

# A systematic approach to formulate and evaluate the stability of topical creams with high concentrations of Transcutol® HP

Masumi Dave, M.S., Ph.D.; Jason M. LePree, Ph.D., R.Ph.  
Gattefossé USA

CONTACT INFORMATION: 115 W. Century Rd.-Plaza 1, Suite 340, Paramus, NJ 07652

## PURPOSE

Transcutol® HP (Diethylene glycol monoethyl ether) is widely used as a solvent for poorly soluble actives and as a permeation enhancer for the skin. Some active ingredients require higher amounts of Transcutol® in a formulation for solubilization. However addition of Transcutol® HP (or P) to emulsions at concentrations above 20% w/w has been challenging.

## OBJECTIVES

1. Develop stable hydrous and anhydrous creams with high concentrations of Transcutol® HP
2. Identify measurable parameters that are predictive of formulation failure prior to stability testing.

## METHODS

### Placebo formulation preparation

The ingredients (Table 1) in Phase I were melted at 70°C and mixed to homogeneity followed by cooling to 50°C before slowly adding Phase II. The contents were mixed continuously using a VMI mixer with a centrifugal deflocculator attachment at 500 to 1000 RPM for 20 to 30 minutes until a homogenous cream was obtained. Creams were equilibrated to room temperature for 24 hours before initial characterization and packaging in flint glass jars with a screw top polyethylene cap.

### Formula characterization on stability

These tests were performed monthly for 6 months during storage at 40°C/75% RH:

- 1) Appearance of creams
- 2) pH (Mettler Toledo 7 Compact S220, Columbus, OH)
- 3) DSC (DSC 6000, Perkin Elmer Waltham, MA) – 10°C/min heating rate from 10°C to 100°C in aluminum pans sealed with lids with 0.1 mm hole in center.

## METHODS

### Formula characterization on stability

- 4) Cross polarized light microscopy (Nikon, Melville, NY & Paxit2 image software, MIS Inc., Villa Park, IL) – 100x magnification to detect crystallinity from birefringence.
- 5) Thermorheology (Merlin VR, Rheosys, Hamilton, NJ) – 30 mm parallel plate geometry with 1 mm gap at 800 RPM using a linear heating ramp from 25° to 75°C at 1°C/min

### Other characterization procedures

- 1) DSC - Melting points of excipients combined with Transcutol® HP and excipients were determined to study potential melting point depression of excipients caused by Transcutol® HP. Studies conducted from 15°C to 80°C at 10°C/min heating rate using aluminum pans sealed with lids with 0.1 mm hole in the center.
- 2) Centrifugation (Sorvall Legend micro 21R centrifuge, Thermo Fisher, Waltham, MA) at 21,000 g for 120 minutes at room temperature was tested as a technique to predict stability.

## RESULTS

Creams that were stable for at least 6 months at 40°C/75% RH are listed below.

Table 1. Anhydrous and hydrous creams with 40% Transcutol® HP.

Anhydrous cream 1 (G99P991709012A)		Hydrous cream 1 (G99P991709005C)		Hydrous Cream 2 (G99P991709006C)		Hydrous Cream 3 (G99P991709008C)	
Phase I	Qty (%w/w)	Phase I	Qty (%w/w)	Phase I	Qty (%w/w)	Phase I	Qty (%w/w)
Gelot™ 64	15	Mineral Oil	15	Mineral Oil	15	Mineral Oil	5
Emulcire™ 61 WL 2659	15	Gelot™ 64	7.5	Gelot™ 64	7.5	Gelot™ 64	8.5
Mineral Oil	5	Compritol® 888 pellets	7.5	Stearyl Alcohol	7.5	Compritol® 888 pellets	8.5
Compritol® 888	15					Geleol™ Mono and Diglycerides	8.5
Labrafil® M 2130 CS	8						
Phase II		Phase II		Phase II		Phase II	
Transcutol® HP	40	Carbopol® 980NF	0.2	Carbopol® 980NF	0.2	Carbopol® 980NF	0.2
Glycerin	2	Methyl Paraben Na salt	0.05	Methyl Paraben Na salt	0.05	Methyl Paraben Na salt	0.05
		Triethylamine	0.4	Triethylamine	0.4	Triethylamine	0.4
		Sorbic acid	0.05	Sorbic acid	0.05	Sorbic acid	0.05
		Transcutol® HP	40	Transcutol® HP	40	Transcutol® HP	40
		DI Water	29	DI Water	29	DI Water	23.8
		Eumulgin® SG	0.3	Eumulgin® SG	0.3	Glycerin	5

The effect on the melting point (MP) of excipients in Transcutol® HP and excipient binary mixtures is shown below.

