



Application of Microstructure Principles to Troubleshoot Topical Formulations

BASF Pharma Solutions



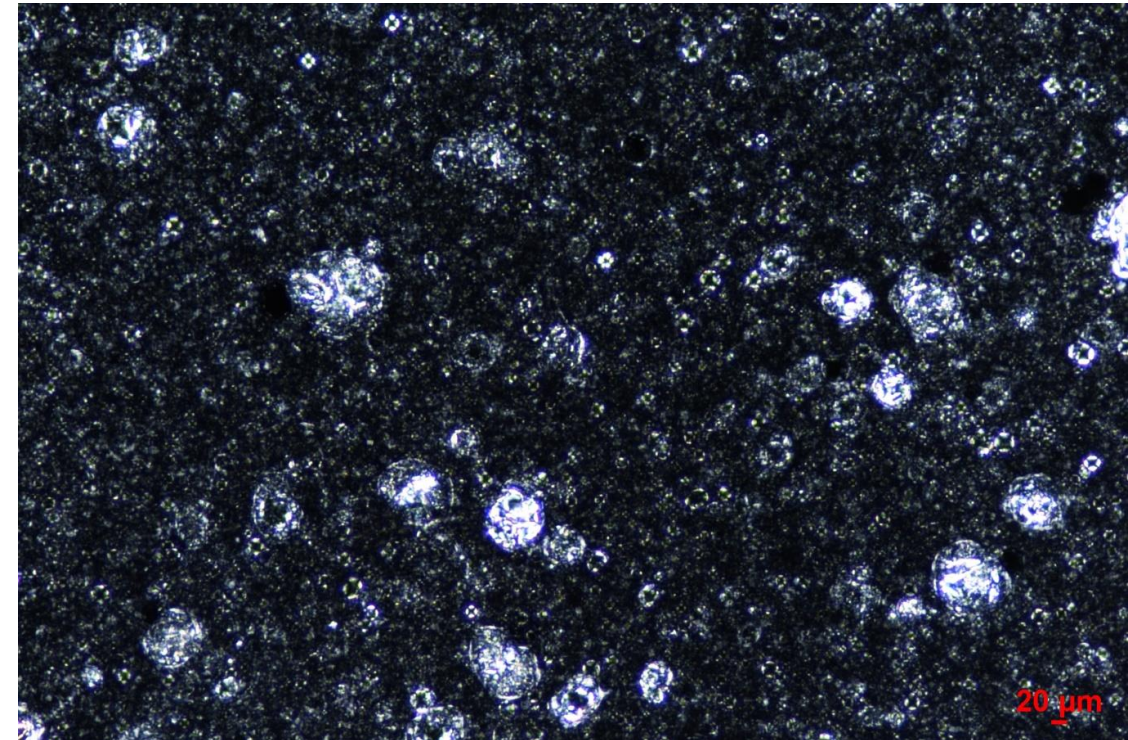
Agenda

- Introduction to microstructure
- Formulation of a cream
- Cream troubleshooting
 - ▶ Structuring agent to emulsifier ratio adjustment
 - ▶ Enhancing stability via excipient selection
 - ▶ Application of processing parameters on microstructure
- Conclusion



Microstructure is the microscale organization of matter in a semi-solid formulation

- To identify different structures, both bright-field and polarized microscopy can be employed
- When analyzing topical semi-solid microstructure, a magnification of 100x to 400x is typically applied; however, it is possible to use a lower or higher magnification if needed (40x to 1000x)
- Microstructure includes the identification of a variety of different structures including, but not limited to, crystalline materials or matrices, emulsion droplets, surfactant phases, and API crystals

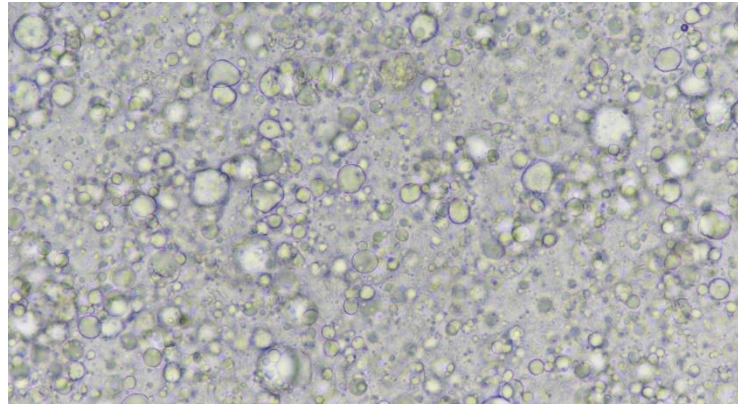


Topical semi-solid microstructure is driven by excipient selection and processing parameters



Formulation Inputs (Q1, Q2)

- Selection (Q1), amount (Q2), and grade of excipients
- Processing methods



Microstructure (Q3)

- Resulting microstructure
- Heterogenous system
- Non-equilibrium state

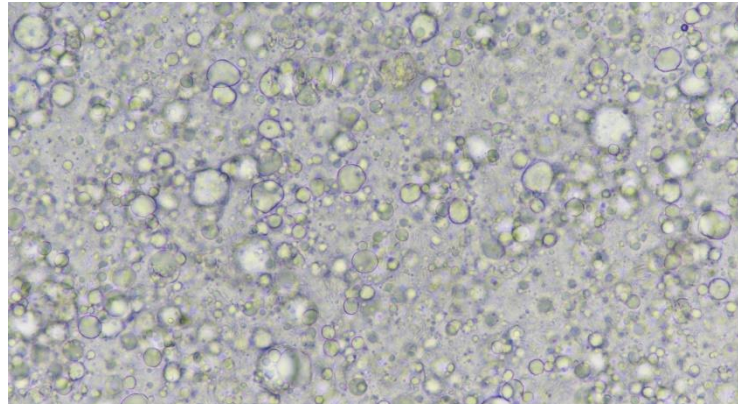


The resulting critical quality attributes and product performance are directly influenced by the microstructure



Formulation Inputs (Q1, Q2)

- Selection (Q1), amount (Q2), and grade of excipients
- Processing methods



Microstructure (Q3)

- Resulting microstructure
- Heterogenous system
- Non-equilibrium state



Product Attributes (CQAs)

- Rheology, sensory properties, appearance, stability
- API solubility, partitioning, release, absorption



Creams, ointments, and gels are the most common topical dosage forms used to achieve dermal drug delivery



Creams

- Provide emollience
- Tunable sensory attributes
- Typically two phase system



Ointments

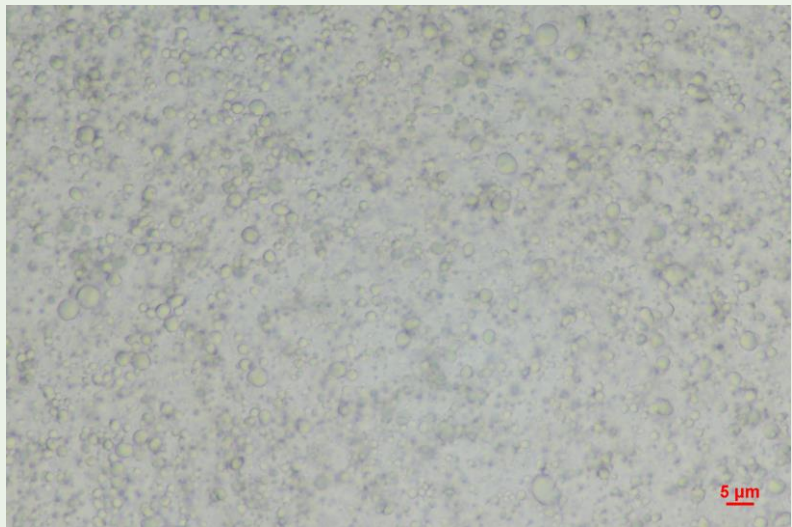
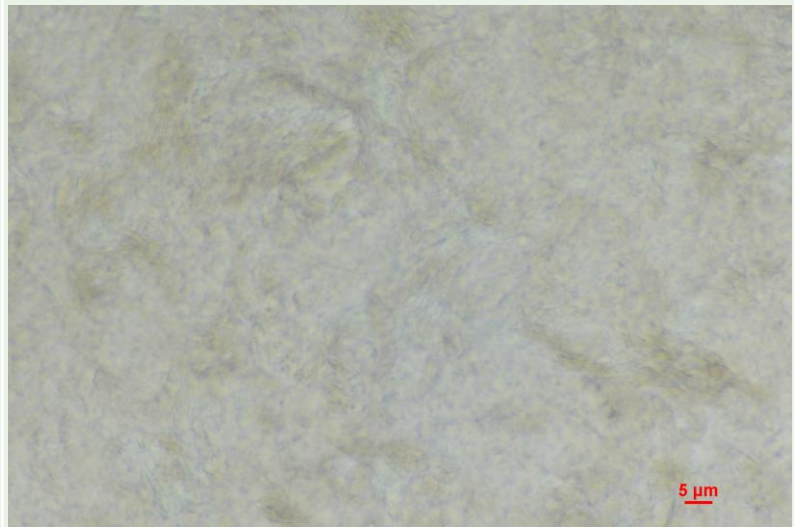
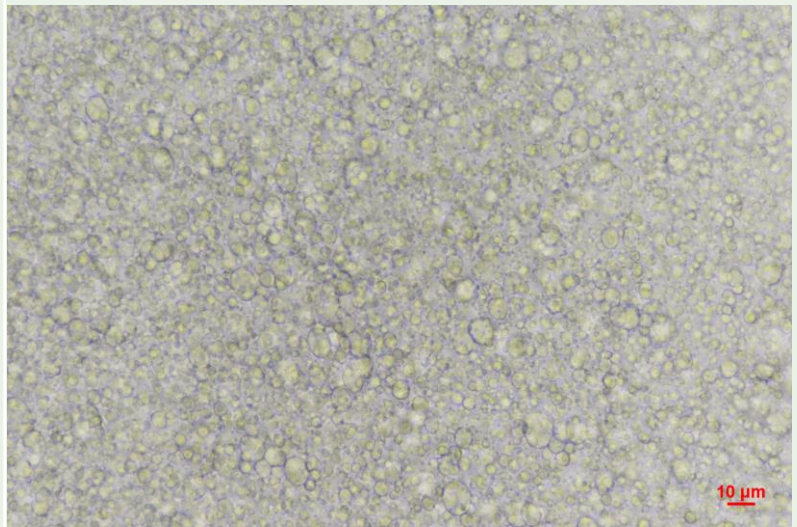
- Rich, higher viscosity
- Provide enhanced occlusivity to form protective barrier
- Typically single phase system



Gels

- Clear or semi-translucent
- Cooling sensation upon application
- Typically single phase system

The general performance of these three dosage forms can be predicted via microstructure

Cream	Ointment	Gel
 <p>5 μm</p>	 <p>5 μm</p>	 <p>10 μm</p>



Creams are composed of three key functionalities: emollients, emulsifiers, and structuring agents

Phase	Ingredient	% (wt/wt)
A	Water	Qs to 100
	Kollisolv [®] PEG	5 – 10
	Xanthan gum	0.1 – 0.3
	Preservative	0.3 – 1
B	Kollicream [®] emollient	10 – 20
	Kolliphor [®] emulsifier	≥ 20% of emollient
	Kolliwax [®] structuring agent	1 – 12



