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Controlling the Physical Properties and Performance of Semi-solid Formulations through Excipient Selection

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Introduction: BASF Skin Delivery Platform

BASF's Skin Delivery platform is focused on four areas. The first one is dermal drug delivery, where we seek to support customers who want to accelerate drug penetration through the skin, target delivery to the epidermis or dermis, aid in retention of actives on the outer surface of the skin when needed, or predict and/or screen formulations for drug delivery potential.

Mildness is the second area. This pertains to the reduction or mitigation of irritation (stinging, itching, redness, etc.) induced by excipients or APIs. BASF conducts studies that demonstrate how mild their excipients are. The third area is sensory, which is important because formulating products that are unpleasant or unacceptable to patients can lead to compliance issues and thereby a lack of efficacy. Here, BASF utilizes excipient selection to create a pleasing experience for improved compliance, deliver efficacy cues, and provide emotional impact.

The last area is formulation design, where BASF collaborates with new product development scientists, assisting them in making decisions around composition and design of topical products and characterizing physical and chemical properties or performance.

BASF offers a portfolio of excipients and APIs that can be used to formulate creams, lotions, gels, foams, sprays, suppositories and ointments, as well as transdermal patches and micro-needles **(Figure 1)**.

Background

When developing an innovative or generic topical semi-solid product, it is standard practice to identify the target performance criteria, with the ultimate objective being that it is therapeutically efficacious. The product design plan should describe what this product should accomplish and its attributes. These can be listed as design criteria. There should be a rationale for each and how each will be measured **(Figure 2)**. Some important criteria are viscosity or consistency, sensory properties, safe/non-toxic, shelf life stability, API concentration, the state of the API, API release from the formulation, and API absorption into the target compartment(s) (e.g. stratum corneum, epidermis, dermis, sebaceous glands, hair follicles, circulatory system, etc.). All of these criteria are determined or driven by formulation inputs.

Formulation Inputs Affect Products

One of the first steps in the formulation design process is deciding which ingredients will be used (Qualitative or Q1) and how much of each ingredient (Quantitative or Q2). While this is a very important part of the early stages of the development process, the ultimate functionality of a semi-solid formulation is not only determined by the list of ingredients and how much of

each ingredient is present in the formulation.

Consider a simple solution of API molecules mixed with solvent molecules **(Figure 3)**. The API molecules are all separately dispersed in the solvent. This is a homogeneous, transparent, and stable system. In this simple solution, the final product is determined by the list of excipients and API (Q1) and the amount of each excipient and API (Q2). No matter how fast you mix them, what order you add them, what shear they experience or what temperature you prepare the solution, you will end up with the same solution with the same characteristics and performance properties.

However, things get much more complicated when working with semi-solid emulsions or ointments as these are more heterogeneous, non-equilibrium systems. In heterogeneous, semi-solid systems the performance is determined by several factors, including the list of excipients and API (Q1), the amount of each excipient and API (Q2), as well as the manufacturing process factors (e.g. temperature, temperature ramp rates, orders of addition, shear rate, etc.), packaging conditions, shelf storage time, the choice of excipients, the grade of the excipient, and the excipient purity. All of these factors put together result in a final complex of microstructures, phases, and liquid and crystalline states (Q3) that influence the final product performance. These solid states, microstructures and phases need also to be reproducible in order to create a product with predictable bioavailability.

Furthermore, the microstructure of this heterogeneous system determines the performance criteria. **(Figure 4)**

Figure 1: BASF Skin Delivery Portfolio–Provides all of the oleochemicals, polymers and APIs needed to formulate a wide range of topical products.

