

ROSSANO Manon<sup>1\*</sup>, PELISSON Delphine<sup>1</sup>, DAUPHIN-CHANARD Elise<sup>1</sup>, CAISSE Philippe<sup>1</sup>

<sup>1</sup> Gattefossé SAS, 36 chemin de Genas, Saint-Priest - France  
\*Corresponding author, mrossano@gattefossé.com

## INTRODUCTION

Topical products play a crucial role in pharmaceutical industries, where their efficacy relies not only on the active ingredient (API) but also on formulation characteristics. The use of solubilizers in a topical formulation helps solubilization of poorly soluble APIs. Therefore, it is essential to have a formulation

chassis that can be modulated to incorporate this quantity of solubilizer. In this study, we investigate the influence of different excipients as solubilizers and their variation on the stability and rheological properties of topical creams.

## MATERIALS AND METHODS

### Materials

Emulsions have been made with ingredients as followed:

Table 1. Table of raw materials used.

Tradename	Chemical name	Supplier
Tefose® 63	Glycol stearate PEG-6 stearate PEG-32 stearate	Gattefossé
Labrafil® M 1944 CS	Oleoyl macrogol-6 glycerides	Gattefossé
Mineral oil	Mineral oil	Aiglon
Pemulen TR2 NF	Carbomer	Lubrizol
NaOH	Sodium hydroxide	VWR
Transcutol® P	Diethylene glycol monoethyl ether	Gattefossé
Capryol® 90	Propylene glycol monocaprylate	Gattefossé
Plurol® Oleique CC 497	Polyglyceryl-3 dioleate	Gattefossé
Geleol™ Mono and Diglycerides NF	Glyceryl Monostearate	Gattefossé
Cetostearyl alcohol	Cetostearyl alcohol	BASF
Xanthan Gum	Xanthan Gum	Jungbunzlauer
Benzyl alcohol	Benzyl alcohol	Sigma

### Methods

#### Preparation of cream formulations

The initial formulation used as a stable and well-known chassis is described in Table 2. It has been chosen because it is a formula known as sensorially very appealing and that includes Tefose® 63, a commonly used emulsifier specifically in topical mucosal treatments<sup>2</sup>.

Batches of 200g of oil-in-water emulsions were conventionally prepared with Raynerie (VMI) equipment. Continuous and dispersed phases were separately prepared and heated to 80°C and then added one to another in the beaker. After emulsification, cream formulations were cooled down to room temperature. All samples were stored at 20–25°C and at 40°C. Their simple physicochemical characteristics were monitored at different time points: pH (Mettler Toledo), microscopy (AX10, Zeiss) and viscosity (Brookfield viscosimeter).

#### Rheological characterization

The rheological profile of all products was investigated using a HAAKE MARS 60 6000 (Thermo Scientific, Karlsruhe, Germany). 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<sup>-1</sup> 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<sup>-1</sup> and down again to 0.01, during twice 15s [ $\tau = f(\dot{\gamma})$ ]. From this analysis, the thixotropic relative area ( $\Delta A$ ) 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 ( $\tau_c$ ). The storage modulus ( $G'$ ), loss modulus ( $G''$ ) were calculated at 1 Hz.

## RESULTS AND DISCUSSION

It was possible to achieve **10 stable formulations** described in Table 2, incorporating varying quantities of additional solubilizer:

up to 25% of Transcutol® P, 5% of Capryol® 90 and 15% of Plurol® Oleique CC 497 with or without the presence of a consistency agent

Geleol™ Mono and Diglycerides NF at 2%. All presented formulas are stable 6 months at 25°C and 40°C.

Rheological tests provided complementary information regarding the structure of the different formulations<sup>1</sup>.

In the rheological flow and yield stress curves for formulations with Transcutol® P (data not shown), we observe that viscosity and yield stress increase with the rising percentage of Transcutol® P. Additionally, the incorporation of 2% Geleol™ Mono and Diglycerides NF further enhances this effect. These findings suggest that both excipients contribute significantly to the viscoelastic properties of the formulations.

In oscillation tests,  $G'$  (storage modulus) represents the material's elastic behavior, while  $G''$  (loss modulus) represents the viscous behavior. All formulas exhibit a predominantly solid structure with  $G' > G''$ , meaning all formulas are viscoelastic solid materials.

