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Effects of variations in physicochemical properties of glyceryl monostearate on the stability of an oil-in-water cream

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Synopsis

During the development of an oil-in-water cream formulation, syneresis of the aqueous phase was observed. A quantitative syneresis test was devised to study the separation of the aqueous phase. Variations in the physical and chemical characteristics of glyceryl monostearate obtained from various sources were identified as the principal factors influencing syneresis of the formulation. A group of diagnostic tests, including variable temperature x-ray diffraction analysis developed for screening various lots of glyceryl monostearate, was used to successfully predict the possibility of the occurrence of syneresis in a cream batch. The acid value of the various lots of glyceryl monostearates correlated well with the propensity of the cream to produce syneresis. Increasing the acid value of the glyceryl monostearate by the addition of small amounts of fatty acids eliminated the observed syneresis. Further, the storage temperature had a profound effect on the syneresis and consistency.

INTRODUCTION

Pharmaceutical cream bases are essentially semisolid emulsion systems that appear "creamy white" due to reflection of light by the internal dispersed phase. The most common creams are oil-in-water emulsion systems, whose structure or semisolid character is dependent upon emulsified liquid droplets or particles that comprise the internal phase. Creams are usually prepared at high temperature (fusion method) using internal-phase materials such as mineral or vegetable oils, liquid emollient esters, solid long-chain fatty acids, alcohols, and esters. Upon cooling, these ingredients exist as dispersed or emulsified microscopic droplets, liquid crystals, solid particles, or spheres, creating a three-dimensional gel structure or matrix that entraps the aqueous external phase (1,2). In many formulations the gel structure may be metastable. Creams are dynamic compositions that are influenced by temperature storage and shear forces. The gel structure may stiffen, contract, and shrink at cold temperatures, or soften, expand, and fluidize at warm temperatures. Gel structure may be broken down due to shear thinning by mechanical mixing, pumping, or rubbing. Many creams possess thixotropic properties that allow recovery of gel structure upon storage after exposure to shear thinning.

Some of the general indications of emulsion instability are:

1. Inversion of emulsion type (e.g., oil-in-water emulsion changes to water-in-oil type emulsion or vice versa)
2. Coalescence of dispersed internal-phase droplets, globules, spheres, or particles
3. Phase separation characterized by liquid "bleed" or syneresis
4. Decrease in viscosity or loss of consistency resulting in softness or fluidity

External factors such as packaging, storage time, temperature conditions, and shear forces may induce emulsion instability. Internal factors of cream composition related to variability of the excipients or raw materials and their source may also affect emulsion stability and cream consistency.

Most commercially available cosmetic raw materials used in oil-in-water emulsion-type creams are not pure excipients, but mixtures of two or more components. Some are complex mixtures that may vary depending on the vendor source. Glyceryl monostearate is an excellent example of a commonly used cream excipient that exhibits a wide range of variability in its constituent composition, and also in its effect on the consistency and quality of the finished cream formulation (3). Glyceryl monostearate is a mixture of the monoglycerides of stearic and palmitic acids, together with variable quantities of di- and triglycerides. It usually contains not less than 90% of total fatty acid glycerides, of which at least 35% are monoglycerides (4). Small quantities of free stearic, palmitic and oleic acids, glycerol, water, and oleate esters may also be present.

Since glyceryl monostearate is used mainly as an emollient lipophilic thickening agent and stabilizer for oil-in-water and water-in-oil emulsion-type creams and lotions, variability of this raw material can result in manufacturing problems. This report discusses some of the causes resulting in soft consistency and syneresis encountered during the scale-up phase of development for an oil-in-water emulsion cream product, when raw materials from multiple vendor sources were used.

The main objectives of the present work were:

1. Investigate the cream formulation and its method of manufacture to determine the cause of the soft consistency and syneresis
2. Identify test methods to evaluate cream consistency and syneresis potential
3. Identify methods to test the raw materials to predict their propensity to cause soft cream consistency and syneresis
4. Recommend options to the manufacturing plants to overcome variable cream consistency and syneresis problems

EXPERIMENTAL

MATERIALS

Glyceryl monostearate NF XII, cetyl alcohol NF, Syncrowax ERL-C (ethylene glycol ester of C18-36 wax fatty acids), Amerchol L-101 (mineral oil and lanolin alcohol), Glucam E-20 (methyl gluceth-20), Tween 60 (polysorbate 60 NF), propylene glycol U.S.P., sodium citrate U.S.P., edetate disodium U.S.P., sodium metabisulfite NF, aluminum hydroxide wet gel, dimethicone, and purified water U.S.P. were used as received. These materials were obtained from a variety of sources.

CREAM PREPARATION

Glyceryl monostearate, cetyl alcohol, Syncrowax ERL-C, and Amerchol L-101 were heated to 80°–85°C in a suitable container with mixing to produce the oil phase.

In a separate 10-gallon Groen kettle equipped with an Arde-Barinco homogenizer set at 3000 rpm, edetate disodium, sodium citrate, and sodium metabisulfite were dissolved in a mixture of purified water, Glucam E-20, Tween 60, and propylene glycol heated to 80°–85°C. A dispersion of aluminum hydroxide in purified water (previously homogenized) was added to the aqueous solution and the combined aqueous phase heated to 90°–95°C.

The oil phase heated to 90°–95°C was added to the aqueous phase at 90°–95°C. The combined mixture was homogenized for 30 minutes at 90°–95°C. The batch was cooled to 70°–75°C by passing cooling water through the jacket of the kettle. Dimethicone was added and the batch was further cooled to 54°–56°C with continuous homogenization. Batch weight was adjusted with purified water at this temperature, followed by further cooling to 50°–52°C with homogenization. At the onset of congealing, homogenization was discontinued. Slow-speed Groen mixing was used to cool the cream to 44°C, whereupon mixing was discontinued. The cream was allowed to cool to 25°–30°C by standing overnight. In order to allow the addition of the active drug to the batch, a portion of the propylene glycol was retained. In the placebo batches made as part of this study, a portion of the propylene glycol was also retained so as to simulate the manufacture of an active batch. This portion of the propylene glycol was added to the cream base at 25°–30°C and mixed at slow speed for 30 minutes.