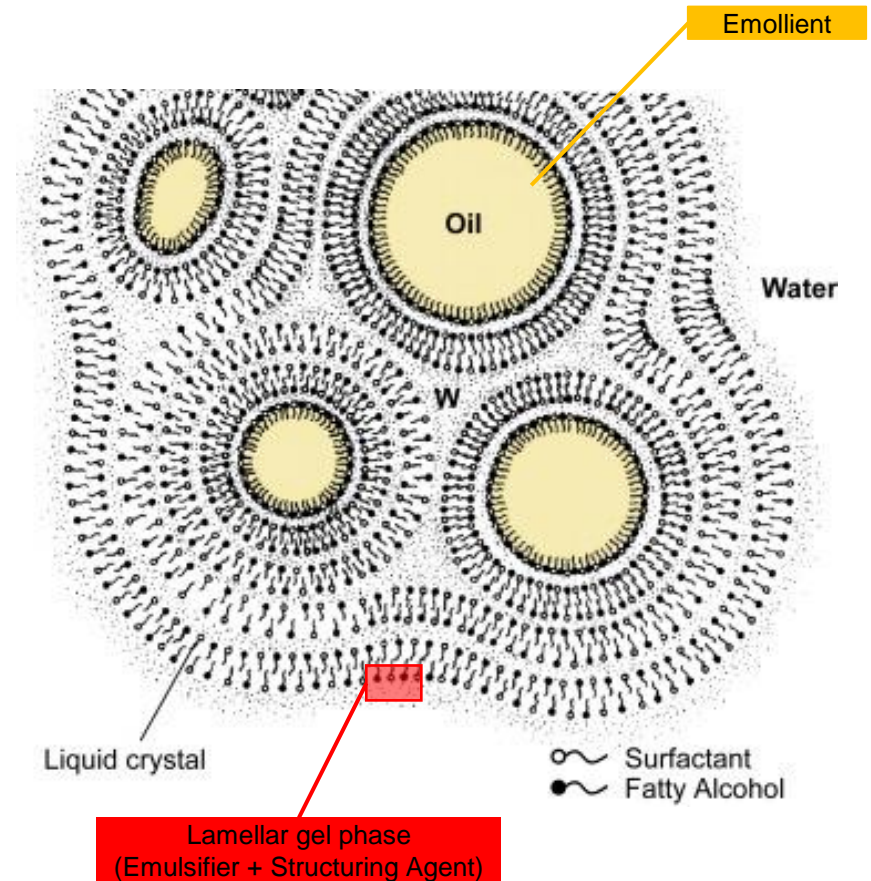
Each functional excipient exerts a different effect on the performance of the cream

Functionality	Description	Applicable BASF Excipients
Kollicream [®] emollient	<ul style="list-style-type: none"> Typically found in oil phase Solubilization of lipophilic API Can improve dermal drug delivery Enhances sensory aesthetics 	<ul style="list-style-type: none"> Kollicream[®] OA Kollicream[®] 3 C Kollicream[®] OD Kollicream[®] DO Kollicream[®] IPM
Kolliphor [®] emulsifier	<ul style="list-style-type: none"> Stabilizes emulsions by enabling two unlike phases to mix Has both hydrophilic and lipophilic properties 	<ul style="list-style-type: none"> Kolliphor[®] CS 12, 20 Kolliphor[®] PS 20, 60, 80 Kolliphor[®] CS A Kolliphor[®] CS L
Kolliwax [®] structuring agent	<ul style="list-style-type: none"> A higher melting point material that is typically a semi-solid or solid at room temperature Builds viscosity and provides structure to enhance stability 	<ul style="list-style-type: none"> Kolliwax[®] CA Kolliwax[®] SA Kolliwax[®] CSA 50, CSA 70 Kolliwax[®] MA Kolliwax[®] S Kolliwax[®] GMS II



Structuring agents and emulsifiers play a major role in stabilizing the cream via the formation of the lamellar gel network

- To build the lamellar gel network (LGN), the lamellar gel phase ($L\beta$) composed of the α -gel need be to formulated
- The α -gel which serves as the basic building block for the lamellar gel phase consists of the emulsifier and structuring agent
- The number of “onion” rings formed is based on the amount of emulsifier and structuring agent (SA) present
- To understand how compositional changes affect the lamellar gel network, microstructural analysis can be applied



Adjusting the composition of the cream has effects on the lamellar gel network, microstructure, and resulting performance properties

- To investigate the effect of the ratio of the structuring agent to the emulsifier, creams composed of the following materials were formulated:
 - ▶ Emulsifier: Kolliphor[®] CS 12, Kolliphor[®] CS 20
 - ▶ Structuring agent: Kolliwax[®] CSA 50, Kolliwax[®] GMS II
 - ▶ Emollient: Kollicream[®] IPM
- While increasing the percentage of the structuring agent in a formulation can shift this ratio upwards, the seemingly apparent enhancement in macrostructural stability and viscosity may only be temporary
- Microstructural analysis can be utilized to predict formulation stability and detect early signs of physical instability including creaming, coalescence, or phase inversion



The four emulsions studied contained various amounts of structuring agent and emulsifier

Phase	Ingredient	A	B	C	D
A	Kolliwax [®] CSA 50	5.9	7.6	8	4
	Kolliwax [®] GMS II	0.85	1.1	2	1
	Kolliphor [®] CS 20	4.1	4.1	4.1	-
	Kolliphor [®] CS 12	-	-	-	2
	Kollicream [®] IPM	10	10	10	10
B	Water	78.45	76.5	75.2	82.3
C	Euxyl [®] PE 9010	0.7	0.7	0.7	0.7

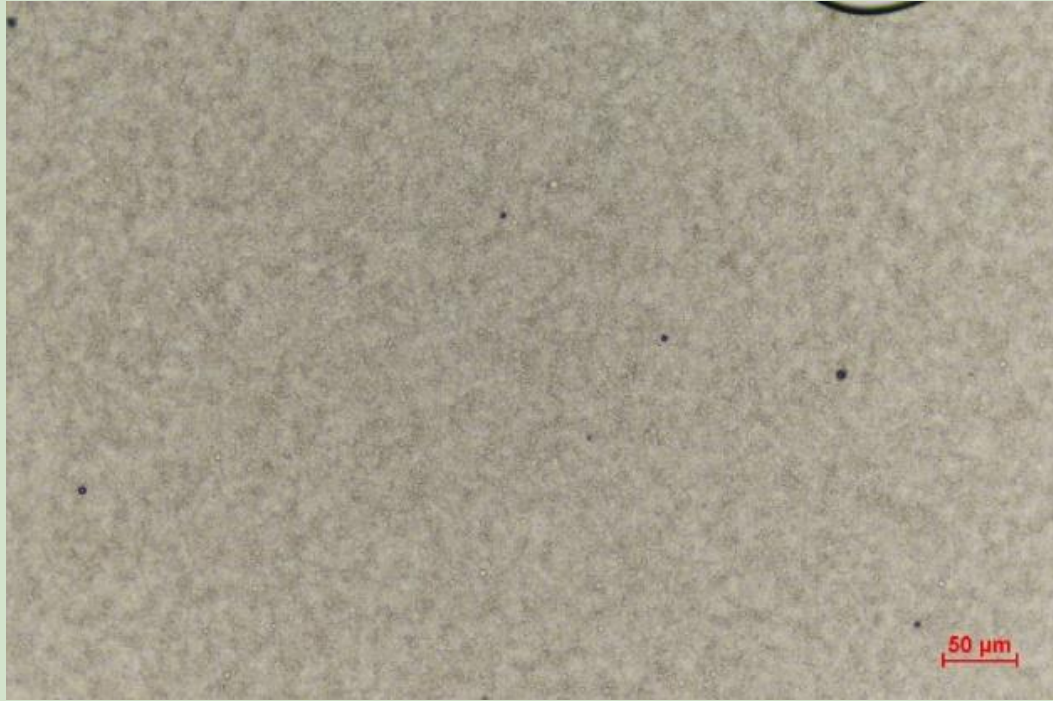


Increasing the structuring agent alone does not guarantee long-term product stability or complete emulsification

Cream A (5.9% CSA 50, 0.85% GMS II, 4.1% CS 20)

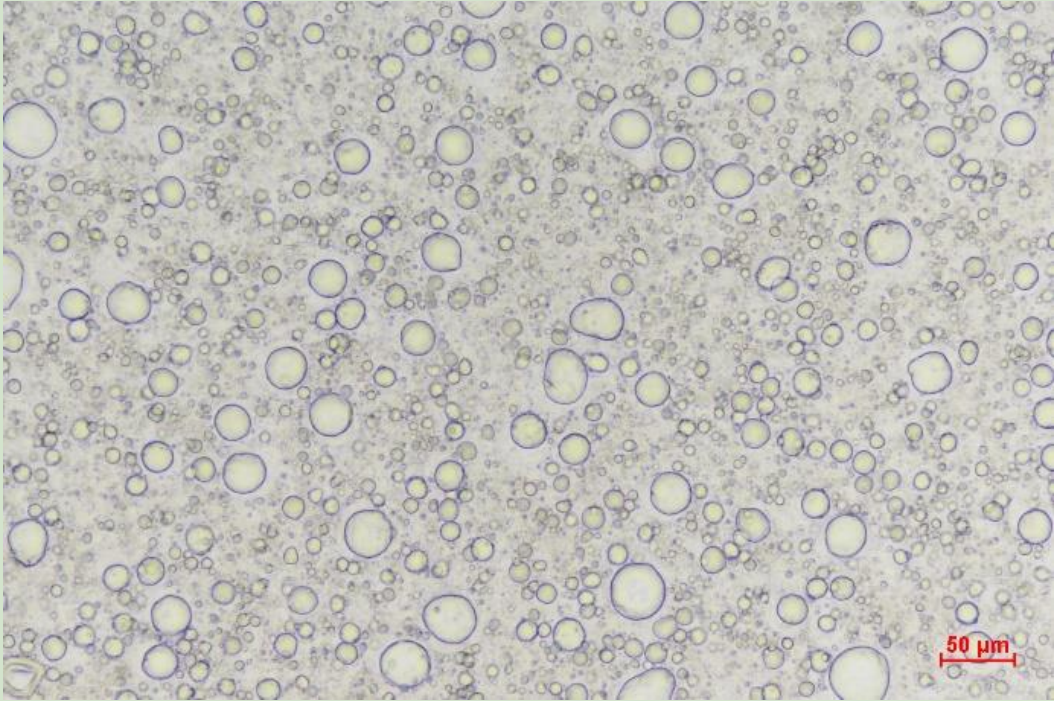


Cream B (7.6% CSA 50, 1.1% GMS II, 4.1% CS 20)

