

INTRODUCTION

Topical products are widely used to manage skin conditions. **Semi-solid dosage forms** for therapeutic purposes are known to be diverse: ointments, pastes, gels, bi-gels, foams, lotions, and creams. This wide range of textures is due to their complex structure and can be deeply characterized by **rheological analysis**.

Rheological characterization of formulations is of major interest for two reasons:
 - Meet the requirements of recently released guidelines by the Food and Drug Administration and the European Medicine Agency, on **quality and equivalence of topical products**. The characterization of rheological behavior is actively highlighted, as the applicants are highly encouraged to submit a complete rheological profile, addressing

rotational and oscillatory measurements^{1,2}.

- Deeper understand the **microstructure** of the different dermocosmetic topical formulations, and put them in perspective with physicochemical stability data and sensorial analysis.

On five creams made of various compositions, a range of well-known rheological critical analytical attributes have been followed through time and at different temperatures. Viscosity, yield point, thixotropic relative area, storage modulus and loss modulus have been measured through different protocols, specifically designed to these products.

MATERIALS AND METHODS

Materials

Table 1. List of raw materials.

Tradename	Chemical name	Supplier
Pluro [®] Diisostearique	Polyglyceryl-3 diisostearate	Gattefossé
Gelot [™] 64	Glyceryl monostearate PEG-75 stearate	Gattefossé
Tefose [®] 63	Glycol stearate PEG-6 stearate PEG-32 stearate	Gattefossé
Emulcire [™] 61 WL 2659	Cetyl Alcohol (and) Ceteth-20 (and) Steareth-20	Gattefossé
Pluro [™] oleique CC 497	Polyglyceryl-3 diolate	Gattefossé
Labrafil [®] M 2130 CS	Lauroyl macrogol-6 glycerides	Gattefossé
Lanette [®] 0	Cetostearyl alcohol	BASF
Lanette [®] 16	Cetyl alcohol	BASF
Labrafac [™] Lipophile WL1349	Triglycerides medium-chain	Gattefossé
Mineral oil	Mineral oil	Aiglon
Light mineral oil	Light mineral oil	Cooper
Methyl paraben	Methyl paraben	Univar
Propyl paraben	Propyl paraben	Nipa
Satiaxane CX 91 NF	Xanthan gum	Cargill
Pemulen TR2 NF	Carbomer	Lubrizol
Carbopol 980-NF	Carbomer	Lubrizol
NaOH	Sodium hydroxide	VWR

Methods

Preparation of cream formulations

Cream formulations (Table 2) were conventionally prepared with Multi Homo equipment (Broggi). Depending on the formulation, continuous and dispersed phases were separately prepared and heated to 80°C and then added one to another in the tank.

After production, cream formulations were cooled down to room temperature. Batches of 2 kg were considered. All samples were stored at 20-25°C for room temperature and at 40°C for accelerated aging. Their simple physicochemical characteristics are monitored at different time points: pH (Mettler Toledo), microscopy (AX10, Zeiss) and viscosity (Brookfield viscosimeter).

Table 2. Composition of formulations.

Ingredients	FRESH FOCUS	CREAM-TO-GO	DUVET	EVANECARE	MRGENCY
PHASE I					
Emulsifier	Gelot [™] 64 3%	Gelot [™] 64 5%	Tefose [®] 63 12%	Tefose [®] 63 10%	Pluro [®] diisostéarique 5%
	Emulcire [™] 61 WL 2659 3%				Pluro [®] oléique CC 497 2%
Co-emulsifier	Cetyl alcohol 2%	Cetyl alcohol 2%		Cetostearyl alcohol 2%	
Oily solubilizer	Labrafac [™] Lipophile WL 1349 6%	Labrafac [™] Lipophile WL 1349 6%	Labrafil [®] M 2130 CS 3%	Labrafil [®] M 1944 CS 5%	
Mineral oil	Light mineral oil 6%	Light mineral oil 10%	Mineral oil 8%	Mineral oil 3%	Mineral oil 15%
PHASE II					
Water	80%	76%	74%	78%	76%
Preservative	Methyl paraben sodium salt	Methyl paraben sodium salt	Benzyl alcohol	Benzyl alcohol	Methyl paraben, Propyl paraben
	Sorbic acid	Sorbic acid			
Viscosity agent		Carbopol 980 NF 0.3%		Xanthan gum 0.3%	Sodium chloride
				Pemulen TR2-NF 0.2%	Magnesium sulfate 7H ₂ O
pH adjuster		NaOH		NaOH	

Rheological characterization

The rheological profile of all products was investigated using a HAAKE MARS 60 6000 (Thermo Scientific, Karlsruhe, Germany) equipped with a peltier system as temperature control unit. The data were evaluated using the Haake RheoWin Data Manager software (Thermo Scientific, Karlsruhe, Germany). All rheological tests were performed with a C35/2°/Ti cone geometry at 20°C.

Flow measurements: a linear CR step test from 0.01 to 1000 s⁻¹ was measured for 200s, to trace the flow curve [$\eta = f(\dot{\gamma})$].

Yield stress measurement: a CS ramp with a strain from 1 to 300 Pa, during 30s.

Thixotropy measurement: a CR ramp test was performed with a shear rate from 0.01 to 20 s⁻¹ and down again to 0.01, during twice 15s [$\tau = f(\dot{\gamma})$]. From this analysis, the thixotropic relative area (ΔA) was calculated.

Oscillatory measurements: An amplitude sweep test between 0.001 and 1 Pa at 1 Hz was conducted to estimate the linear viscoelastic region (LVER) plateau, and crossover point (τ_c). The storage modulus (G'), loss modulus (G'') were calculated at 1 Hz.