In order to determine the reproducibility of the physical properties of a cream batch type, preparations were performed at least in duplicate. Full physical characterization was performed on each preparation, and the data reported reflect averages of these determinations.

WIRE-MESH BLEED TEST

A 30-g sample of cream was spread evenly with a spatula onto a rectangular stainless steel 30-mesh wire screen ($1\frac{1}{2}'' \times 1\frac{3}{4}''$) supported by a 1-oz clear-glass jar (height $1\frac{5}{8}''$, base diameter $1\frac{5}{8}''$, neck diameter $1\frac{1}{2}''$) contained within a 4-oz clear-glass jar (height $2\frac{1}{2}''$, base diameter $2\frac{1}{4}''$, neck diameter $2''$). During the transfer of the cream sample onto the screen, very little sheer, if any, was applied and no mixing was performed. The 4-oz jar was covered with a tight-fitting liner cap and stored at 20°–25°C for observations of separated liquid until no further bleed was observed. Any separated liquid was collected at the bottom of the jars. This liquid was then removed and quantitated by weight. The reported percent bleed was obtained by dividing the mass of collected liquid by the total mass of the cream sample used for the test. Each reported data point represents an average of four individual determinations.

UNIVERSAL CONE PENETROMETER FOR MEASUREMENT OF CREAM CONSISTENCY

A universal grease cone made of brass with a steel stem and needle tip (wt. 102.5 g), affixed to the base of a metal rod, was initially held in a stationary position with needle tip just in contact with the surface of the cream sample, contained in an aluminum cup

(83 ml volume). The cream sample was placed with a spatula into the aluminum cup without applying any significant shear to the product. When the release mechanism was activated, the needle tip cone was allowed to penetrate the sample for 5 seconds. Depth of penetration was then measured in scale units up to 380 on scale dial. Consistency measurement was reported as scale units for convenience but could also be converted to mm (each scale unit is equal to 0.1 mm). Each reported data point represents an average of three individual determinations.

DSC MEASUREMENTS

DSC measurements were obtained on the DuPont model 9900 thermal analysis system. 1-mg samples were accurately weighed into the DSC pan, and the pans were hermetically sealed. Conventional DSC curves were obtained by heating the samples at a rate of 10°C/minute, up to a final temperature of 100°C. The DSC profiles of thermally processed glyceryl monostearate materials were obtained by heating the sealed sample only to 95°C, maintaining this temperature for 10 minutes, allowing the system to cool back to room temperature, and then obtaining a conventional DSC thermogram of this melted and congealed material. The melting points of the various materials were obtained as the temperature maxima associated with the DSC melting endotherms.

X-RAY DIFFRACTION MEASUREMENTS

Powder x-ray diffraction (XRD) measurements were obtained on a Philips model APD 3720 powder diffraction system, equipped with a vertical goniometer in the theta/2-theta geometry. The x-ray generator (Philips model XRG 31000) was operated at 45 kV and 40 ma, using the K-alpha line of copper at 1.544056A as the radiation source. The sample was scanned between 2° and 32° 2-theta, at a scan rate of 0.04° 2-theta/sec, and in steps sizes of 0.04° 2-theta. The XRD powder patterns of melted and congealed glyceryl monostearate materials were obtained using the Anton-Parr XRD hot stage, with the x-ray data being collected as just described. The powder pattern of initial material was obtained, and then the stage was heated to 95°C. The glyceryl monostearate was held at this temperature for 10 minutes and then allowed to cool back to room temperature, whereupon the full XRD powder pattern was remeasured.

CHEMICAL TESTS

The determination of acid value, saponification value, ester value, and iodine value of each lot of glyceryl monostearate was performed as described in USP XXI.

RESULTS AND DISCUSSION

CREAM FORMULATED WITH U.S.-SOURCED RAW MATERIALS

A thixotropic cosmetic oil-in-water type vanishing cream base vehicle for a topical drug product was formulated using commercially available U.S.-sourced raw materials. Penetrometer consistency results for the cream initially after manufacture were within the range of 260–295. After storage at 24° ± 3°C for several weeks, the cream developed firmer consistency due to formation of the gel structure (1) and exhibited penetrometer

values within the range of 230–280. No liquid bleed separation was observed in samples of cream after 24-month storage between −20°C and 40°C. Additionally, samples of cream packaged in tubes did not exhibit any liquid separation. Scale-up batch sizes of 50 kg to 200 kg were prepared successfully using planetary (Glen) type mixers equipped with variable-speed homogenizer agitators for emulsification.

CREAM FORMULATED WITH U.K.-SOURCED RAW MATERIALS

In consideration of worldwide manufacture of the cream product and as part of scale-up development evaluations to support the use of raw material sourced from other countries, batching studies were initiated using selected raw materials obtained from the United Kingdom (U.K.). A 20-kg placebo cream batch was prepared in a 10-gallon Groen mixer. The cream contained U.K.-sourced glyceryl monostearate, cetyl alcohol, Syncrowax ERL-C, Amerchol L-101 (oil phase components essential for gel structure and consistency), Tween 60 (emulsifier) and Glucam E-20 (humectant), which was soluble in the aqueous phase. All other ingredients in the cream were U.S.-sourced.

The finished bulk cream immediately after manufacture had a soft fluid consistency and exhibited excessive liquid bleed when stored in tubes and when subjected to the wire-mesh bleed test. This was also obvious when pockets or crevices were made in the surface of the cream. A portion of the bleed was analyzed and found to contain mainly water and propylene glycol, which indicated that the external aqueous phase was not entirely entrapped within the gel matrix of the cream. Also, the soft fluid gel consistency of the cream indicated the absence of a rigid gel structure, which may have been due to shear thinning or delayed gel formation. A comparison of the key differences between creams prepared using U.S.- and U.K.-sourced ingredients is summarized in Table I.