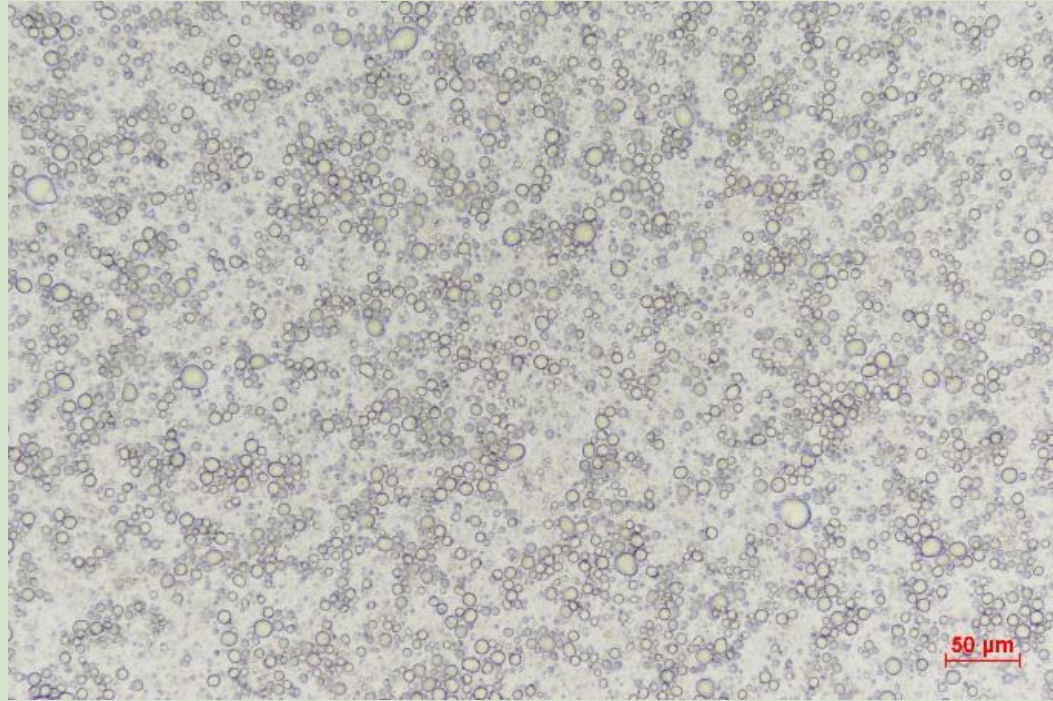


Rather, identification of the most suitable emulsifier and corresponding SA:emulsifier ratio promotes overall stability

Cream C (8% CSA 50, 2% GMS II, 4.1% CS 20)



Cream D (4% CSA 50, 1% GMS II, 2% CS 12)



When troubleshooting cream formulations, it is also important to consider the functionalities of the individual components

- While most excipients have one major functionality, some offer dual functionalities that can be leveraged to improve formulation microstructure and thus overall emulsion stability
- Kolliwax[®] GMS II, which is composed primarily of 1-glycerol monostearate and 2-glycerol monostearate, is a mixture that is traditionally used as a structuring agent
- Owing to free hydroxyl groups on the glycerol end of the molecule, Kolliwax[®] GMS II exhibits an amphiphilic character that is reflected in its HLB value of approximately 3.8



To address stabilization challenges, Kolliwax® GMS II can be synergistically incorporated into formulations with fatty alcohols

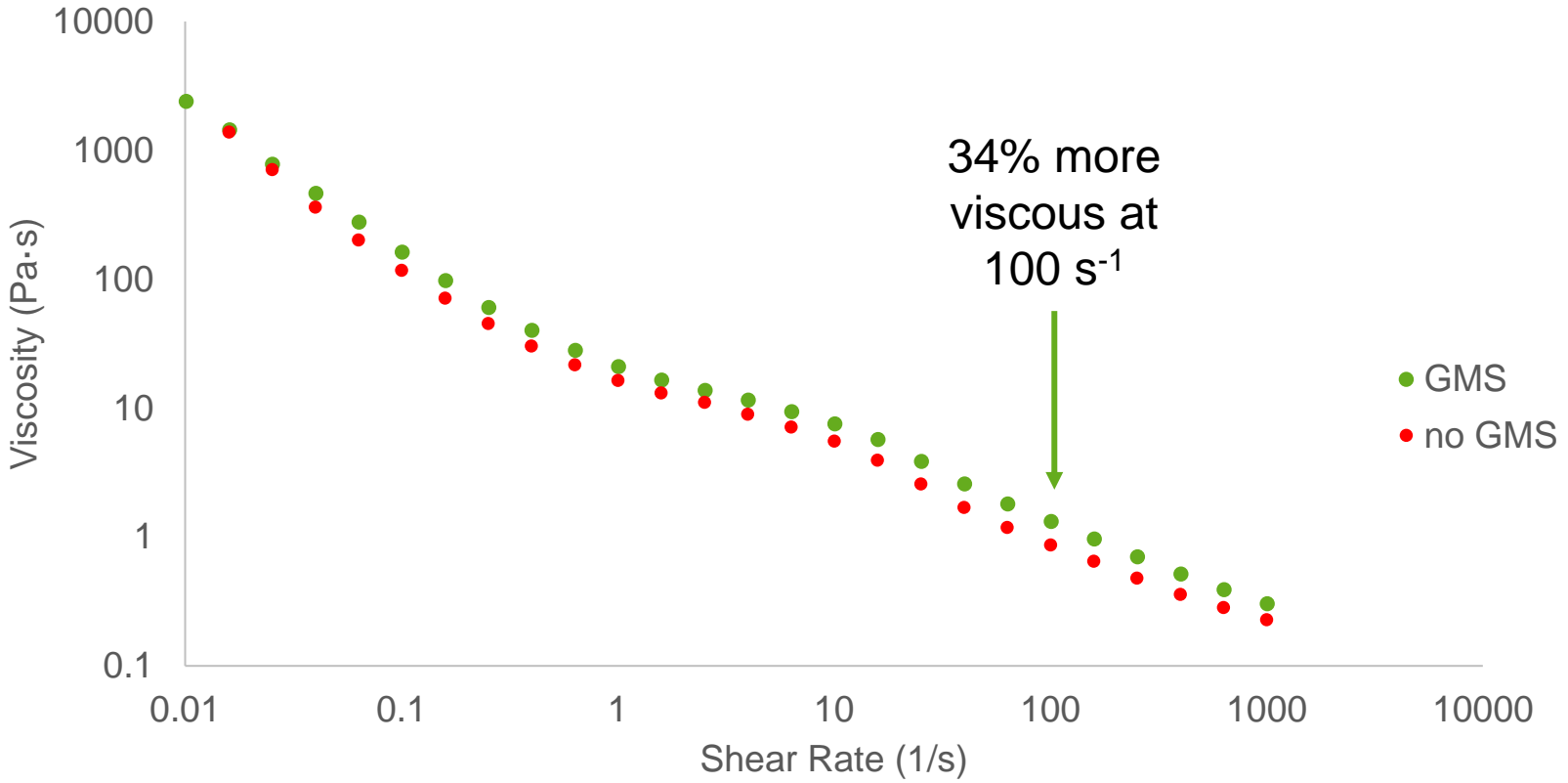
Phase	Ingredient	A	B	C
A	Kolliwax® CSA 50	8	8	10
	Kolliwax® GMS II	2	0	0
	Kolliphor® CS 20	4	4	4
	Kollicream® IPM	10	10	10
B	Water	75.3	77.3	75.3
C	Euxyl® PE 9010	0.7	0.7	0.7



Differences in microstructure reflects the compositional adjustments



Composition adjustments resulting in microstructural alterations influence performance parameters such as rheology



Alterations to the methodology or procedure can also influence microstructure and product performance

- When formulating topical semi-solids, three processing methods are commonly used:
 - ▶ Direct conventional method
 - ▶ Liquid crystalline lamellar gel method
 - ▶ Phase inversion method
- The selection of the method is dependent on a variety of factors including, but not limited to:
 - ▶ API sensitivity to heat
 - ▶ Emulsifier, structuring agent, and emollient selection
 - ▶ Preferred sensory profile

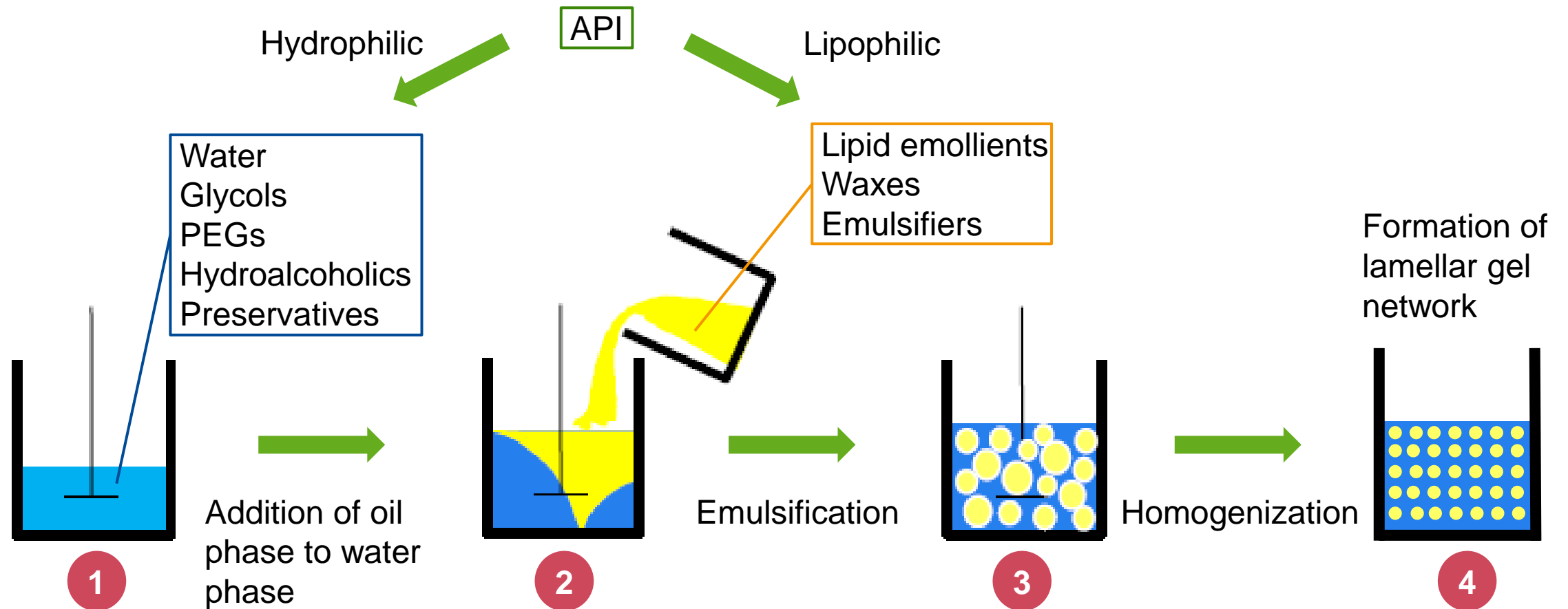


Alterations to the methodology or procedure can also influence microstructure and product performance

