear thinning material. At higher ω, however, this trend is reversed. The reversal in the trend for some of these foams is difficult to interpret. Mathematically, it is due to the increase in the slope of G', the elastic modulus. The measurements for the pharmaceutical foams have this in common with the ones shown previously for the shaving foam, and we propose the same mechanism here for the behaviour. The change is related to the inertia of the sensor system, which is high, and at high frequencies when the direction of oscillation changes, this inertia is manifested as an apparently more viscous (stiffer) structure.

Another explanation could be that increasing angular velocity aligns molecules and bonds, allowing the carrier liquid to drain from the walls of the bubbles into the struts. Consequently, without the lubricating effect of the carrier phase, the bubble walls become more rigid and the bubble structure resists deformation at high frequency.

A third explanation could be that at low frequencies, the material has time to flow and deform in response to the deformation imposed on it by the sensor. At higher frequencies, the time to react is progressively shortened, and as a result the material behaves with greater rigidity and the viscosity is increased. This effect would be exacerbated by the high inertia of the system, as speculated previously, and as discussed in the case of the shaving foam investigation. Data above the point of inflection should be treated with suspicion.

Changes in the slope of the elastic modulus G' curves for different foam products versus temperature imply a change in the internal structure of each material. It is assumed that these changes are as a result of changing temperature only, and not also a time-related phenomenon.

4.2.3. *Foam drainage*

The stability of foams is somewhat limited due to environmental or compositional limitations. Temperature, composition, and gravitational effects also give rise to eventual coarsening and collapse of the foam. From a pharmaceutical perspective, it would be ideal that the foams are physically stable for at least 1–2 min, until the patient has the opportunity to actually handle and apply the dose. A longer time may be desirable due to potential distraction of the patient or handling of the foam by the patient to apply to their skin. Gravitational drainage has been cited as probably the most critical destabilizing effect to standing foam, as it irreversibly drains liquid from the foam (Saint-Jalmes et al., 2004). Gravity causes liquid to flow through foam and accumulate at its bottom, leading to a drier and more fragile foam, for which coarsening and film rupture then tend to play a role. It is therefore critical that the foam structure remain stable, particularly to enable application of foam by the patient.

Additionally bubble size distribution may change as the foam ages, which affects surface area, adsorbed hold up, and liquid content. Changes in bubble size distribution with age has also been noted for other aggregates including emulsions (Cheng and Lemlich, 1985).

Foam is a transient structure, and when applied to the skin, leaves very little residue and therefore offers the potential for delivering higher concentrations of drug compared to other topical delivery vehicles. Properties of foams are summarized below:

(i) Solution products (e.g., HF formulation) employ a propellant that acts as a solvent for the foam structuring agent. The propellant diffuses away and the structuring agents precipitate, giving rise to a solid structure with adsorbed liquid.
(ii) Emulsion products (e.g., EF foam) have a similar mechanism to solution products; however,
(iii) Inclusion of additional oils (eg. emollients) softens the structuring agent.
(iv) Aqueous suspension foam products (e.g., BPO) rely on a combination of dispersed solids and thickening agents to provide a semi-rigid foam structure.

There are several properties that distinguish foams from other dosage forms (Purdon et al., 2003). The structural matrix and composition of foam vehicles can undergo considerable changes after being expelled from the can and subsequently applied to the skin. The changes occur during and after initial agitation (spreading) and physico-chemical events including evaporation of volatiles and will influence the rate of drug transfer from the foam vehicle and into the skin in a time-dependent manner. Depending on the amount of volatile components and their rate of evaporation the drug will achieve saturation and even supersaturation, which will influence drug transfer from the foam vehicle into the skin.

5. Summary

The ability to distinguish between various aerosol foams is based primarily on their composition and resulting physicochemical properties. These properties allow for differentiation between the three aerosol foam types: hydroethanolic, emulsion, and aqueous. It is important to note that a foam is a multiphasic form, consisting of (i) the substance inside the container and (ii) the substance that is expelled from the container. As with creams, ointments, gels, and lotions, foam types are distinguished by composition and rheology.

The data showed that the three foam types tested behaved in similar fashions, as might be predicted because of their common uses. They differ, however, in the magnitude of the various properties measured. Hydroethanolic foams appeared to have higher yield stresses, higher elastic moduli, higher complex viscosities, and lower temperatures of decomposition. Consequently, their macrostructure showed greater strength and a greater ability to reversibly deform than the aqueous and emulsion foams, until a critical temperature was attained. At the critical temperature, the failure of the structure for the hydroethanolic foams was rapid compared with the emulsion foams, and occurred at lower temperatures. Aqueous foams showed good temperature stability—better than either the hydroethanolic- or the emulsion-based foams.

A combination of the measured rheological properties appeared to be most effective at differentiating between the different foams. G' and η^* showed clear and quantitatively large differences, probably, because they are fundamental measures of the macrostructure at rest. The macrostructure is dependant on the composition contained within the aerosol container. Further, the valve and actuator used to dispense the can contents may alter physical appearance of the foam. Yield stress appeared to differentiate HF, EF and AF, while temperature distinguished HF from EF and AF. Thus, the yield stress has some promise, but should be used in combination with viscoelastic and other data to better define the differences.

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