EFFECTS OF STORAGE TIME AND TEMPERATURE ON CONSISTENCY AND BLEED POTENTIAL OF CREAM CONTAINING U.K. INGREDIENTS

The cream batch containing U.K.-sourced excipients was subdivided on the second day after manufacture. Portions of the cream were placed in tightly sealed stainless steel containers and stored at 5°C, 24° ± 3°C, and 33°C. Consistency and the extent of bleed were determined after 3, 6, and 17 days of storage. The results shown in Figures 1 and 2 indicate that warm temperature storage (33°C) for 3 days caused accelerated gel

Table I
Observed Differences Immediately Upon Manufacture of Cream Bases Prepared Using U.S. and U.K. Raw Materials

	Cream prepared using U.S. ingredients	Cream prepared using U.K. ingredients
Appearance	Firm	Soft, flowable
Consistency	282–288	315–320
Bleed (% w/w)	0	8–12
Microscopic	Finely dispersed spheres of internal oil-wax phase	Uniformly distributed spheres of clear aqueous phase interdispersed with internal oil-wax phase

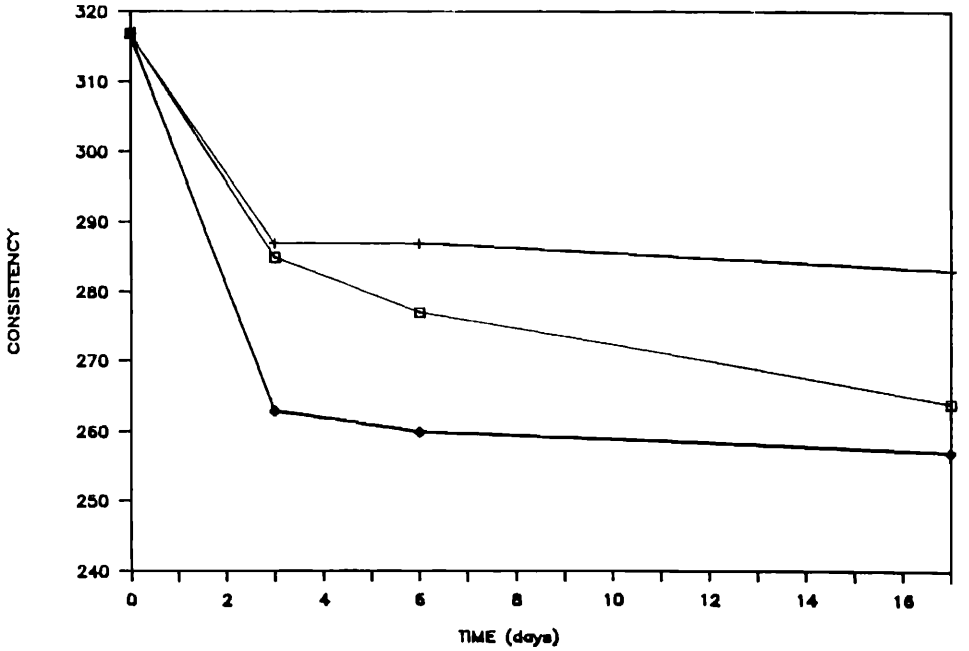

Figure 1. Time dependence of the consistency as a function of storage temperature for cream prepared using U.K.-sourced ingredients. Data are shown for 5°C (+), 24°C (□) and 33°C (◆) storage temperatures.

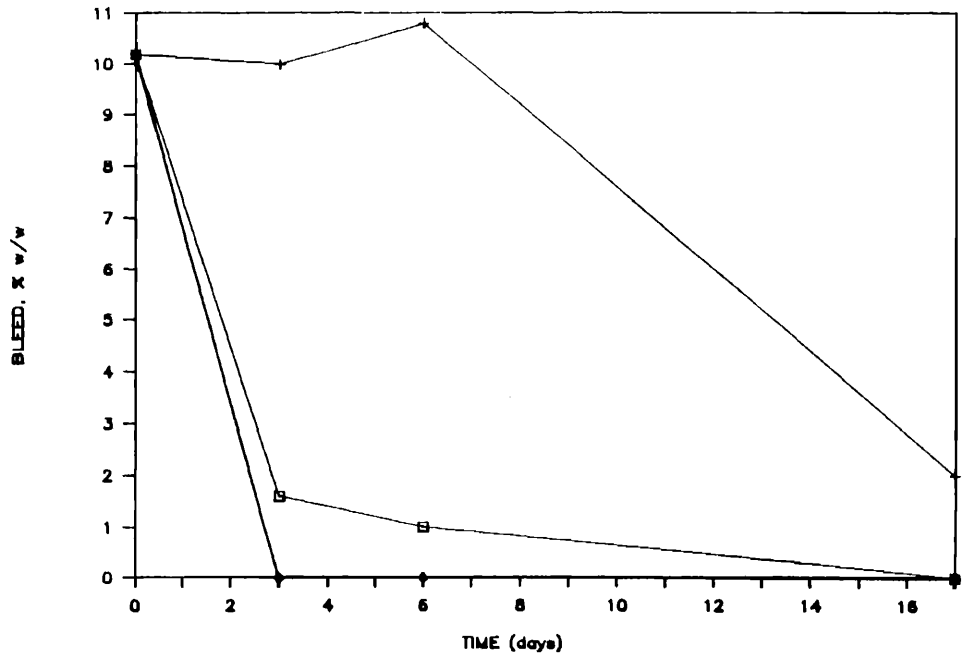

Figure 2. Time dependence of the extent of bleed as a function of storage temperature for cream prepared using U.K.-sourced ingredients. Data are shown for 5°C (+), 24°C (□) and 33°C (◆) storage temperatures.

formation, promoted firmer consistency, and eliminated the bleed potential of the cream. Storage at 5°C for 3 to 6 days inhibited or delayed gel formation, promoted a softer consistency, and increased the bleed potential of the cream. Storage at 24°C for 3 to 6 days gradually increased the consistency firmness and decreased the bleed potential of the cream.