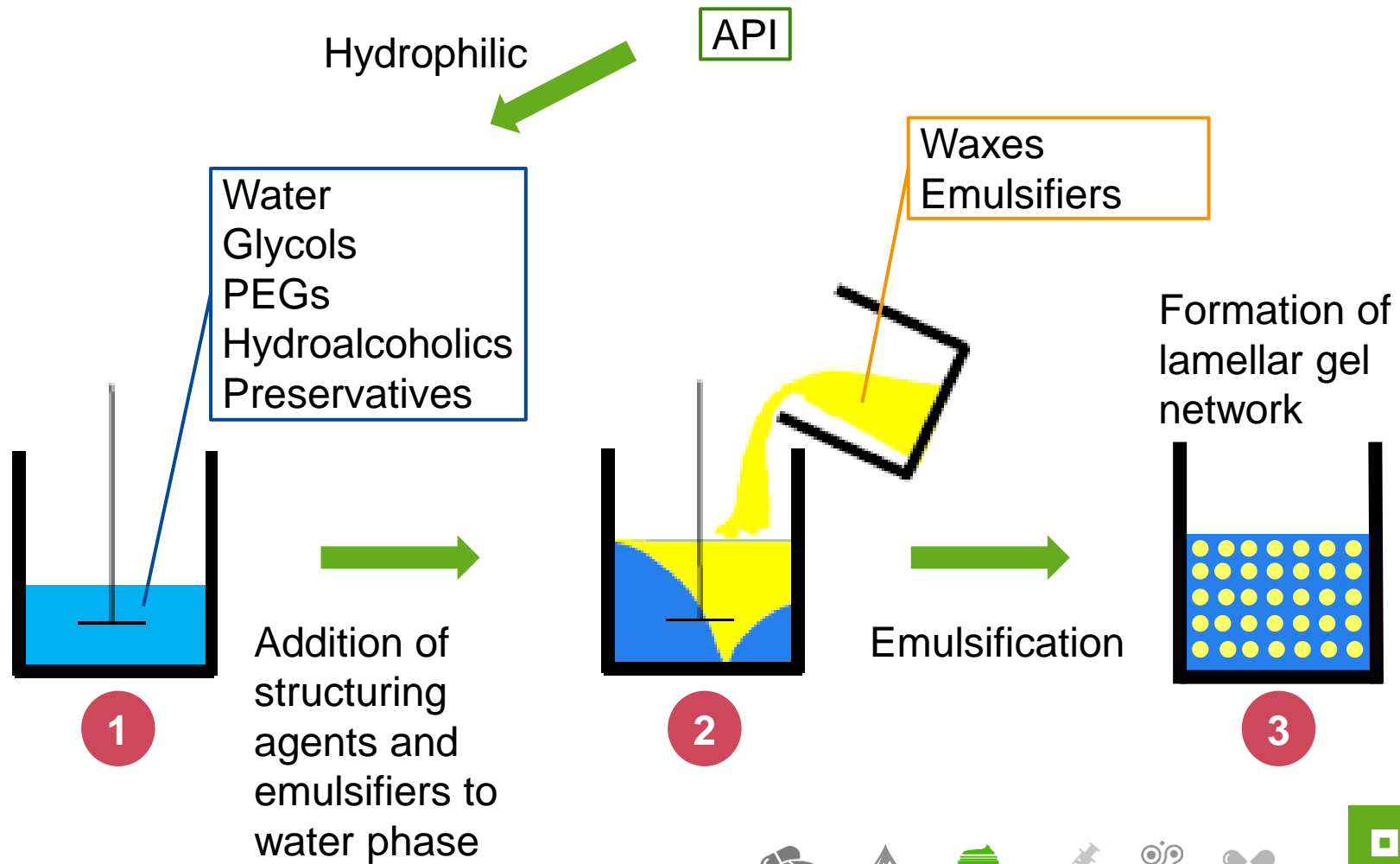
- When formulating topical semi-solids, three processing methods are commonly used:
 - ▶ **Direct conventional method**
 - ▶ **Liquid crystalline lamellar gel method**
 - ▶ Phase inversion method
- The selection of the method is dependent on a variety of factors including, but not limited to:
 - ▶ API sensitivity to heat
 - ▶ Emulsifier, structuring agent, and emollient selection
 - ▶ Preferred sensory profile



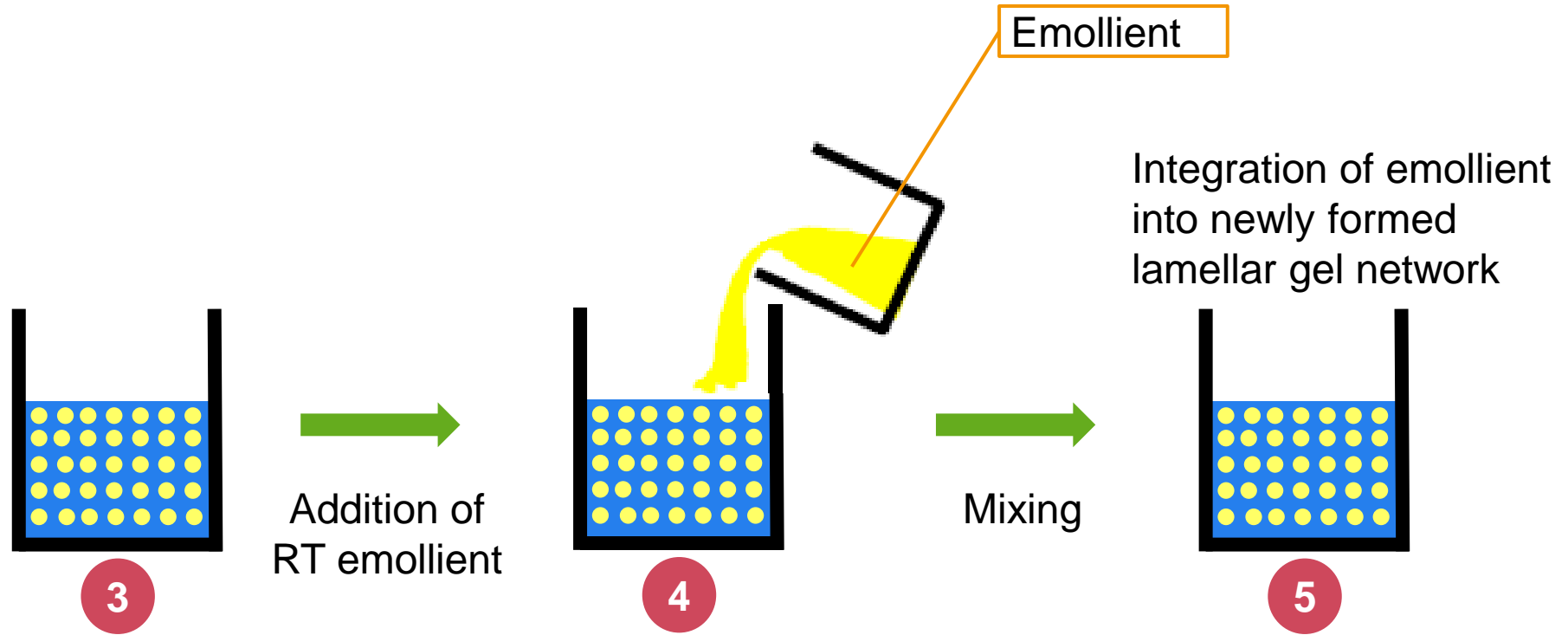
The direct conventional method is the most common processing procedure



The liquid crystalline lamellar gel method avoids the addition of heat to lipid soluble APIs

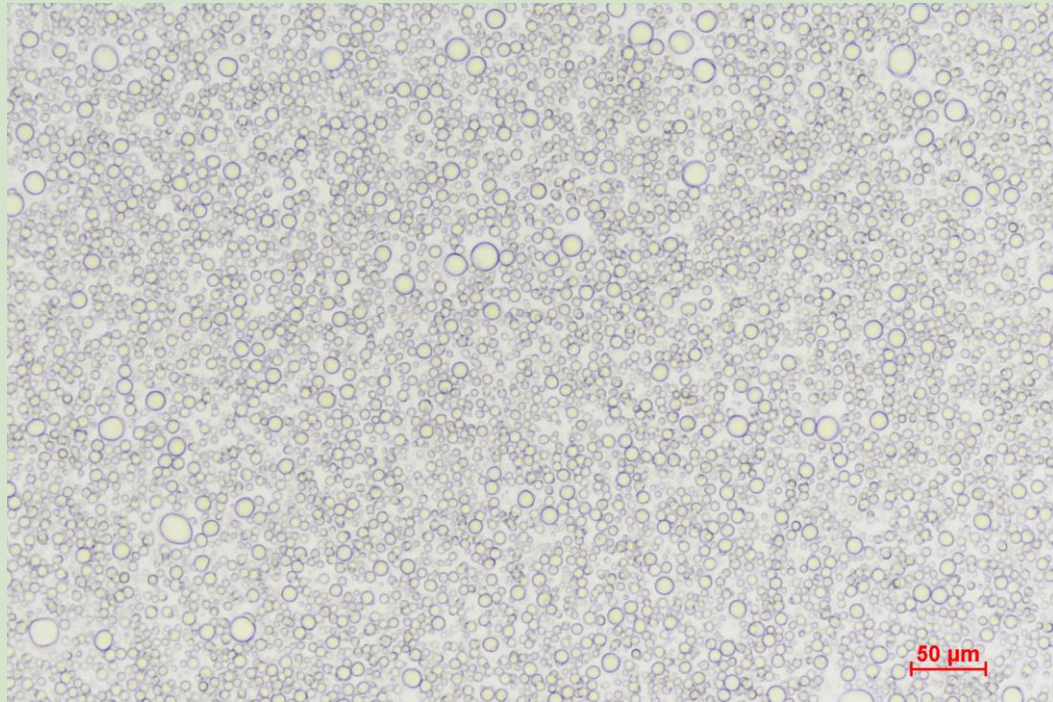


The liquid crystalline lamellar gel method avoids the addition of heat to lipid soluble APIs

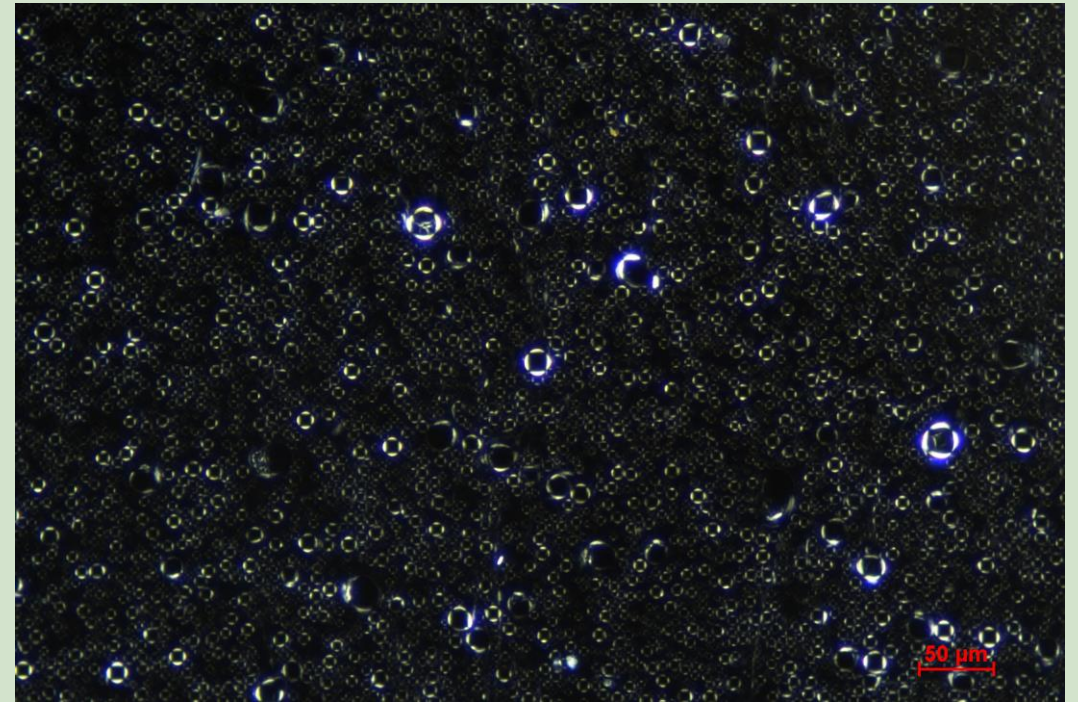


Dispersed oil droplets and Maltese crosses can be visualized when formulating via the direct conventional method