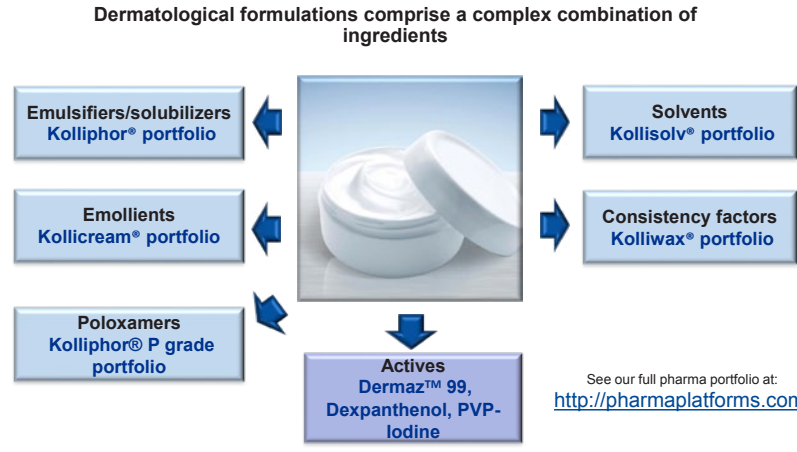
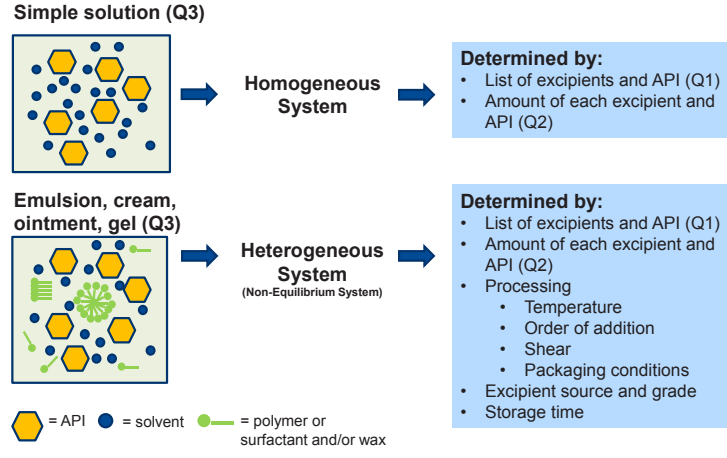


Figure 2: Topical semisolid products are designed to meet specific performance criteria–All of which should lead to therapeutic efficacy

Design Criteria	Rationale	Measurement
Consistency (viscosity, stiffness, etc.)	1.Must be able to package, extrude and apply product as needed (to target body sites). 2. Ensure and maintain product homogeneity and uniformity.	Rheometer: Shear viscosity or Dynamic viscoelasticity measurements.
Acceptable sensory properties	Patient compliance	Sensory evaluations
Safe/non-toxic	Presents no hazards or risks to user	Toxicological tests and evaluations Clinical phases
Shelf life stability (physical and chemical)	Maintain (a) product uniformity and (b) API concentration, with time and environmental stresses	Stability studies with ICH conditions and appropriate analytical methods
State of API	Drug delivery is determined by solubilization of or solid state of API	Microscopy, XRD, DSC
API release from formulation	API must be able to come out of the formulation matrix	In vitro release tests
API absorption into target compartment (epidermis, dermis, dermal appendages, circulatory system, etc.)	API must be able to diffuse through the skin and reach the appropriate site for therapeutic effect	*Ex vivo* dermal penetration tests *In vivo* preclinical models Pharmacokinetic studies

Figure 3: Performance Criteria of Semi-Solid Formulations – Performance criteria are influenced by more than the qualitative (Q1) and quantitative (Q2) compositional attributes



So it is not just the list of ingredients, but it is how all of these ingredients interact and the phases that they form that drives the performance criteria. The structures that form will affect the viscosity, stability, and sensory, as well as API solubilization, the API release, and the API absorption.

Exploring this relationship with a simple model system

A simple PEG ointment system can be a model to explore fundamental issues associated with excipient choice, product microstructure (Q3) and product performance. A PEG ointment base usually contains two or three ingredients: polyethylene glycol 400, polyethylene glycol 3350, and an optional solvent like propylene glycol **(Figure 5)**.

Even though these are simple systems, there can be some challenges. One is achieving acceptable sensory properties and tuning these properties properly. Problems that can occur with PEG ointments include, weeping or syneresis and API solubilization.

Our first study looked at varying the molecular weight of the higher molecular weight PEG in the formulation **(Figure 6)**. This is a series of different molecular weight PEGs forming the structure in the ointment. These were evaluated under cross-polar microscopy. The PEG 1450 (Pluriol® E 1450) image shows less birefringence (or bright regions) indicating less crystallinity, while the remaining three have higher levels of birefringence which results from a higher concentration of solid, crystalline PEG phases.

Does this crystallinity influence consistency or viscosity?

Figure 4: Performance Criteria of Semi-Solid Formulations – Numerous factors determine the non-equilibrium state which in turn impacts the performance criteria.