Microscopic observations were made in studying the effects of storage temperature on the consistency and bleed potential of the bulk cream. Initially after manufacture, the cream had the appearance of discrete microscopic spheres of internal phase, closely packed, but floating freely in the aqueous external phase. The spheres were not fused together and a rigid three-dimensional gel structure was not observed, which accounted for the soft cream consistency and bleed propensity. The presence of uniformly distributed droplets of clear aqueous phase loosely entrapped throughout the internal oil-wax phase also signified an increased bleed potential.

Microscopic examination of the cream sample stored at 33°C showed that the internal phase spheres were fused together and that the aqueous external phase was securely entrapped in the matrix. Through the use of polarizing optical microscopy it was concluded that the gel structure was liquid crystalline in nature. These properties yield firm cream consistency without the potential for the cream to bleed.

The 5°C-stored sample of the cream was similar microscopically to the sample stored at 24°C. The oil-wax spheres were packed more closely due to shrinkage of the wax structure at 5°C, but after the sample equilibrated at 24° ± 3°C, it was observed that the spheres were not fused and a rigid gel structure was not present. The physical shrinkage of the wax structure at 5°C apparently expelled or "squeezed out" a larger portion of the aqueous external phase from the loosely bound matrix, which resulted in a greater amount of bleed after 6 days storage at 5°C.

EFFECT OF INDIVIDUAL U.K. EXCIPIENTS ON CREAM CONSISTENCY AND BLEED POTENTIAL

A series of 20-kg cream batches was prepared using a 10-gallon Groen mixer. The batches consisted of the U.S.-sourced excipients and a systematic substitution by U.K.-sourced excipients.

Penetrometer and bleed testing indicated that the cream base containing U.K.-sourced glyceryl monostearate (with all other excipients U.S.-sourced) demonstrated softer consistency and extensive bleed. U.K.-sourced cetyl alcohol, Syncrowax ERL-C, Tween 60, and Amerchol L-101 did not promote bleed in the cream bases prepared using the Groen mixer (Table II). The results of this study led to a focus on the differences between U.S.- and U.K.-sourced glyceryl monostearate.

ANALYTICAL AND THERMAL ANALYSIS TESTING OF U.S.- AND U.K.-SOURCED GLYCERYL MONOSTEARATE

Thermal analysis, including DSC and powder x-ray diffraction measurements, were determined for each cream excipient. No significant differences were observed between U.S. and U.K. excipients except for glyceryl monostearate.

Differential scanning calorimetry was used as the first characterization tool for glyceryl monostearate since slight variations in chemical composition could yield variations in

Table II
Initial Consistency and Bleed Potential in Cream Bases Containing Individually Substituted U.K.-Sourced Excipients

Substituted U.K. excipient	Penetrometer consistency	Bleed (% w/w)
Glyceryl monostearate	299	9–10
Cetyl alcohol	281	0
Syncrowax ERL-C	284	0
Amerchol L-101	282	0
Tween 60	270	0

the glyceryl monostearate melting points. Furthermore, since the processing used in the manufacture of the cream involved melting and congealing of glyceryl monostearate, the DSC thermogram of melted and congealed glyceryl monostearate was also obtained.

The DSC profile of U.S.-sourced glyceryl monostearate, as it was received, is shown in Figure 3, as is the DSC thermogram obtained on glyceryl monostearate which had been melted and allowed to solidify. It is evident from the data that glyceryl monostearate does not solidify back into its original physical state. Most samples were found to exhibit an initial melt around 60°C, and after the melting/congealing process they

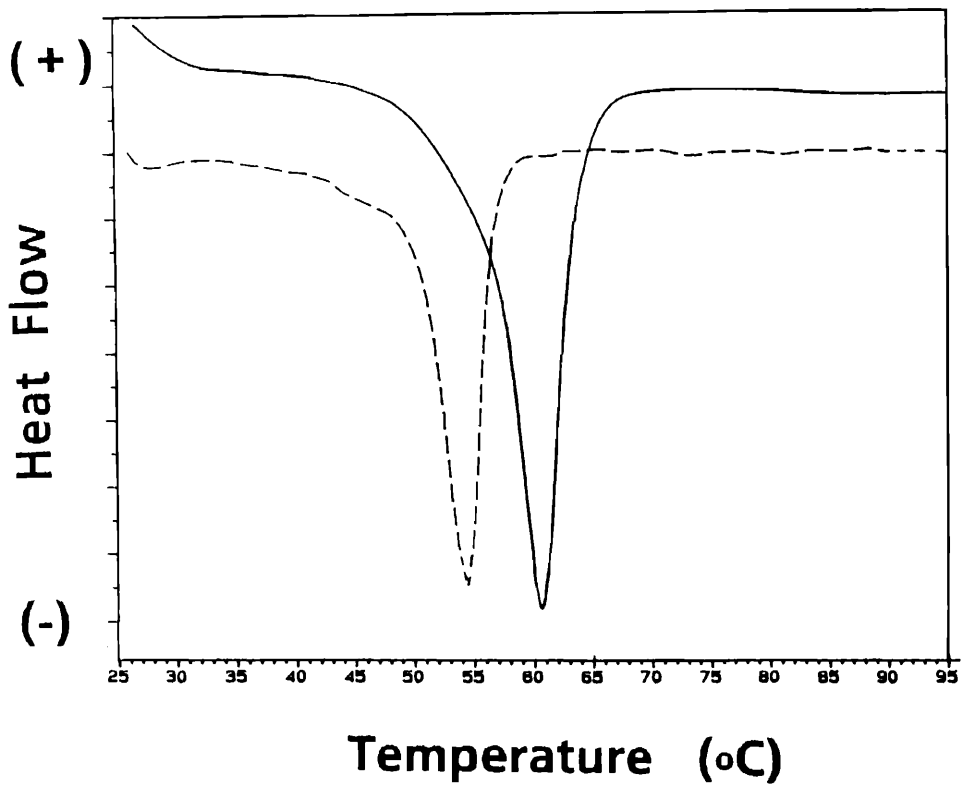

Figure 3. Differential scanning calorimetry thermograms obtained for U.S.-sourced glyceryl monostearate as received (solid trace) and after being melted and congealed (dashed trace).