Bright-Field (200x magnification)

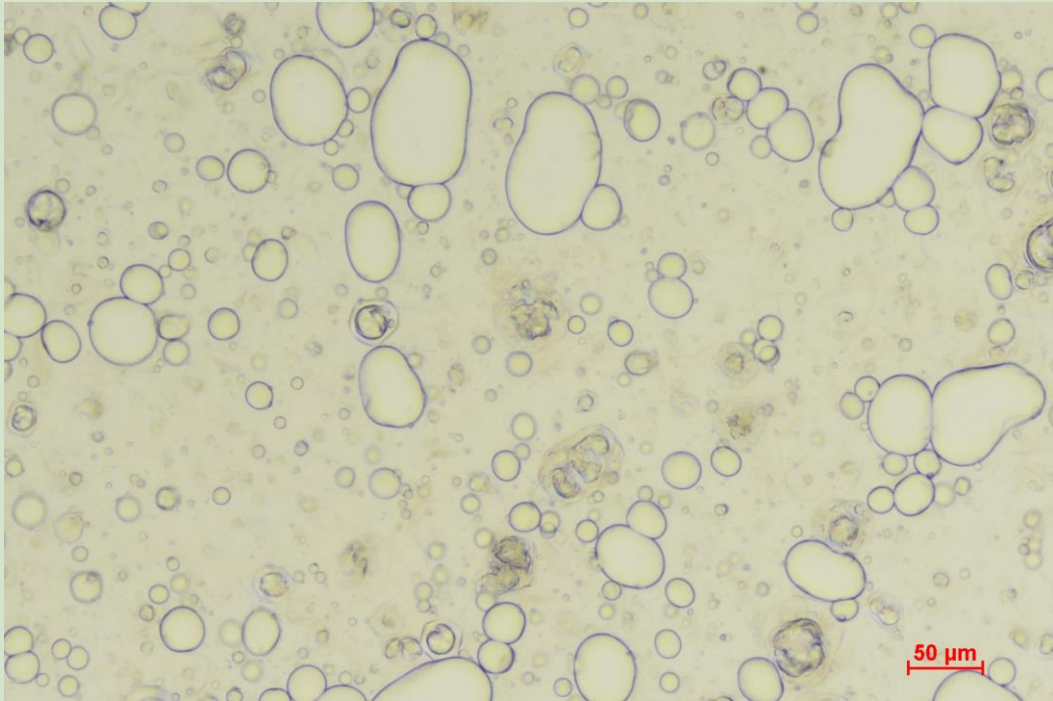


Polarized Light (200x magnification)

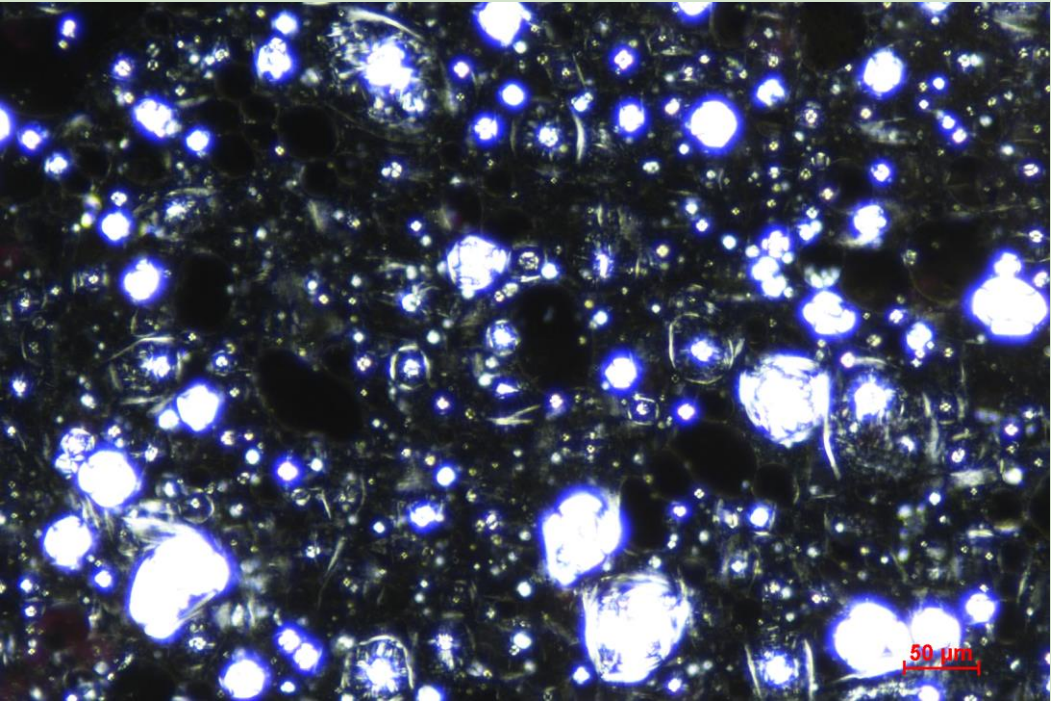


In contrast, processing creams via the liquid crystalline lamellar gel method allows for easy visualization of the “onion” layers

Bright-Field (200x magnification)



Polarized Light (200x magnification)



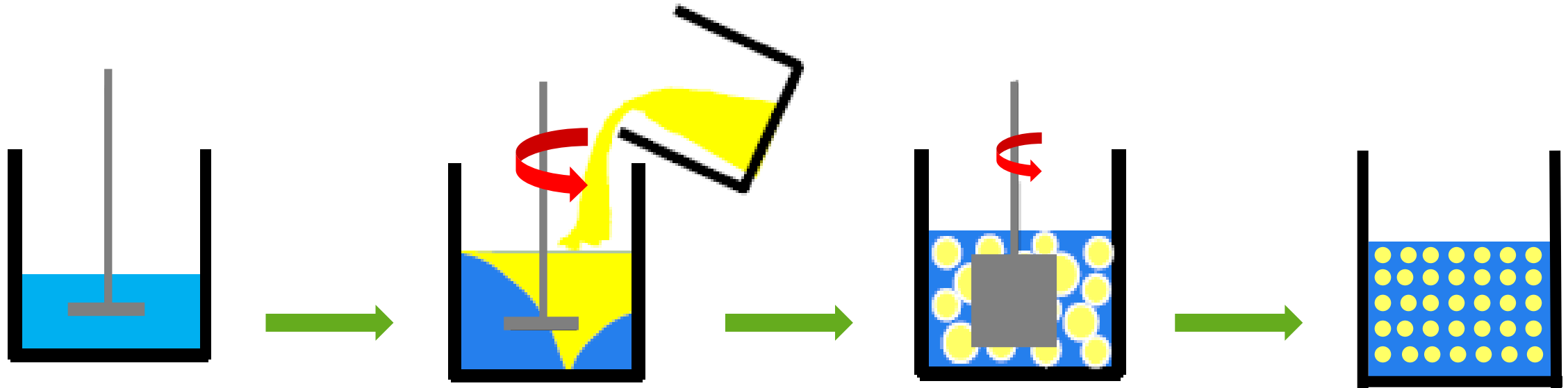
Rich Cream Formulation and processing

Phase	Ingredient	Chemical Name	% (wt/wt)
A	Kolliwax CSA 70	Cetostearyl Alcohol	7.00
	Kolliwax GMS II	Glycerol Monostearate 40-55 (Type II)	2.50
	Kolliphor PS 60	Polysorbate 60	4.20
	Kollisolv MCT 70	Medium Chain Triglycerides	11.50
	Kollicream IPM	Isopropyl Myristate	1.30
B	Deionized Water		69.20
	Glycerin		3.30
C	Euxyl PE 9010	Phenoxyethanol	1.00

- The direct conventional method is used to process this formulation



Direct conventional method as a processing procedure



1

Addition of heated oil phase to heated water phase

2

Emulsification

3

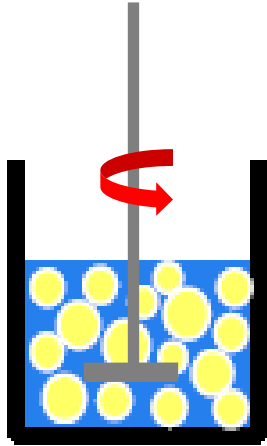
Homogenization

4



Different Processing Speeds

Slow



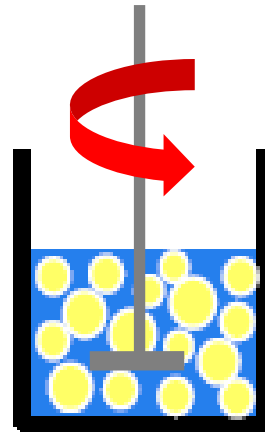
Speed

- Emulsifying: 100/130 rpm
- Cooling: 70 rpm

Mixer Type

- Emulsifying: Propeller (3 bladed)
- Cooling: Paddle

Medium



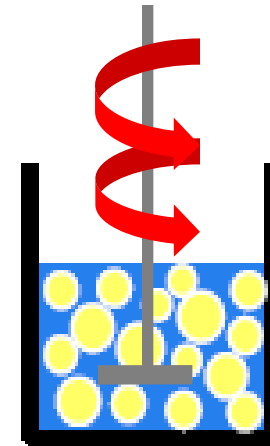
Speed

- Emulsifying: 300 rpm
- Cooling: 200/180 rpm

Mixer Type

- Emulsifying: Propeller (4 bladed)
- Cooling: Paddle

Fast



Speed

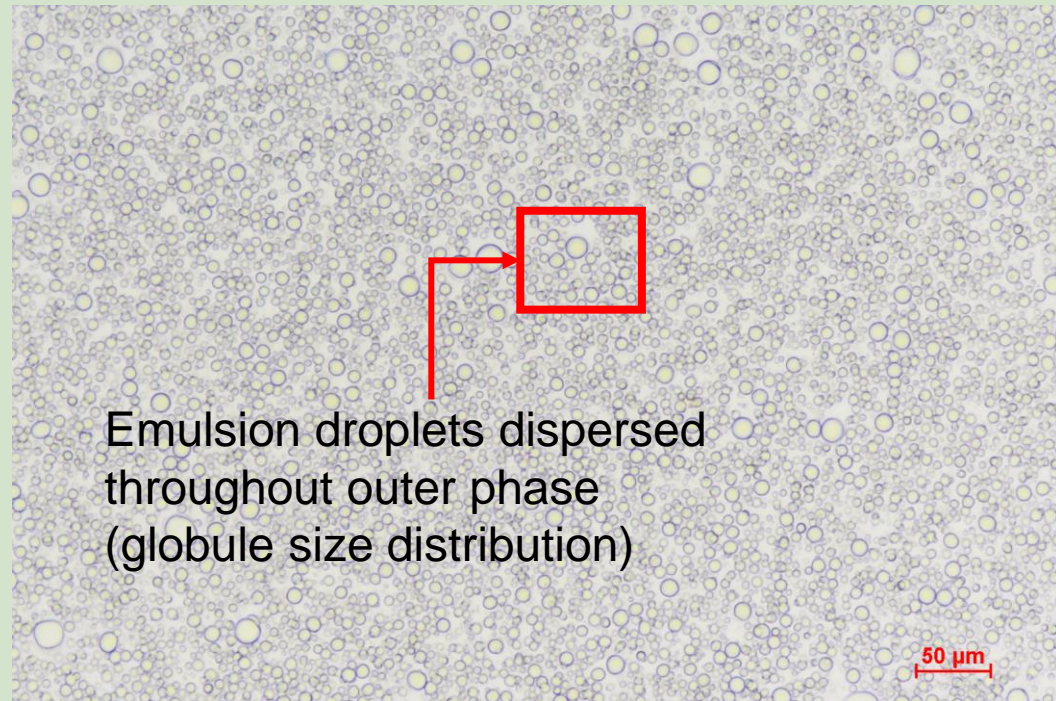
- Emulsifying: 450/500 rpm
- Cooling: 250/300 rpm