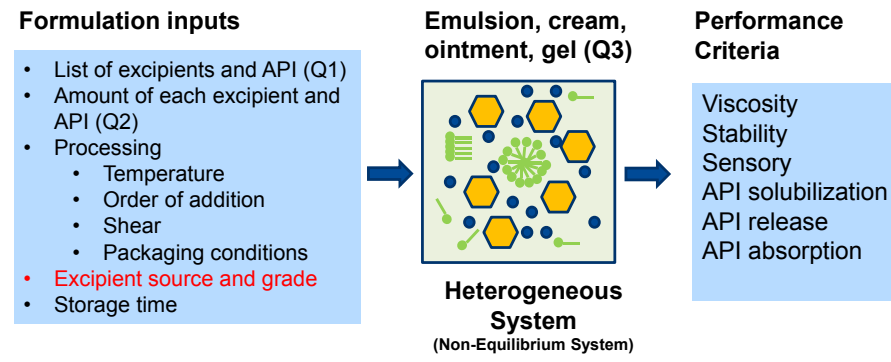


Figure 5: Model Formulation: PEG Ointment – Simple PEG ointment system can be a model to explore fundamental issues associated with excipient choice and product performance

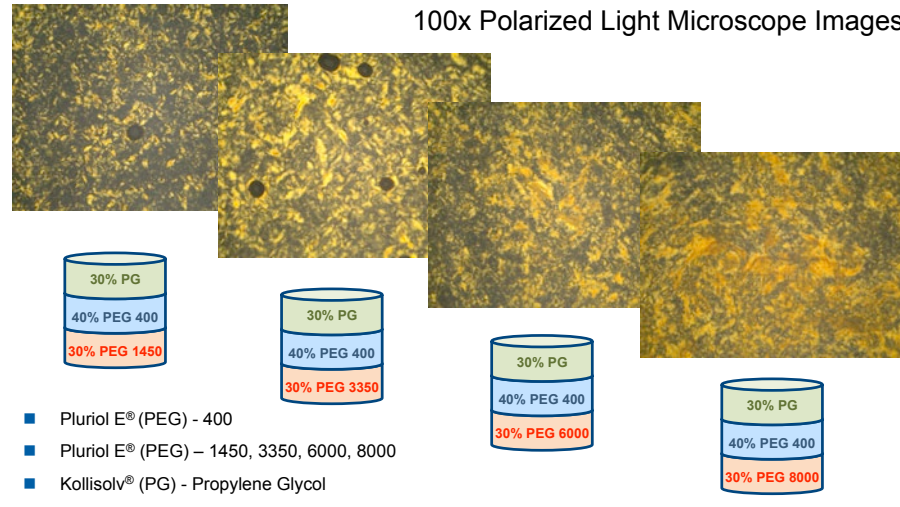
Examples of PEG-based ointments In the market place

- Bactroban Mupiricin Ointment USP
- Lidocaine (5%) Ointment USP

Example of Weeping/Syneresis in PEG Ointment

- PEG ointment base contains
  - Polyethylene glycol 400
  - Polyethylene glycol 3350
  - Optional Solvent (e.g. Propylene Glycol)
- Potential issues
  - Acceptable sensory properties
  - Weeping/Syneresis
  - API solubilization

Figure 6: Variations of the Solid (PEG) Phase – Visual Representation of Microstructure by varying PEG Mol. Wt.



- Pluriol E® (PEG) - 400
- Pluriol E® (PEG) – 1450, 3350, 6000, 8000
- Kollisolv® (PG) - Propylene Glycol

Rheology studies were performed to address that question **(Figure 7)**. The PEG 3350, 6000, and 8000 (Pluriol E® 3350, 6000 and 8000) all had similar rheology. All of them had the same viscosity and showed similar rates of shear thinning with increased shear rate. In the case of PEG 1450, an overall lower viscosity was observed. Typically viscosity and shear thinning in semi-solids is determined by the balance of fluid, gel and solid states in the formulation. Higher concentrations of solids and gels will increase overall viscosity. This study suggests that the higher melting point, higher molecular weight PEGS (Pluriol E® 3350, 6000 and 8000) all demonstrated higher levels of crystallinity that resulted in a higher viscosity.

In another study, the amount of PEG 3350 was varied in an ointment. **Figure 8** shows a schematic starting with 40% PEG 3350 and decreased solids to 5%. The degree of birefringence resulting from crystalline content, under cross polar microscopy, decreased sequentially with decreasing PEG 3350. For example, the 40% and the 35% show a lot of birefringence, while at 10% and 5% there is much less birefringence.