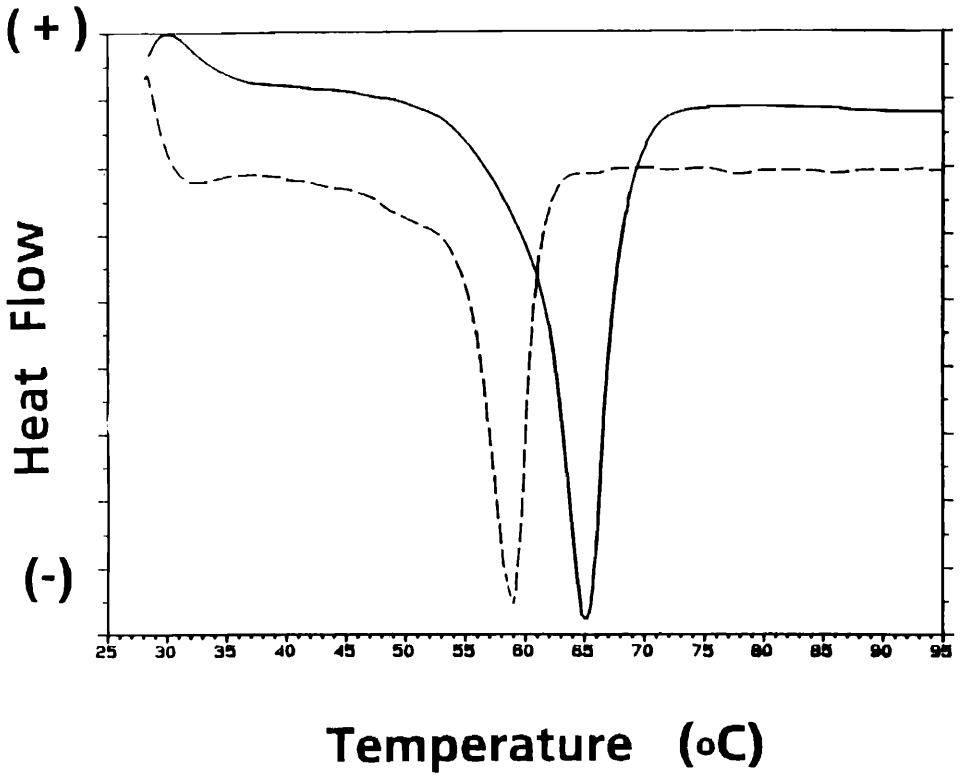

Figure 4. Differential scanning calorimetry thermograms obtained for U.K.-sourced glyceryl monostearate as received (solid trace) and after being melted and congealed (dashed trace).

yielded a melting point around 55°C. This behavior of glyceryl monostearate is consistent with previous findings (5,6).

The DSC profile of U.K.-sourced glyceryl monostearate (see Figure 4) was found to exhibit a slightly different trend. The DSC melting point of material as received averaged around 65°C, and after being allowed to melt and solidify the DSC melting point decreased to 59°C. This material also appears to undergo a structural change upon melting and congealing, but the different temperature values noted between U.S.- and U.K.-sourced glyceryl monostearate suggests that the structural changes are not equivalent.

The acid values of the two sourced glyceryl monostearates were found to differ significantly (see Table III). The acid value of the U.S.-sourced material was found to be 5.1 eq. KOH/gm, while the acid value of the U.K.-sourced material was measured as 1.1 eq. KOH/gm. These differences in acid value are significant and definitely indicate differences in chemical composition between the two lots. In fact, when U.K.-sourced glyceryl monostearate was spiked with approximately 2% w/w stearic acid (raising the acid value of this material to about 5), its DSC melting point was found to decrease down to 60°C. The ester value, which is the difference between the saponification value less the acid value, was 166.9 for the U.K. material and 158.9 for the U.S. material, which indicated that the U.K. glyceryl monostearate was slightly more lipophilic. Fur-

Table III
Comparative Properties of Glyceryl Monostearate Sourced From U.S. and U.K.

	U.S.	U.K.
Appearance	Flakes	Powder
Total % monoglyceride	41.0	36.3
Iodine value	1.6	0.6
Acid value	5.1	1.1
Saponification value	164.0	168.0
Ester value	158.9	166.9
Melting point By DSC	60°C	65°C

ther, the total monoglyceride and diglyceride contents were lower and the triglyceride content was higher for the U.K. source, which indicated fewer free hydroxyl groups and therefore a more lipophilic character.

Since the DSC experiments implicated the existence of a structural change upon melting and congealing, variable temperature XRD experiments were carried out to identify the nature of this structural alteration. Although the material is of relatively low crystallinity, sufficient structure exists to yield some x-ray scattering at 2-theta angles between 18° and 25°. As shown in Figure 5, the XRD pattern of U.S.-sourced glyceryl monostearate consists of at least four features. A new XRD pattern was ob-