Figure 1. MP of excipients vs. Transcutol® HP concentration

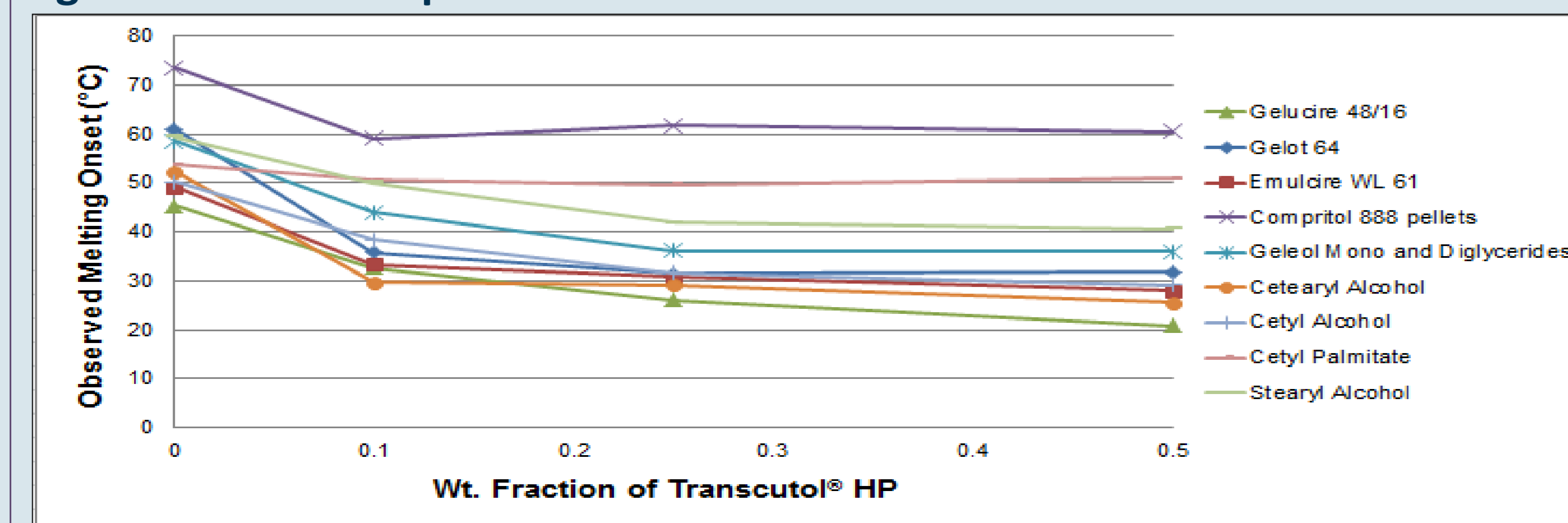
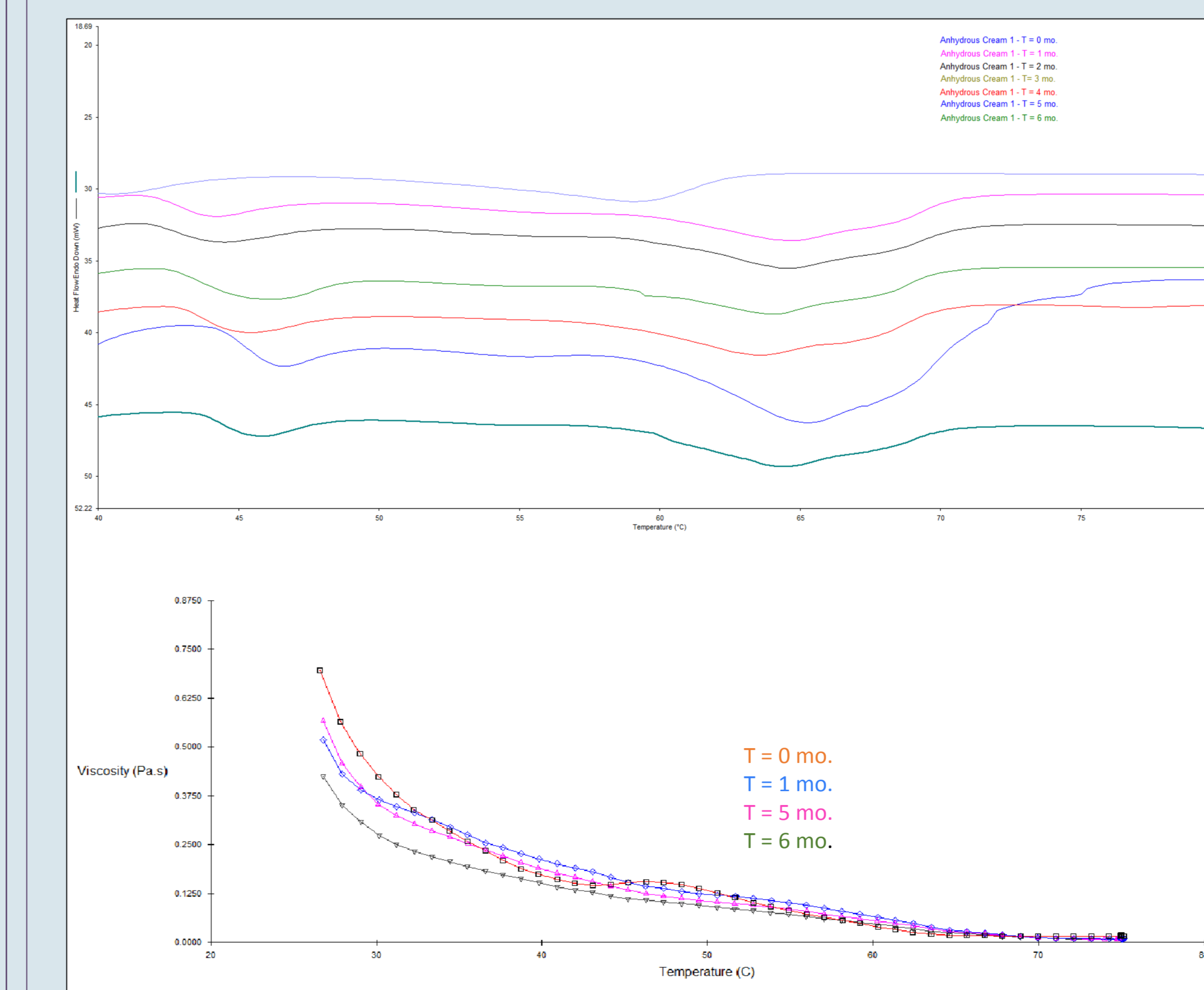