At 10% PEG 3350, the ointment will have a light consistency. Under the microscope one can see the rounded edge of the droplet. There is some crystallinity, a clear space, and a dark line curving across the field of view. The space between the crystallinity and the dark line is fluid weeping out of the 10% PEG 3350 formulation.

With regard to stability, at 5% there was immediate weeping; after 24 hours weeping occurred in the 10% of the 3350 formulation; and at seven days, weeping at the 20%. Somewhere between 25% and 30% PEG 3350 a very stable ointment can be made without weeping.

These formulations were also evaluated with a rheometer. As seen earlier there is a correlation between the solids content (crystallinity) and viscosity; for example a low solids content results in a lower viscosity **(Figure 9)**. Stress data also show a correlation with the amount of high melting point PEG 3350.

One way to evaluate crystalline states or mixing in complex phases is by differential scanning calorimetry (DSC). In **Figure 10** the DSC profiles from two different formulations with 30% PEG 3350 and 15% PEG 3350 were plotted. DSC samples temperatures started at -50ºC, were heated to almost 100ºC (lower curve) and then re-cooled to -50o=ºC (upper curve). Several observations can be made:

- Both formulations contain 30% propylene glycol (Kollisolv® PG) thus there is a depression in melting and freezing points. (Melting point for pure PEG 400 is typically 4-8ºC, PEG 3350 is 54-58ºC).

Figure 7: Variations of Solid (PEG) Phase – Rheological Comparison of Ointments with varied PEG Mol. Wt.

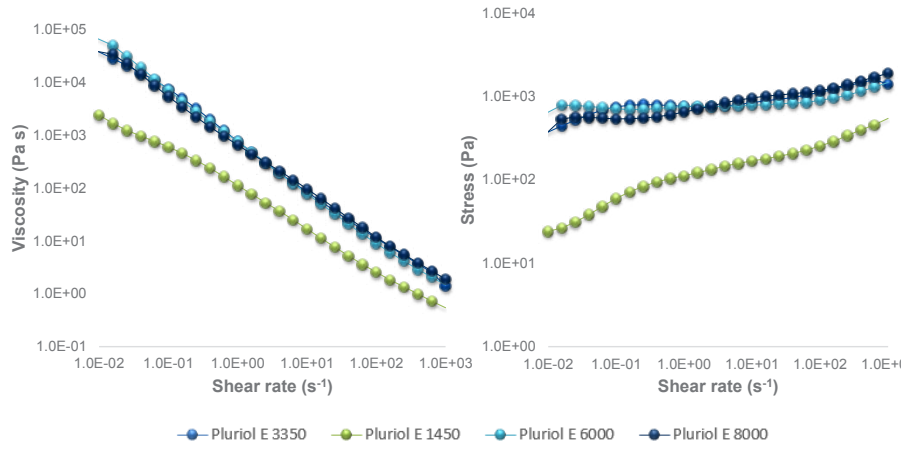
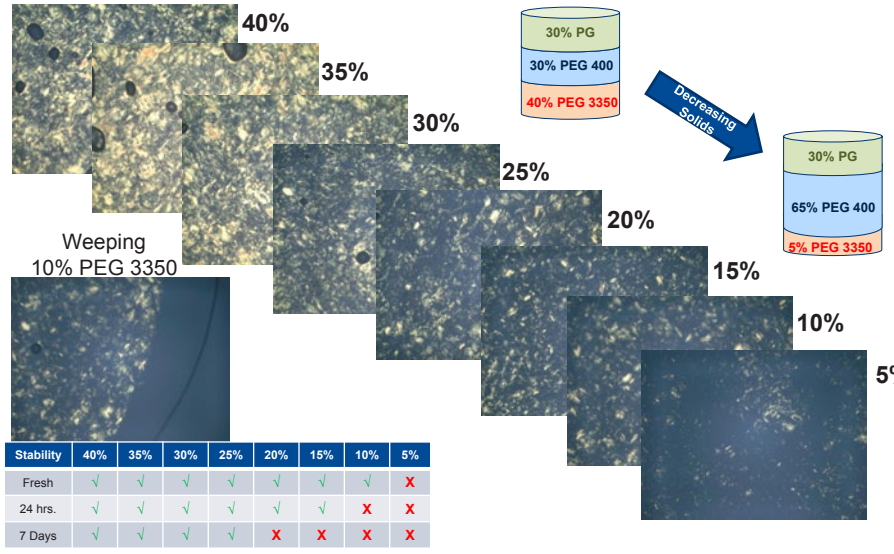


Figure 8: Variations of Solid (PEG) Phase – PEG 400 and PEG 3350 ratio has an effect on microstructure (100x microscopy).



