The Relationship Between Critical Quality Attributes and the Microstructure of Topical Semi-Solid Formulations

Overview

Researchers developing topical semi-solid products must understand the factors that influence the formation of the complex microstructures that compose the Q3, how the microstructure influences the critical quality and performance attributes of the drug product, and how analytical studies can reveal vital information to improve a drug’s quality and performance.

Microscopy, image analysis, x-ray diffraction, and other methods can be used to evaluate and quantify the microstructure of cream formulations and show how excipient selection can influence product stability, rheology, drug delivery, and other performance factors.

Norman Richardson, global technical marketing manager, skin delivery, BASF, explained the challenges of formulating semi-solid drug products for skin delivery in a webcast, Understanding the Relationship Between Critical Quality Attributes and the Microstructure of Topical Semi-Solid Formulation. This summary highlights key points of that presentation.

Microscopic analysis of over-the-counter creams for different medical applications reveals, as expected, differences in API morphologies, oil droplet distribution, and excipient and wax crystals. A comparison of branded and generic products with the same API and concentration, however, also reveals differences in formulation that could impact product performance and patient response.

When rubbed on the skin, a branded cream and a generic equivalent with a 1% API concentration feel the same. A microscopic analysis of the two samples shows different crystal morphologies (Figure 1). Both creams use the same emulsifier, but other excipients used as emollients, solvents, and for consistency may contribute to the difference in the crystal morphology, said Norman Richardson, global technical marketing manager, skin delivery, BASF.

The complex formulation of a generic semi-solid cream is determined qualitatively by the selection of API and excipients (Q1) and quantitatively by the amount of excipients (Q2). Formulators must assess how various excipients can interact with the API, and determine the best approach to optimize the stability, release of the drug, and the delivery of the API through the skin. In addition, manufacturing and packaging conditions, excipient sources and grades, and shelf life must be evaluated.

All of these inputs result in a complex, heterogeneous system, the Q3, composed of complexes and colloidal structures that result from the self-assembly of the various ingredients that go into the formulation (Figure 2). “When we look under the microscope, we’re actually visualizing some of these structures, these entities that have formed by the mixing of the excipients,” said Richardson. A variety of analytical techniques reveal the effects of various excipients and the interactions in a formulation’s microstructure.
Understanding the Role of Excipients

To understand the actions of various excipients in a branded formulation, experts at the BASF dermatology laboratory examined and estimated the ingredients in a brand-name clotrimazole cream. Using this product as a model, they systematically changed individual excipients to evaluate the impact on product microstructure, rheology, and state of matter.

In one study, the emollient octyldodecanol was changed in different samples to isopropyl myristate, mineral oil, and cocoyl caprylocaprate; all other ingredients stayed the same. Similar systematic studies were conducted on other parts of the formulation using microscopy and other analytical techniques to evaluate what occurs in the formulation microstructure and its performance based on changing a single excipient.

Comparing a formulation at varying magnifications using a Zeiss Axio bright-field microscope revealed different levels of detail for the crystals and emulsion and provided information about the oil droplets. The 40x magnification shows a fairly homogenous distribution of oil droplets with some air bubbles. At 100x, individual droplets can be seen. At 400x, multiple emulsion droplets are visible, including some that appear to be droplets within droplets and some folded structures between the droplets. These structures are the wax phases, which have mixed with the emulsifier and are forming layered shells around the oil droplets or extending through the spaces between the oil droplets as a gel network, explained Richardson.

A visual comparison of the four formulations, octyldodecanol, isopropyl myristate, mineral oil, and cocoyl caprylocaprate, are shown in Figure 3. The oil droplet sizes and distribution of populations of oil droplets are different in each formulation.

Next, the laboratory quantified the oil droplet distributions using the ImageJ software, an open-source imaging program available through the National Institutes of Health. Using a 3 mg of product, they examined each formulation in a 2-cm diameter sample under the microscope. The ImageJ software identified all the droplets, measured each as an area measurement in square pixels, and then it plotted a histogram that shows the distribution of these oil droplets.