Mixer Type

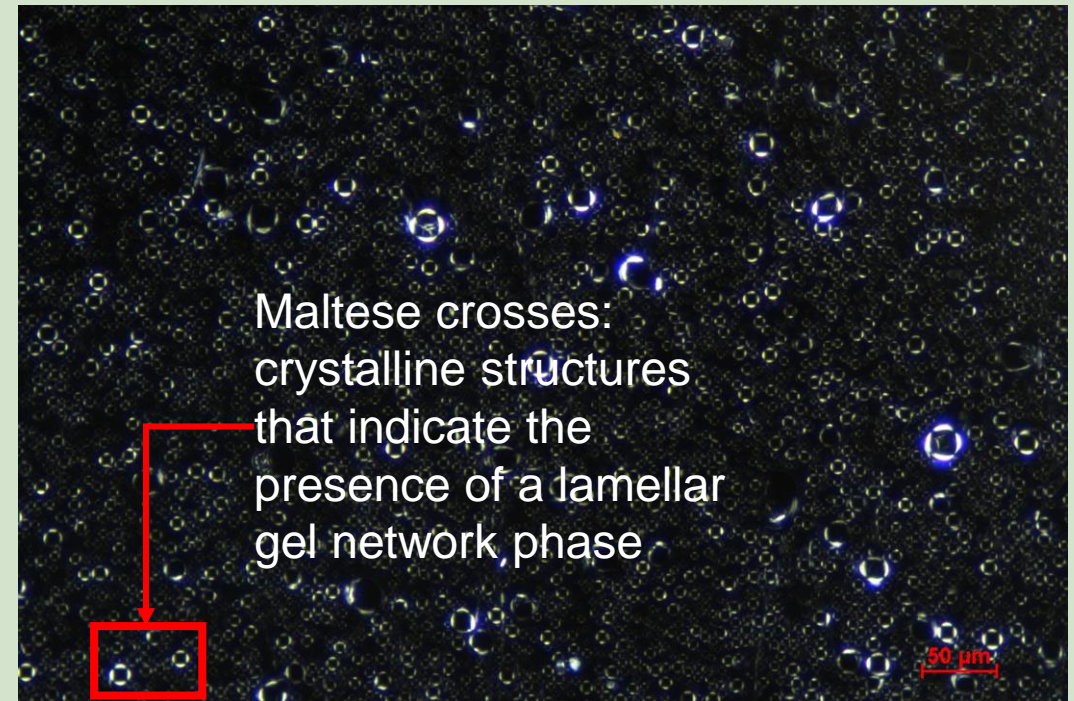
- Emulsifying: Propeller (4 bladed)
- Cooling: Spiral

Structures commonly found in cream or emulsion-based products

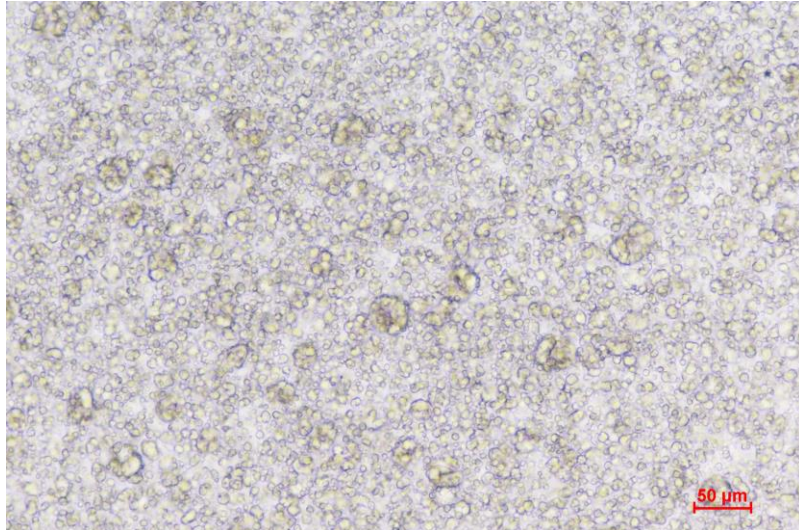
Bright-Field (200x magnification)



Polarized Light (200x magnification)

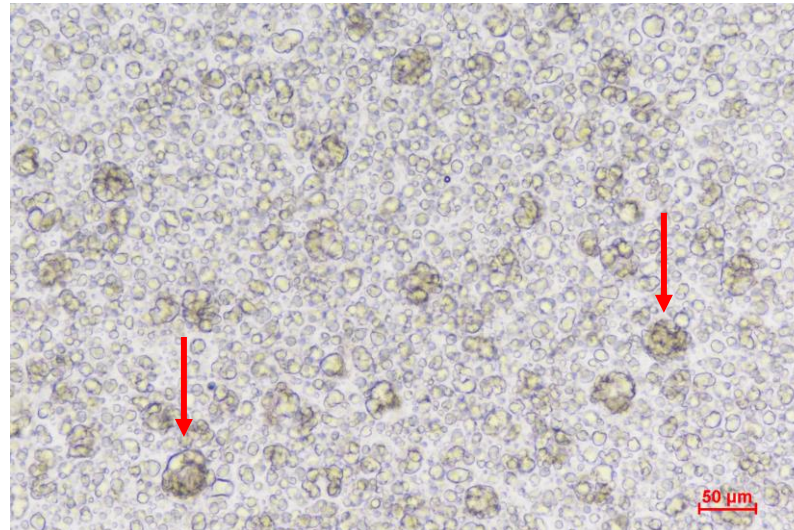


Brightfield Microscopy of Rich Cream Immediately Following Processing



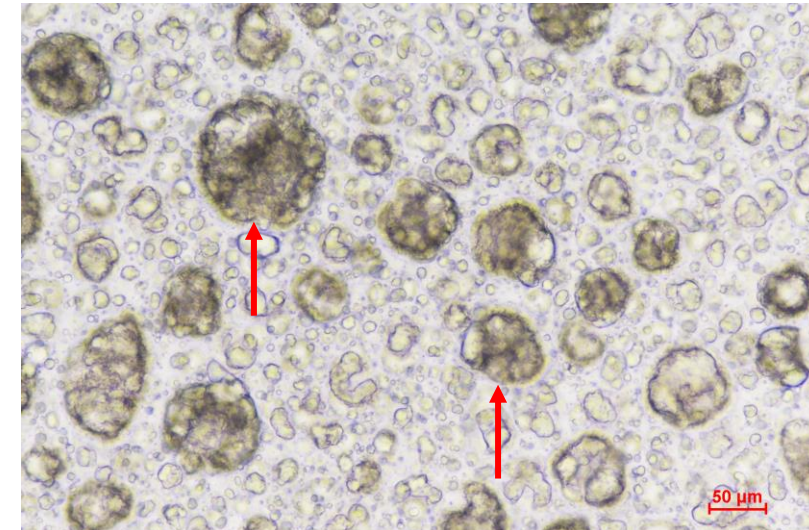
Slow Processing

- Small droplet size
- Even droplet dispersion
- Mild variance in droplet size



Medium Processing

- Small droplet size
- Even droplet dispersion
- Occasional small solid components visible (arrows)
- Moderate variance in droplet size

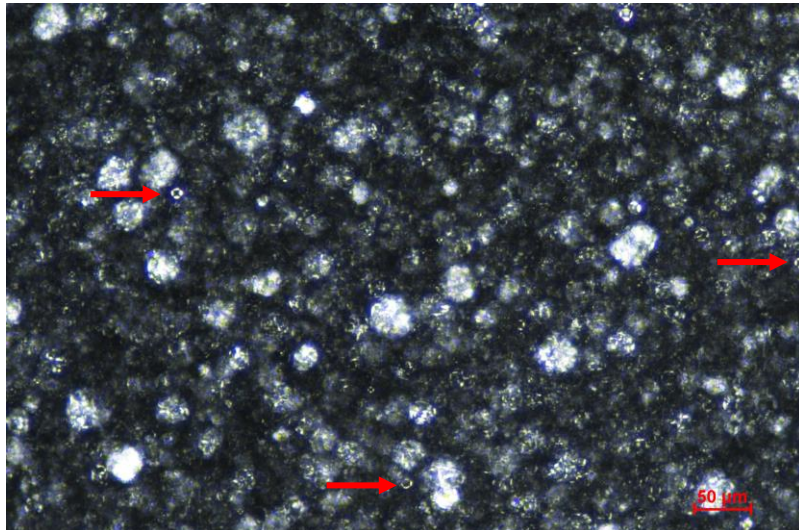


Fast Processing

- Large droplet size
- Uneven droplet dispersion
- Frequent large solid components visible (arrows)
- High variance in droplet size

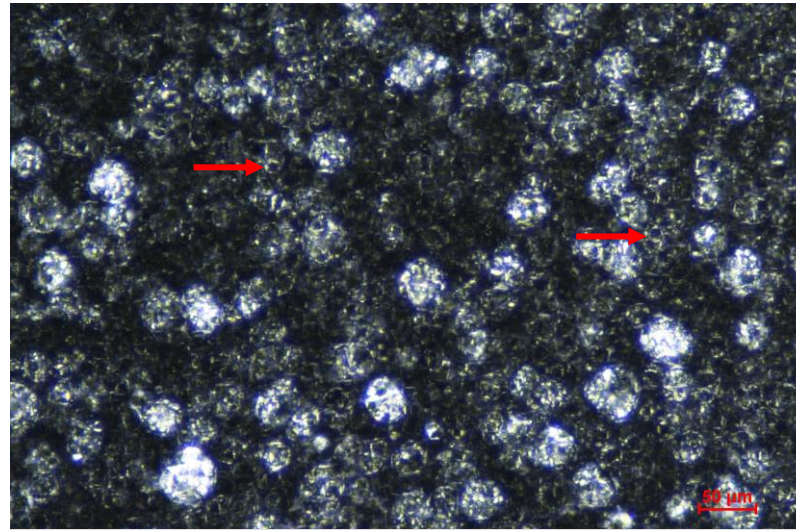


Polarized Microscopy of Rich Cream Immediately Following Processing



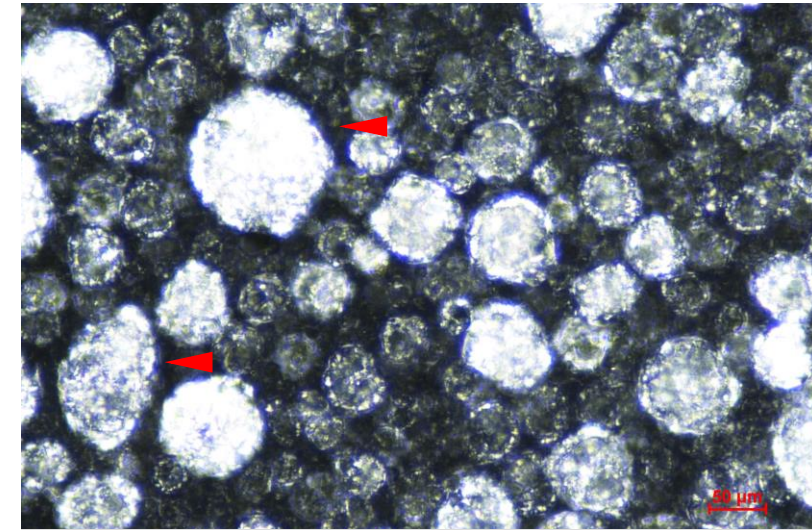
Slow Processing

- Uniform crystal structure size
- Smaller sized Maltese crosses (arrows)