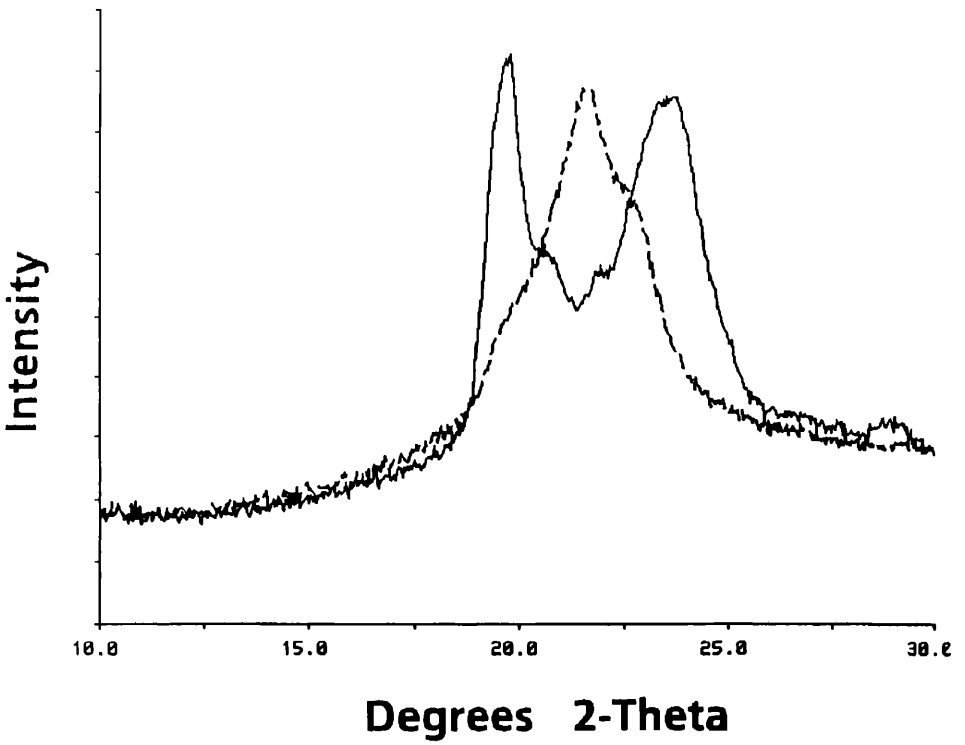

Figure 5. X-ray powder diffraction patterns obtained for U.S.-sourced glyceryl monostearate as received (solid trace) and after being melted and congealed (dashed trace).

tained after melting this sample on the XRD hot stage and allowing the material to congeal. This new pattern is far simpler than originally observed and consists of at least two features. The width and location of the XRD peaks suggest that they do not represent individual d-spacings, but instead reflect the ordering of the material as a whole.

Quite different behavior was observed for U.K.-sourced glyceryl monostearate. As evident in Figure 6, the material consisted of the same four-peak system, although the relative intensities of these were not equivalent to the U.S.-sourced material. Melting and congealing the U.K.-sourced material caused the total collapse of all peaks into a single gaussian peak, centered at 22° 2-theta. This observation is interpretated to imply that the U.K.-sourced glyceryl monostearate congeals into a single-phased material.

The implications of the XRD studies are that a chemical difference between the U.S.- and U.K.-sourced glyceryl monostearate yields structural differences after these are melted and congealed. A material capable of solidifying into a single phase would contract significantly upon cooling, while a material that would solidify into a multiphasic mixture would not be able to contract upon solidification. This behavior has indeed been observed for bulk glyceryl monostearate: if the slide holding the U.K.-sourced material is inverted after the melt congeals, the material will actually fall out of the XRD slide holder of its own accord. The U.S.-sourced material is extremely difficult to remove from the slide holder and requires mechanical scraping for its removal. It

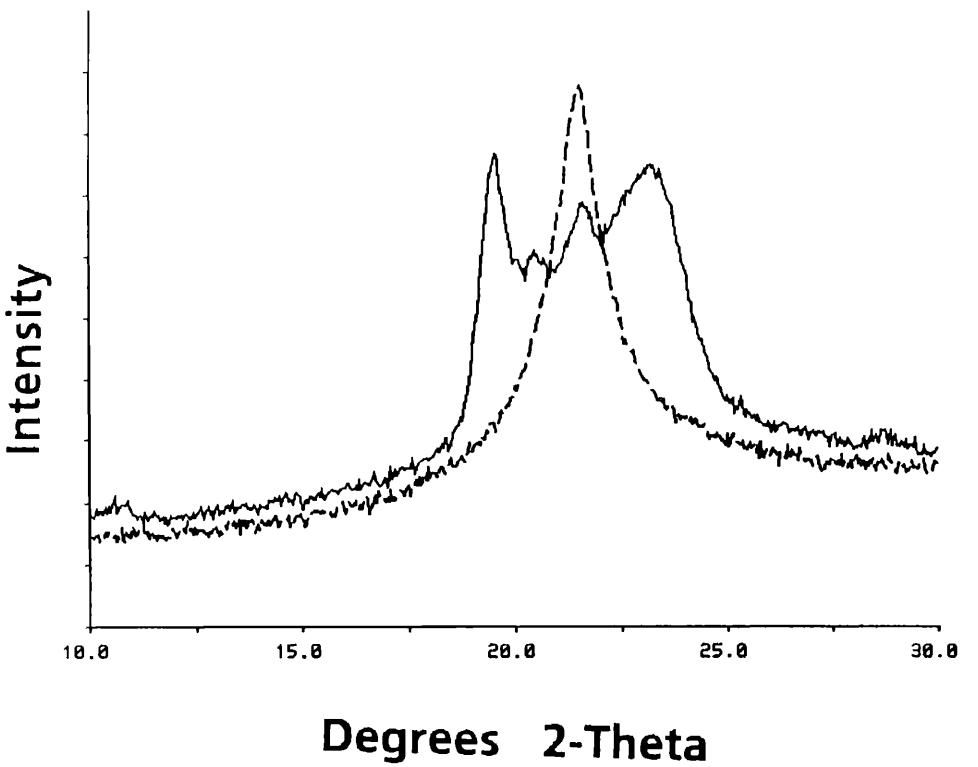

Figure 6. X-ray powder diffraction patterns obtained for U.K.-sourced glyceryl monostearate as received (solid trace) and after being melted and congealed (dashed trace).