RESULTS AND DISCUSSION

Initial microstructure

Flow curve measurements (Figure 1) showed that all formulas are **shear-thinning fluids**: viscosity becomes lower at higher shear rates.

Considering the tested formulations, three groups can be distinguished, mainly driven by the emulsifier:
 - Combination of Pluro[®] oleique and Pluro[®] diisostéarique in MRGENCY bring higher viscosity, meaning the fluid is thicker and more resistant to flow.
 - Gelot[™] 64 in Cream-to-go and Fresh Focus provides the less viscous emulsions.
 - While with Tefose[®] 63 formulas (Duvet and Evanecare) of medium viscosity are obtained.

From a **thixotropic** (Figure 2) point of view, creams containing Gelot[™] 64 are also similar since they both exhibit a small thixotropic hysteresis area. MRgency cream has also a very small thixotropic hysteresis area, while Duvet formula shows a higher area. This area reflects the amount of energy dissipated during the cycles of deformation and recovery of the material.

Small hysteresis area: the material's internal structure remains relatively stable and resilient under repeated stress cycles: they are stable and well-structured materials.
Higher hysteresis area: This could suggest that the material's internal structure goes through substantial changes as it transitions between the deformed state and the recovered state. Such materials tend to be more prone to experiencing degradation due to the repeated stress cycles.

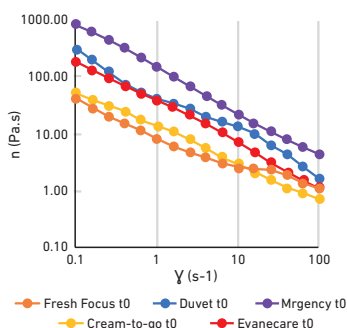


Figure 1. Flow curves of formulations.

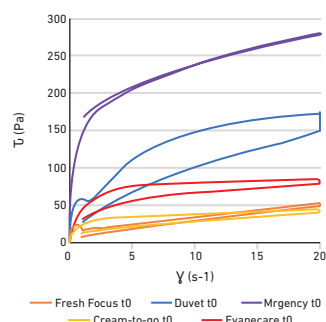


Figure 2. Thixotropy curves.

Oscillation tests are valuable for characterizing material's viscoelastic behavior. These tests involve subjecting the sample to alternating shear strain. Oscillation tests yield two primary parameters: G' (storage modulus) and G'' (loss modulus). G' represents the material's elastic behavior, while G'' represents the viscous behavior. Differences in these moduli reveal the dominance of elasticity or viscosity in the material's response.

Each formula **exhibits a predominantly solid structure with $G' > G''$** , but they exhibit different values for LVER and crossover point (τ_c), showing that there are **different viscoelastic behaviors** for these five formula.

Considering all these different rheological data on initial structure, different rheological and well discriminated profiles were observed. Duvet and Fresh Focus appear to be formulas that may experience instabilities over time, while Evanecare, MRgency and Cream-to-go seem more stable.

Accelerated aging and stability monitoring

Accelerated exposure to aging conditions can help detect early signs of instability, such as abnormal variations in rheological properties. Some emulsions become **less viscous with time at higher temperature**, this is the case for Duvet and MRgency. However, Cream-to-go for example appears to show **higher viscosity with time and temperature**, as shown on oscillation measurements (Figure 3).

The stability monitoring for 6 months at 40°C enabled to follow the evolution of the various rheological tests described. Duvet cream appeared to be the less stable of the five formulas, as this could have been suggested during the initial characterization. These different rheological evolution between emulsions can be explained not only by their composition, but also by the **droplet size of emulsions, the presence of thickening agents and the molecular interactions** within ingredients.

From a sensorial point of view, creams with **higher yield stress tend to be perceived as thicker**, which is the case of MRgency cream, while those with **lower yield stress** are seen as more fluid and **easier to spread**, as shown Figure 4. It appears that all formula were very close to one another from a sensorial point of view, that make rheological parameters difficult to precisely correlate with sensorial attributes.

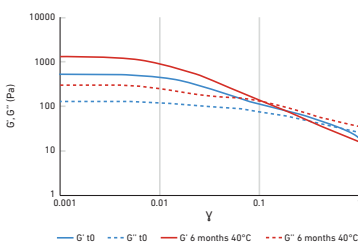


Figure 3. Oscillation curve of Cream-to-go at t_0 (blue) and after 6 months at 40°C (red).

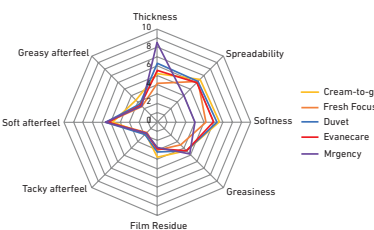


Figure 4. Sensorial analysis of formulations.

CONCLUSION

In this study, rheology emerged as a **large and complex tool** for the comprehensive characterization of five distinct cream formulations regarding their **initial structure and after accelerated aging**. While rheological measurements provide **valuable insights into the mechanical behavior and stability of creams**,

translating these findings into sensory attributes, such as texture, spreadability, or feel, can be a complex endeavor. It can be used to precisely discriminate formulations on their viscoelastic parameters and thus will find crucial application in the **development of generic pharmaceutical creams** containing active ingredients.

REFERENCES

¹ US Food and Drug Administration Guidance for Industry—Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs. Available online: <https://www.fda.gov/media/162471/download> (accessed on 4 March 2023)

² Draft Guideline on Quality and Equivalence of Topical Products CHMP/QWP/708282/2018; European Medicines Agency: London, UK, 2018; pp. 1–36.