Figure 4 compares a formulation with mineral oil and a formulation with isopropyl myristate; all other ingredients are the same. The microscopic images show great differences, confirmed by the histograms, that show the oil droplet distribution. For the mineral oil, the distribution for the oil droplet size...
CRITICAL QUALITY ATTRIBUTES AND MICROSTRUCTURE OF TOPICAL SEMI-SOLID FORMULATIONS

Figure 3: Emollient variations are shown in microscopic images of different excipients (octyldodecanol, isopropyl myristate, mineral oil, and cocoyl caprylocaprate) tested in a clotrimazole formulation. Consistency factor (wax) = Kolliwax CSA 50 (cetostearyl alcohol); Emulsifier = Kolliphor CS 20 (Polyoxyl 20 cetostearyl ether); Emollient (oil) selected from Kollicream series (i.e. Kollicream OD, IPM, 3C).

Figure 4: Microscopy and image analysis provides information about excipient impact on droplet size distribution. MO is mineral oil. IPM is isopropyl myristate.

is quite wide with some measuring up to 500-square pixels. For the isopropyl myristate, a majority of the oil droplets are less than 80-square pixels in the area with few droplets above 210-square pixels. An analysis of the data showed a correlation between the physical stability at 40 °C and the average oil droplet sizes for 10 formulations. Formulations with an average oil droplet size of 127-square pixels or less remained stable for four weeks. Those with oil droplets more than 135-square pixels failed after one week. This comparison was limited to the oil droplet sizes and the stability, and did not consider other variables, explained Richardson. He hypothesized that the narrow difference in the oil droplet size of 127-square pixels versus

Increasing frequency

Increasing area
135-square pixels indicates that other factors need to be considered, including the status of the matter between the oil droplets.

**Evaluating Gel Networks**

High melting point lipophiles—such as fatty alcohols, and emulsifiers—mix to form structured gel networks that can influence physical stability, rheological properties, the API solubilization capacity, the API release, and product aesthetics during application.

In a typical structure using polyoxyl 20 cetostearyl ether as an emulsifier along with fatty alcohols, stiffer regions layer with fluid regions to create a gel network. Analysis of the gel network by x-ray diffraction (XRD) yielded the three curves in Figure 5, separated from each other to show the details. In this study, only one component, the fatty alcohol, was changed in each formulation.

For each formulation’s curve, the large, broad peak extending from approximately 10 degrees to approximately 40 degrees represents amorphous structures that could be related to the gel network, but is not pure crystalline matter, explained Richardson. The blue curve represents the formulation with stearyl alcohol; the distinct peaks show that crystalline stearyl alcohol separated out of the formulation to form crystals. The green curve, which represents the cetyl alcohol formulation, indicates a small amount of crystallinity, but much less than the stearyl alcohol. The red curve for the cetyl stearyl alcohol cream formulation shows a more pronounced peak than the cetyl alcohol formulation, but much less crystallinity than the stearyl alcohol formulation. All of the stearyl alcohol is not being effectively incorporated into the gel network that builds rheology and consistency.

Rheology studies showed that the cetostearyl alcohol and the cetyl alcohol formulation were similar; however, the stearyl alcohol had significantly lower viscosity. “We can hypothesize that the good mixing of the emulsifier and the wax, where you have less crystalline wax and more of the gel network, is building up the rheology and that you get a more effective rheology and consistency in the formulation,” said Richardson.

To evaluate drug delivery, an *in-vitro* diffusion study using a skin model demonstrated differences in diffusion of the API, clotrimazole, for the different formulations. Isopropyl myristate had the highest flux rate; cocoyl caprylocaprate had the lowest diffusion rate. For treatments with clotrimazole, where the API should stay on the surface of the mucosal membrane, a cocoyl caprylocaprate may be the better choice for the formulation.

Figures courtesy of BASF.