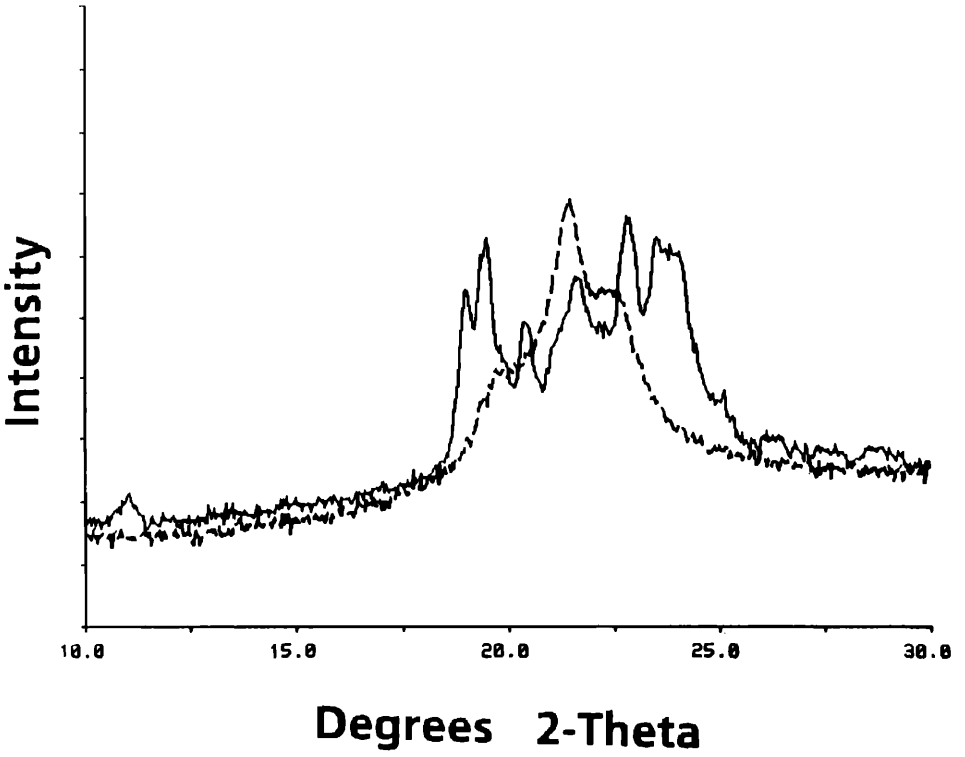

Figure 7. X-ray powder diffraction patterns obtained for U.K.-sourced glyceryl monostearate to which sufficient stearic acid had been added so as to raise the acid value to approximately 5. Data are shown for the unheated material (solid trace) and for the sample after it had been melted and congealed (dashed trace).

would appear that the chemical composition of the U.K.-sourced glyceryl monostearate is such that all non-idealities cancel and the overall material behaves as if it were a chemically pure material.

To test this hypothesis, U.K.-sourced glyceryl monostearate spiked with stearic acid was subjected to the variable temperature XRD study. As evident in Figure 7, the complicated initial XRD pattern simplified after the material was melted and congealed, but the resulting XRD pattern now contained several scattering peaks. In addition, the congealed material remained firmly attached to the XRD slide holder after solidification and was removable only with difficulty. These observations indicate that addition of the stearic acid altered the composition of the glyceryl monostearate sufficiently that it could not congeal into a single phase capable of contraction.

The effect on cream properties resulting after chemical modification of the glyceryl monostearate composition was then investigated. U.K.-sourced glyceryl monostearate (acid value 1.1) was modified by the addition of stearic acid until the final acid value was adjusted to approximately 5. Upon manufacture of a 20-kg cream batch, no initial bleed was observed. Relative to a cream made with U.K.-sourced glyceryl monostearate, the consistency of the modified formulation (with stearic acid) was firmer initially, and the gel structure developed more rapidly (see Figures 8 and 9).

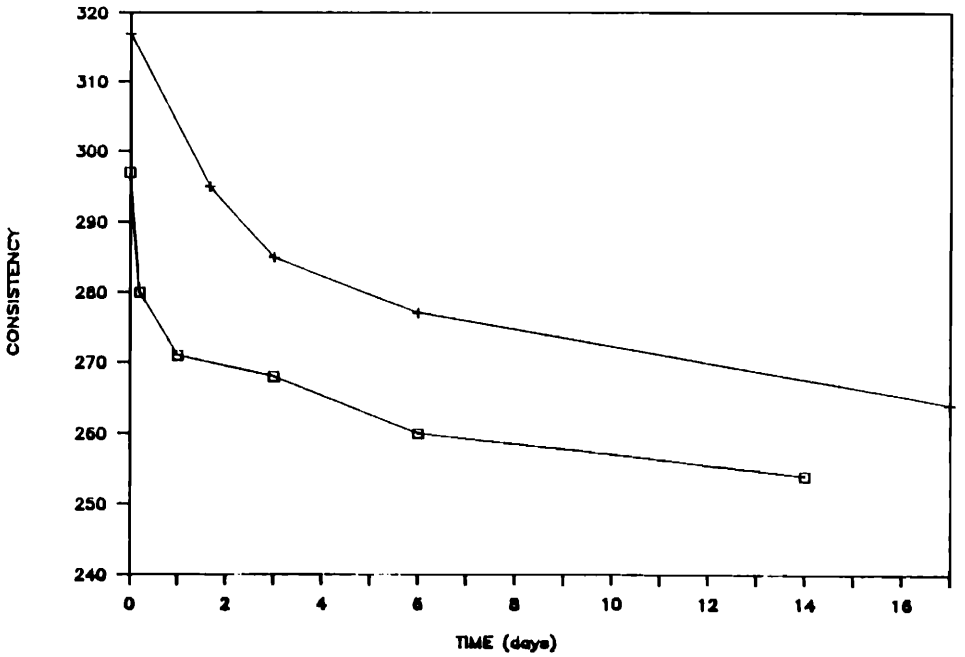

Figure 8. Time dependence of the consistency as a function of cream prepared with U.K.-sourced glyceryl monostearate with (□) and without (+) added stearic acid.