Stability	40%	35%	30%	25%	20%	15%	10%	5%
Fresh	√	√	√	√	√	√	√	X
24 hrs.	√	√	√	√	√	√	X	X
7 Days	√	√	√	√	X	X	X	X

- The area under the curves of the melting and freezing peaks is indicative of the mass of material going through the transition. Differences between peak areas for the two different compositions are consistent with expectations.
- Interestingly, the PEG 3350 peak has a shoulder, indicating that there may be a phase which is not pure PEG 3350 but may include PEG 400 or propylene glycol.
- During refreezing the peak profiles are not identical suggesting that the mixture is not going back to its original state.

Another important tool for evaluation of excipient and API solid states is X-ray diffraction. In **Figure 11** ointments with 30% PEG 3350 and 15% PEG 3350 were compared. Usually the X-ray diffraction plot from a pure crystalline material will have a flat baseline with sharp spikes. In this case we see that the "baseline" curves up and down like a very wide singular peak with several small sharp peaks arising from it at intervals. These smaller peaks result from diffraction by highly ordered crystal structures that we associate with pure PEG 3350. The larger "mountainous" profile is indicative of amorphous structure in the PEG ointment. This amorphous structure may arise from mixing of PEG 3350 with PEG 400 and/or propylene glycol. It is noteworthy that with PEG 1450 these sharper peaks are almost completely absent, suggesting that with lower molecular weight PEGs there will have more amorphous structures.

Now let us look at a formulation that actually contains an API **(Figure 12)**. This is a 2% mupiricin ointment. In this se-

Figure 9: Variations of Solid (PEG) Phase – PEG 400 and PEG 3350 ratios have an impact on performance attributes (rheology).

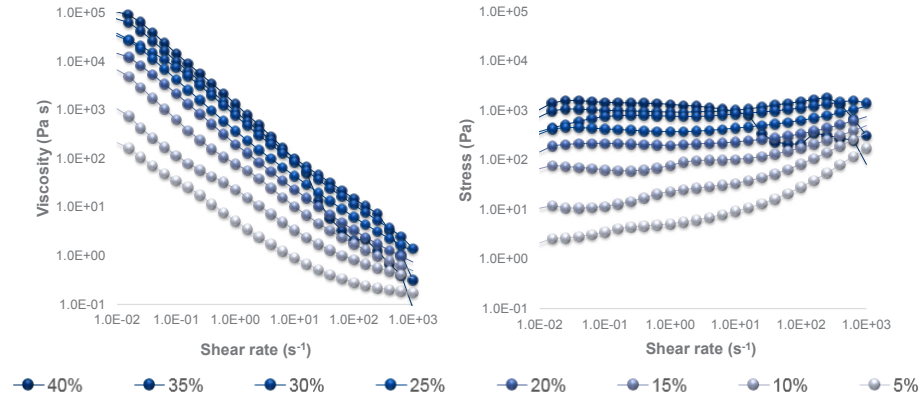


Figure 10: Variations of Solid (PEG) Phase – PEG 400 and PEG 3350 ratios have an impact stability visible through differential scanning calorimetry.

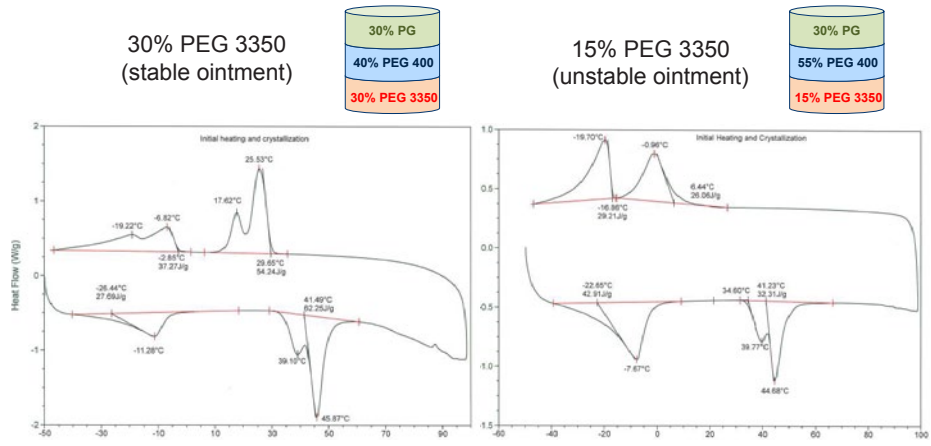


Figure 11: Variations of Solid (PEG) Phase and Concentration – Solid Phase and Concentration exhibit clear effect using XRD