Figure 2 shows the large melt endotherms observed above 40°C and 55°C and the thermorheograms that demonstrate measurable viscosities up to reaching 65°C for each sample pull. (Note some samples exhibited wall slip during viscosity measurement with the smooth parallel plate. These data are not shown.)

Birefringence of Anhydrous Cream 1 is shown in Figure 3. Similar results were observed for all stable creams listed in Table 1.

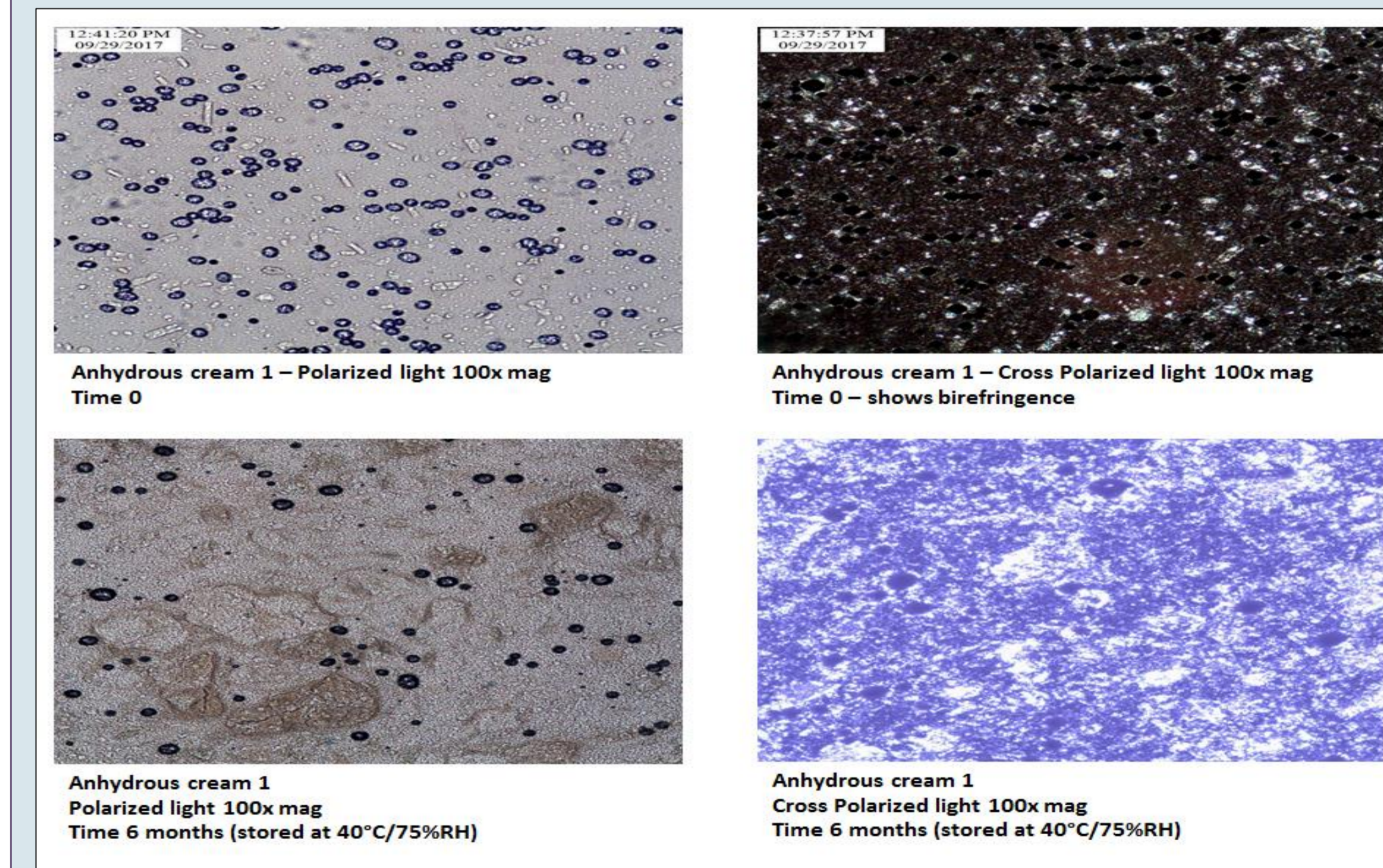
Figure 2. DSC and thermorheology of Anhydrous Cream 1



## CONCLUSIONS

1. Stable anhydrous and hydrous creams containing 40% Transcutol® HP were developed. Anhydrous creams are beneficial for formulation of moisture sensitive actives.
2. To improve cream stability, DSC studies were used to select excipients whose melting points were least affected by addition of Transcutol® (See Figure 1.)
3. Centrifugation was not predictive of cream stability during this work. Most creams did not phase separate even after 2 hours of centrifugation at 21,000 g, but would later phase separate after a few hours at room temperature.
4. Stable creams had melt endotherms above 40°C and 55°C and measureable viscosities up to 65°C. (See Figure 2.)
5. Birefringence was observed in all stable creams and also predictive of stability. (Figure 3.)

Figure 3. Microscopy images of Anhydrous cream 1



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