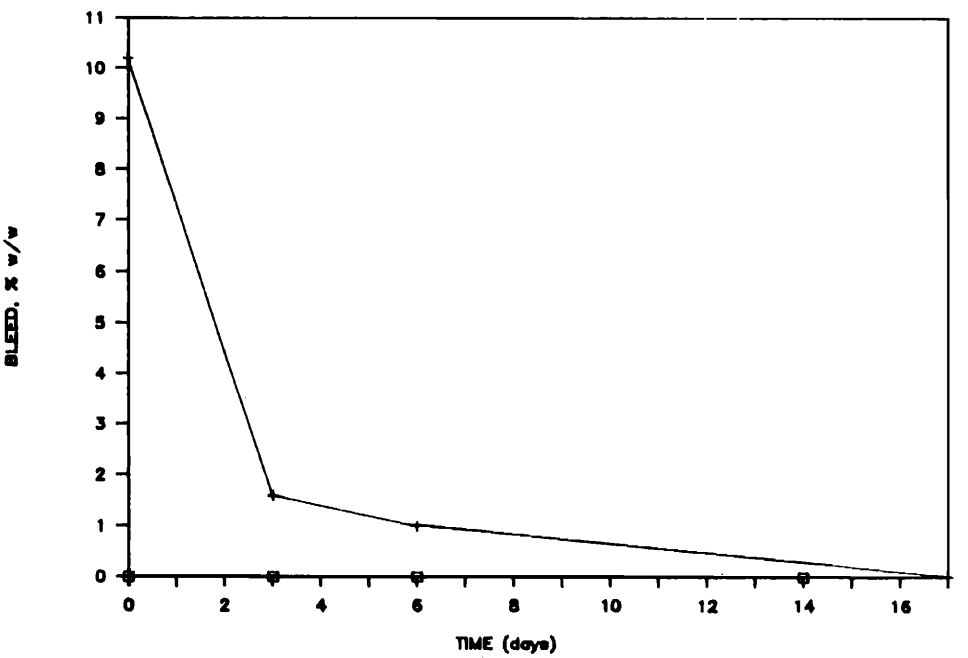

Figure 9. Time dependence of the extent of bleed as a function of cream prepared with U.K.-sourced glyceryl monostearate with (□) and without (+) added stearic acid.

EVALUATIONS OF GLYCERYL MONOSTEARATE SOURCED FROM NON-U.S. MANUFACTURING PLANTS

Glyceryl monostearate samples sourced from inventory supplies of manufacturing plants located in Canada, Germany, Greece, South Africa, and Spain were obtained. Analytical and thermal analysis results were compared to those previously obtained for U.S. and U.K. samples. Five cream batches (20 kg each) were prepared. Each of the cream bases contained glyceryl monostearate supplied from one of the above-mentioned plant sources.

As shown in Table IV, there appeared to be a rank correlation between the bleed potential of the cream and the acid value of the glyceryl monostearate raw material. The creams containing glyceryl monostearate with very low acid values of about 1 or less exhibited the most initial bleed. Those with acid values of 2–3.5 showed slight initial bleed, and those with acid values of about 5 and greater did not exhibit bleed. Initial higher penetrometer results, which are indicative of softer cream consistency, were obtained for creams containing glyceryl monostearate, having lower acid values. Thermal analysis and variable temperature x-ray diffraction measurements accurately classified and predicted the probable effects that each glyceryl monostearate source would have on the consistency and bleed propensity of the finished cream. All of the multi-sourced glyceryl monostearate cream bases developed firmer consistency and diminished bleed potential after 7 days of bulk storage at 24° ± 3°C.

CONCLUSIONS

Glyceryl monostearate was identified as the key excipient influencing the gel structure, consistency, and bleed properties of the oil-in-water emulsion-type cream base.

Acid value, which is a measure of the free fatty acids in the glyceryl monostearate, was found to be an important indicator of raw material quality. Creams prepared using glyceryl monostearate with low acid value (1–3.5) had soft consistency and exhibited liquid bleed separation initially after manufacture. Creams containing glyceryl monostearate with higher acid value (5–15) had satisfactory firm consistency without bleed.

Table IV
Influence of Glyceryl Monostearates Sourced From Various Countries on the Consistency and the Propensity for the Occurrence of Bleed in Cream Base

Sourced from	Acid value	X-ray type	Initial penetrometer	Observation on wire-mesh test for bleed	
				Initial	After 7 days storage at 24 ± 3°C
Germany	0.85	2	298	Bleed	Slight bleed
U.K.	1.1	2	317	Bleed	Slight bleed
Greece	2.0	2	297	Slight bleed	No bleed
Spain	3.5	2	293	Slight bleed	No bleed
U.S.	5.1	1	285	No bleed	No bleed
Canada	10.0	1	266	No bleed	No bleed
South Africa	14.9	1	284	No bleed	No bleed

DSC and VTXRD thermal analysis methods were used to characterize and classify multi-sourced grades of glyceryl monostearate. These accurately predicted the effects that each lot of glyceryl monostearate would have on the consistency and bleed propensity of the finished cream.

Cone penetrometer and wire-mesh screen testing were utilized for assessing consistency and bleed potential of the bulk cream immediately after manufacture and during bulk cream storage prior to approval for packaging.

Based on this study, in order to overcome variable consistency and bleed problems, the following recommendations can be made:

1. If possible, use only glyceryl monostearate with higher acid value (5–15) and optimal thermal analysis VTXRD pattern.
2. Cream batches prepared using glyceryl monostearate with low acid value (below 5) should be stored at 20°–33°C until a firm consistency develops and no bleed is evident when tested by the wire-mesh screen method.

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