As observed in Figure 1, whether combined with Transcutol® P or Capryol® 90, the addition of 2% Geleol™ Mono and Diglycerides NF generally increases  $G'$  value and extends the length of the Linear Viscoelastic Region (LVR) plateau. This results in more rigid products with greater resistance to strain.

The thixotropy tests in Figure 2 showed larger hysteresis areas under the curve with the use of solubilizers in the formulation. By adjusting the thixotropic properties, it is possible to tailor the cream's spreadability and texture to meet specific preferences or application requirements. This flexibility allows the creation of a range of products with various sensory profiles, enhancing user satisfaction and adherence.

Table 2. Composition of formulations.

Ingredients	Function	Initial chassis	169	170	176	192	193	182	177	185	186	187
<b>PHASE I</b>												
Tefose® 63	Emulsifier	10	10	10	10	10	10	10	10	10	10	10
Labrafil® M 1944 CS	Co-emulsifier	5	5	5	5	5	5	5	5	5	5	5
Cetostearyl alcohol	Thickener	2	2	2	-	-	-	2	2	2	2	2
Mineral oil	Oily phase	3	3	3	3	3	3	3	3	3	3	3
Geleol™ Mono and Diglycerides NF	Thickener	-	-	-	2	2	2	-	2	-	-	-
<b>PHASE II</b>												
Xanthan gum	Gelling agent	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Pemulen TR2-NF	Gelling agent	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Deminerized water	Water phase	QSP	QSP	QSP	QSP	QSP	QSP	QSP	QSP	QSP	QSP	QSP
Benzyl alcohol	Preservative	1	1	1	1	1	1	1	1	1	1	1
Sodium hydroxyde (10%)	Neutralizer	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Transcutol® P	Solubilizer	-	5	10	15	20	25	-	-	-	-	-
Capryol® 90	Solubilizer	-	-	-	-	-	-	5	5	-	-	-
Plurol® Oleique CC 497	Solubilizer	-	-	-	-	-	-	-	-	5	10	15
<b>Total</b>			<b>100</b>									

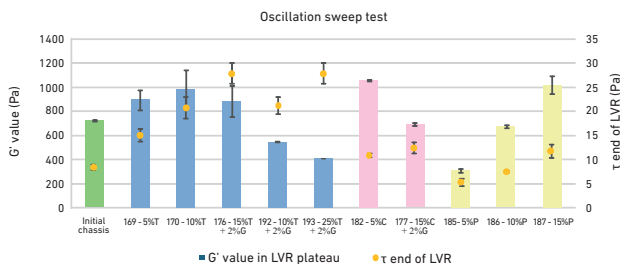


Figure 1.  $G'$  values and stress  $\tau$  of end of LVR values for formulations measured during Oscillation sweep tests after six months of stability at room temperature.

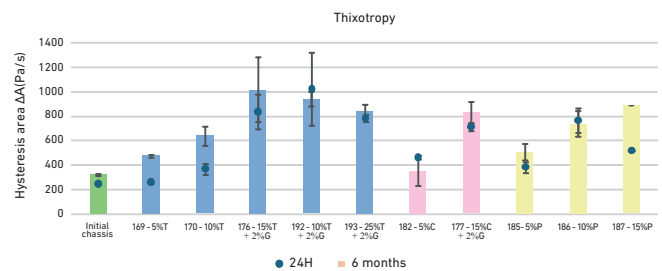


Figure 2. Hysteresis area  $\Delta A$  (Pa/s) values for formulations measured during Thixotropy tests after 24h and six months of stability at room temperature.

## CONCLUSION

These findings highlight the potential of combining various Gattefossé excipients as solubilizers and Geleol™ Mono and Diglycerides NF as thickener to obtain stable formulas and offering a range of viscoelastic properties.

## REFERENCES

<sup>1</sup> Chiarentin, L.; Cardoso, C.; Miranda, M.; Vitorino, C. Rheology of Complex Topical Formulations: An Analytical Quality by Design Approach to Method Optimization and Validation. *Pharmaceutics* 2023, 15, 1810. <https://doi.org/10.3390/pharmaceutics15071810>

<sup>2</sup> Poster Rossano, M.; Pelisson, D.; Yu, J.; Caisse, P.; Advanced rheological characterization of topical products: an accurate tool to discriminate and optimize formulations, presented during *Skin formulation, 6th symposium*, Nantes 2023