Medium Processing

- Uniform crystal structure size
- Moderately sized Maltese crosses (arrows)

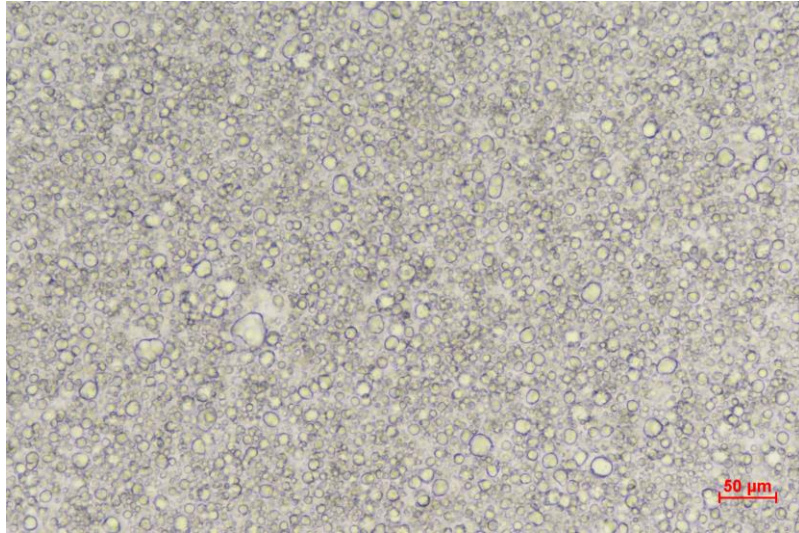


Fast Processing

- Unequal crystal structure size
- High presence of excess crystalline material
- Low presence of Maltese crosses

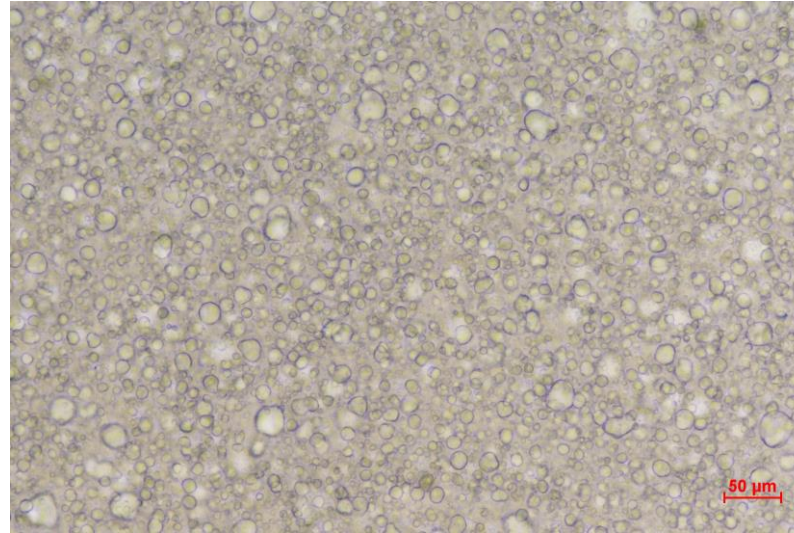


Brightfield Microscopy of Rich Cream 1 Month Post Processing



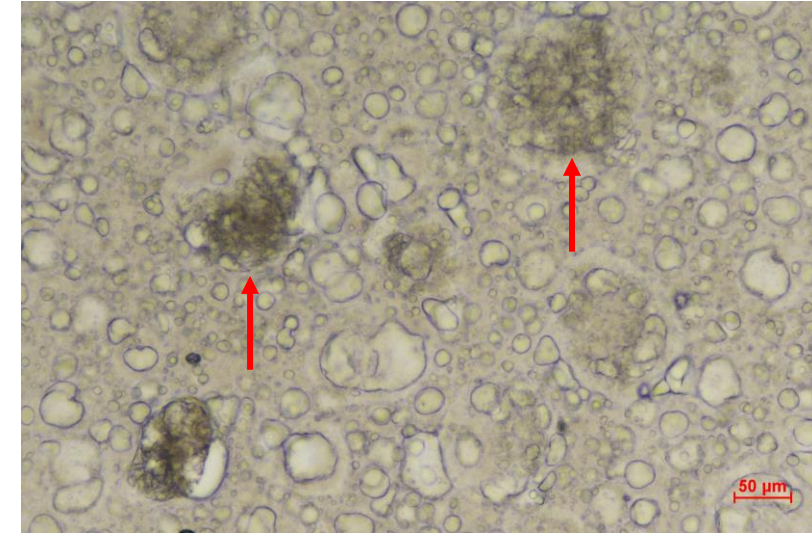
Slow Processing

- Small droplet size
- Even droplet dispersion
- Mild variance in droplet size



Medium Processing

- Small to medium droplet size
- Even droplet dispersion
- Moderate variance in droplet size

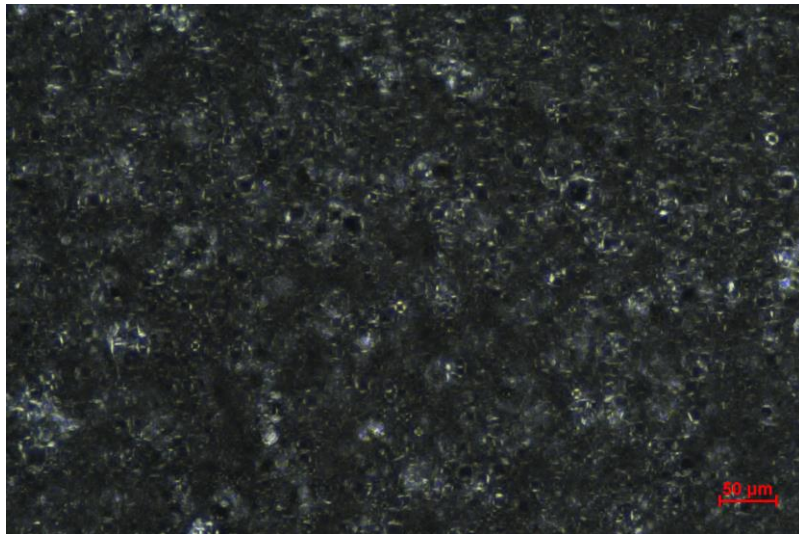


Fast Processing

- Large droplet sizes
- Uneven droplet dispersion
- Coalescence of droplets (arrows)
- Many large crystal formations; high variance in droplet size

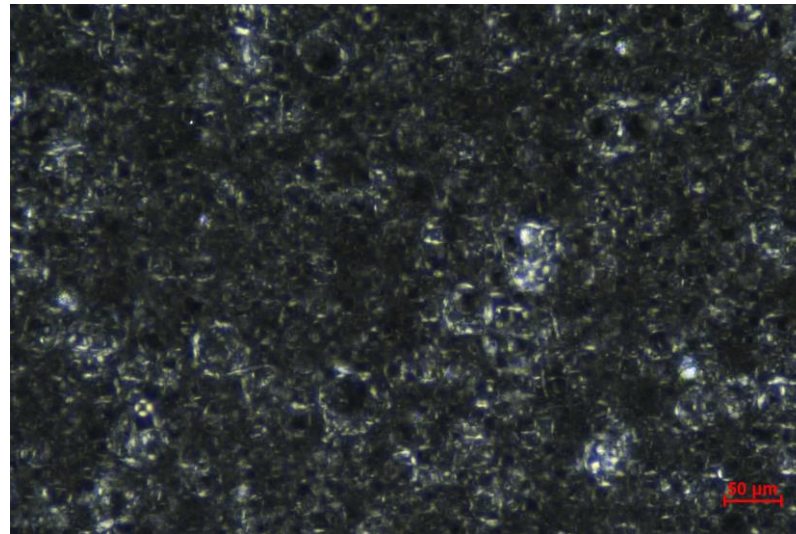


Polarized Microscopy of Rich Cream 1 Month Post Processing



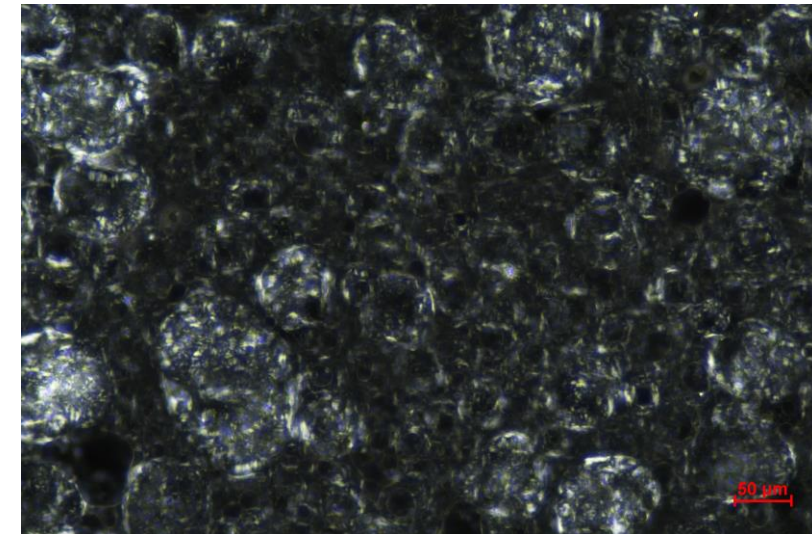
Slow Processing

- Uniform crystal structure size
- Moderate presence of Maltese crosses
- Smaller sized Maltese crosses



Medium Processing

- Uniform crystal structure size
- Moderate presence of Maltese crosses
- Moderately sized Maltese crosses