- **X-Ray Diffraction**
- **Traces are offset for clarity**

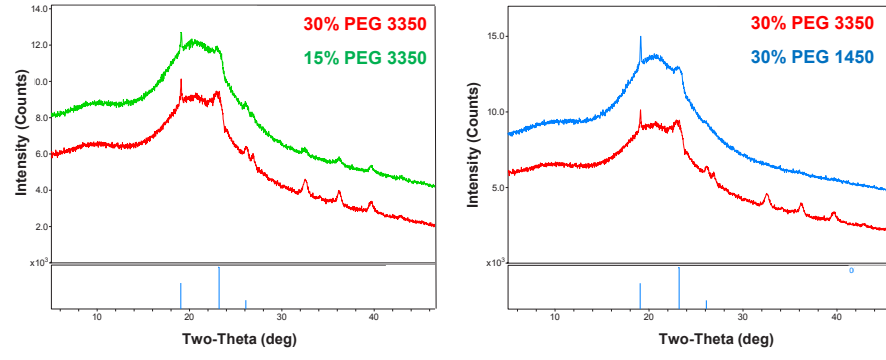
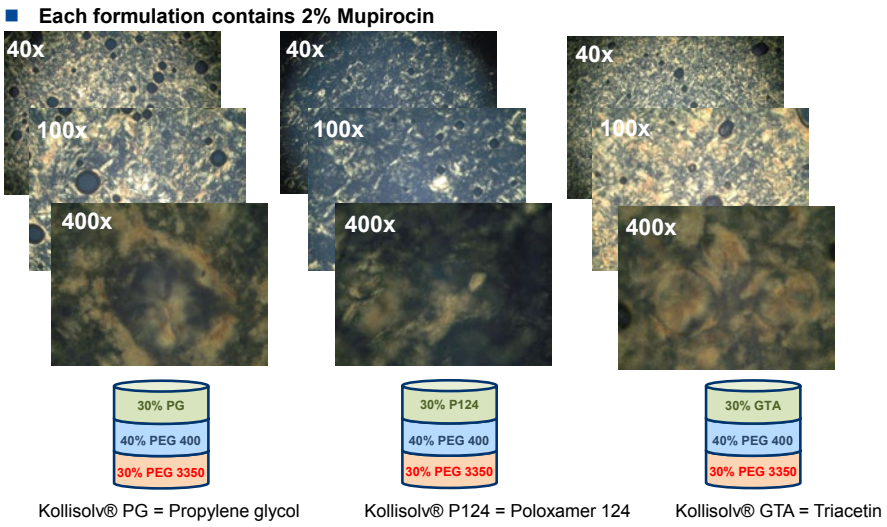


Figure 12: Variation of the Solvent Phase – Addition of miscible excipients affect the solubilizationof APIs



Kollisolv® PG = Propylene glycol Kollisolv® P124 = Poloxamer 124 Kollisolv® GTA = Triacetin

ries we varied only the solvent in the formulations. The first mixture produced was with propylene glycol (Kollisolv® PG) at 30%. The middle one has Poloxamer 124 (Kollisolv® P124), and the third one was with Triacetin (Kollisolv® GTA). The sensory properties for the first one with propylene glycol felt like a typical PEG ointment, whereas the poloxamer 124 had a very white opaque appearance and tended to be stickier. The triacetin with the Kollisolv GTA had the best absorption when rubbed in, spreadability was good, and it had a lighter feel. Also note in the photomicrographs the differences in the amount of crystallinity or birefringent solids that are present.

At the higher magnifications (400x) has rounded radial type structures, which is the mupiricin forming a crystalline structure of some sort. Poloxamer 124 has the lowest amount of birefringence suggesting that it is a very good solvent for both the solvent PEG and perhaps the mupiricin.

Effect of microstructure on bioavailability: Next steps

How does all this influence the bioavailability of the API and its delivery through the skin? Using Franz diffusion cells, the Strat M membrane, and analyzing mupirocin permeation by HPLC we can explore these three formulations with propylene glycol (Kollisolv™ PG), poloxamer 124 (Kollisolv™ P124), and triacetin (Kollisolv™ GTA). Studies are on-going and anyone interested in the results may contact us directly to learn more. We expect to be reporting these results in future communications.