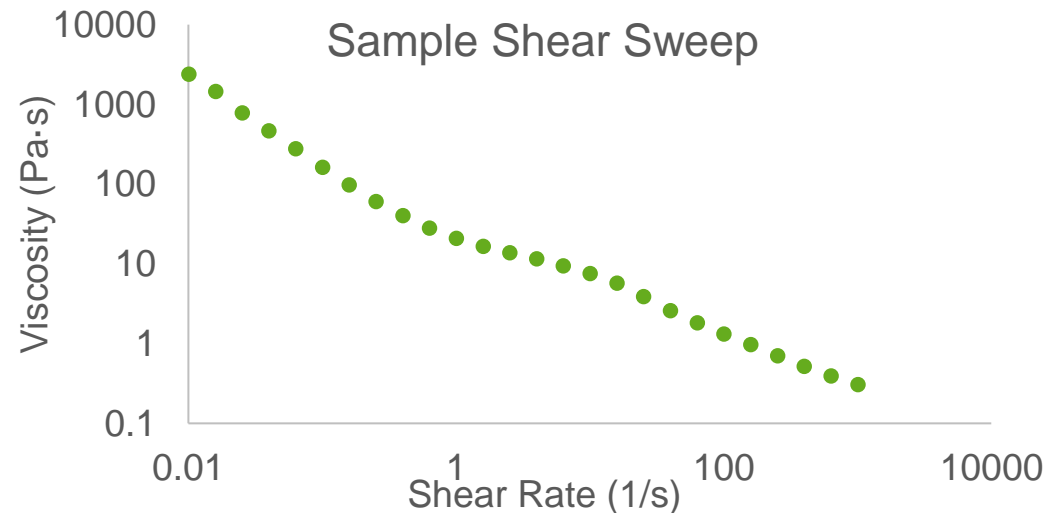
Fast Processing

- Varying crystal structure size
- High presence of excess crystalline material
- Low presence of Maltese crosses

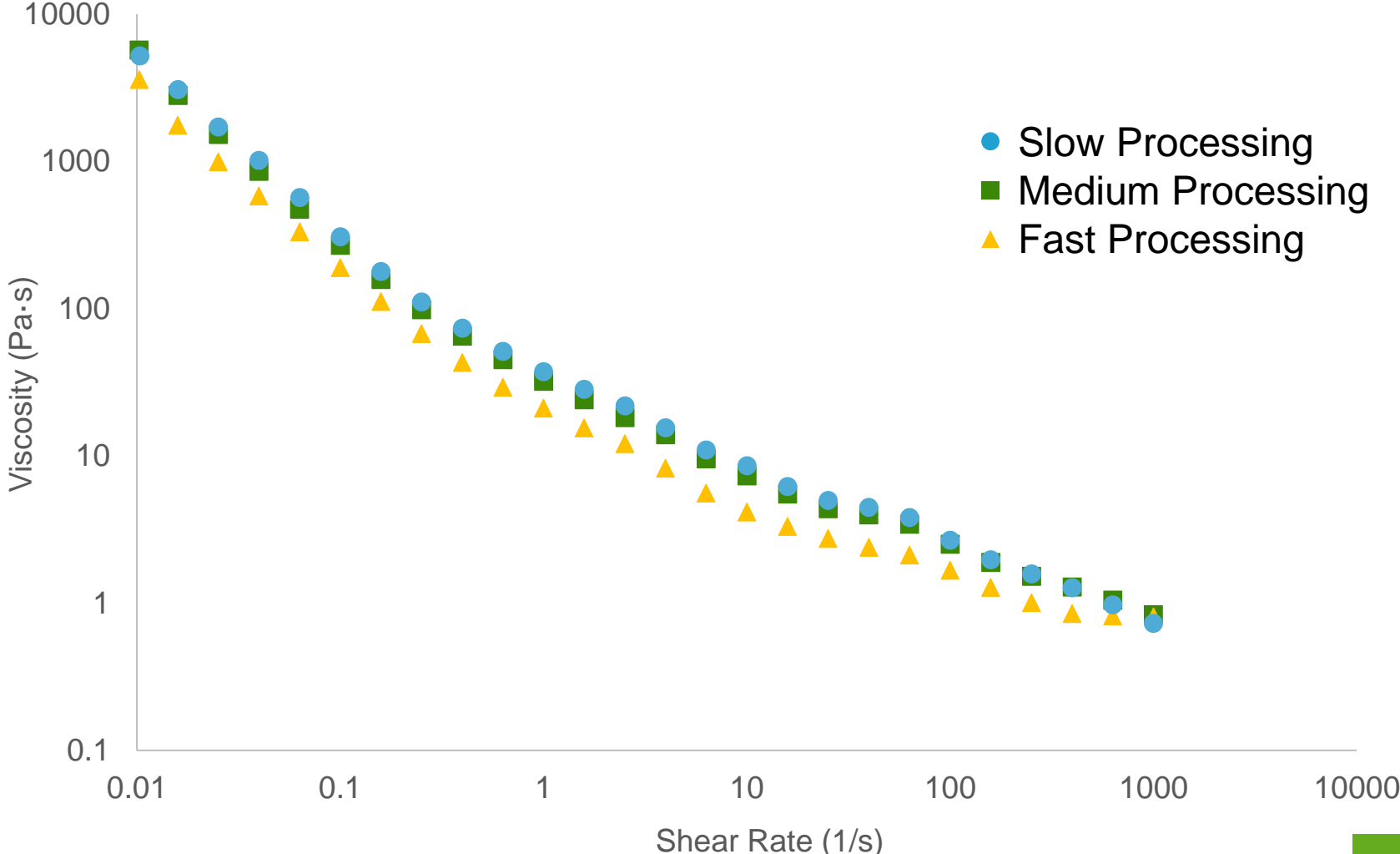


Rheology in analyzing semi-solid formulations

- Rheology data can indicate performance properties including:
 - ▶ Viscosity
 - ▶ Spreadability
 - ▶ Stability
- The resulting graph of the viscosity at a certain shear rate when plotted on a logarithmic scale should result in downward, linear-looking line



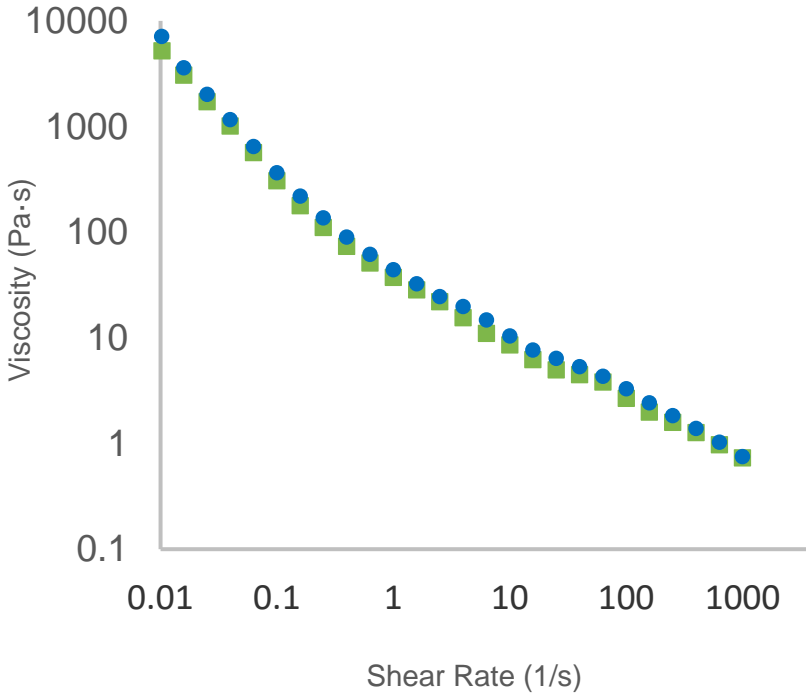
Rheology of Different Processing Methods Immediately After Homogenization



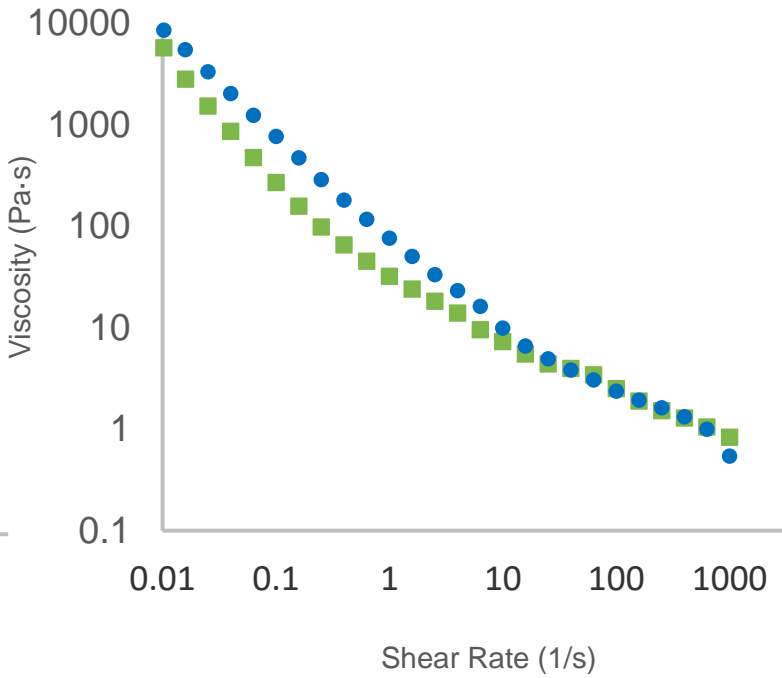
Internal

Rheology of Different Processed Rich Cream: Immediately and 1 Month Post-Processing

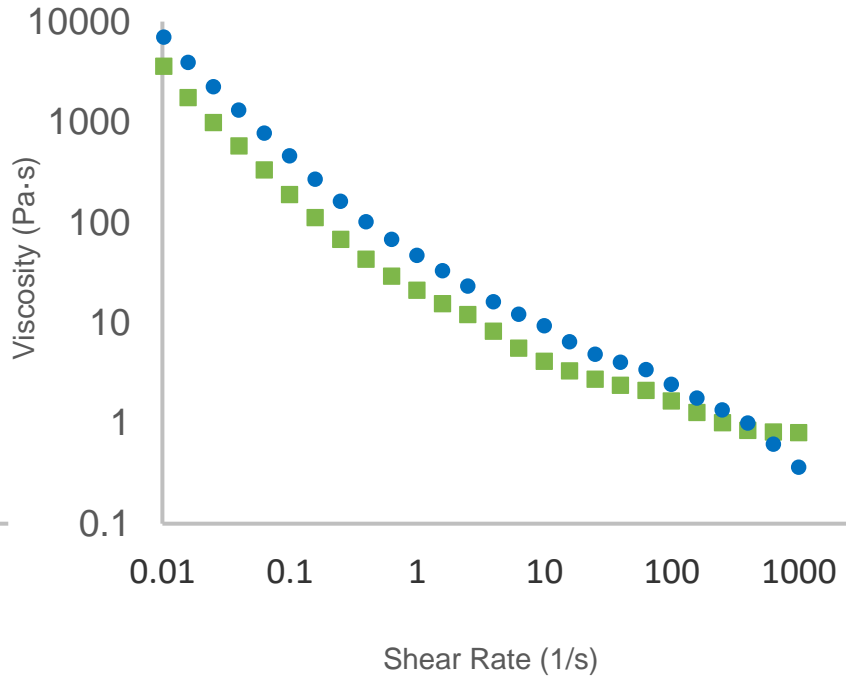
Slow



Medium



Fast



- Immediately Post-Processing
- 1 Month Post-Processing



Internal



Microstructure plays a pivotal role in the troubleshooting process

- Microstructure is the microscale organization of matter in a semi-solid formulation including structures such as crystalline materials or matrices, emulsion droplets, surfactant phases, and API crystals
- Driven by formulation inputs such as excipient selection and processing parameters, topical semi-solid microstructure influences performance properties of the resulting formulation
- To troubleshoot critical quality attribute challenges, microstructure analysis can be applied to identify causes of physical instability, differences in sensory profiles, and rheological differences
- Partner with BASF's technical experts to leverage the application of microstructure principles to troubleshoot topical formulations challenges





We create chemistry