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PHASE BEHAVIOR CHARACTERIZATION OF OINTMENTS CONTAINING LANOLIN OR A LANOLIN SUBSTITUTE

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ABSTRACT

Ointment vehicles consisting of mineral oil, white petrolatum and either anhydrous lanolin, or the lanolin substitute SOFTISAN® 649 were investigated by determining the binary and ternary phase behavior of these mixtures. Rheology measurements related changes in viscosity with changes in phase behavior. Lot to lot variability of the anhydrous lanolin caused significant shifts in the binary and ternary phase behavior which resulted in changes in viscosity of the ointment base. While replacement of anhydrous lanolin with the lanolin substitute SOFTISAN® 649 significantly changed the ternary phase behavior of they system, suitable ointment vehicles could be prepared that were very reproducible utilizing different lots of SOFTISAN® 649.

INTRODUCTION

Mixtures of mineral oil, white petrolatum and lanolin provides the ointment base for various topical ointment products. The 25/55/20 by weight mixture of mineral oil/white petrolatum/lanolin is a specific formulation that has presented challenges with regard to the manufacture of a pharmaceutical ointment having consistent quality. Unacceptably low product viscosities have routinely occurred for this formulation, and have been linked with lot to lot

variability in the composition of the lanolin. The component(s) responsible for these viscosity variations has not been identified.

Lanolin is the secretion of the sebaceous glands of sheep which is deposited onto the wool fibers. Chemically, lanolin is a complex mixture of esters, diesters, and hydroxy esters of aliphatic alcohols/sterols (C_{12}-C_{36}), and normal, iso, anteiso, and hydroxy acids[1]. Based upon experimentally determined compositions of lanolin alcohols/sterols and lanolin acids, the theoretical number of lanolin mono-ester combinations totals 10,350[1]. Lanolin is a by-product of the wool scouring industry, and the quantity of wool grease varies depending upon the breed of sheep, the anatomical area sheared, inner and outer fleece, and season. Varying degrees of oxidation of the lanolin may occur depending on the storage conditions of the sheared wool prior to scouring. Following the wool scouring procedures, the lanolin is separated and purified by techniques including acid cracking or centrifugal washing, neutralization , removal of soaps, filtration, bleaching and deodorization[1]. These techniques are not uniform throughout the wool scouring industry, and thus considerable variation in composition is typical for lanolin from different wool scouring industries. Lanolin from numerous sources is pooled prior to purchase by the U.S. supplier of lanolin. These sources vary and are generally not known to the U.S. supplier. Thus, source history for a particular lot of lanolin is generally not available to the pharmaceutical manufacturer.

In an effort to improve quality of mineral oil/white petrolatum/lanolin ointment formulations, two investigations were completed. First, the phase behavior of the mineral oil/white petrolatum/lanolin system was characterized to determine the relationship between the viscosity changes and the phase boundaries discernable within the system. Phase behavior studies have been previously used to characterize semisolid formulations in general[2,3], and ointments in particular[4]. Secondly, a lanolin substitute was evaluated as a possible replacement for lanolin. The lanolin substitute is a mixture of caprylic, capric, isostearic and adipic triglycerides, and is stable against oxidation[5]. Since this product is manufactured by hydrolyzing coconut oil,

distilling the fatty acid fractions, and then recombining these materials to form the appropriate triglyceride mixtures, very low lot to lot variability is anticipated for this material.

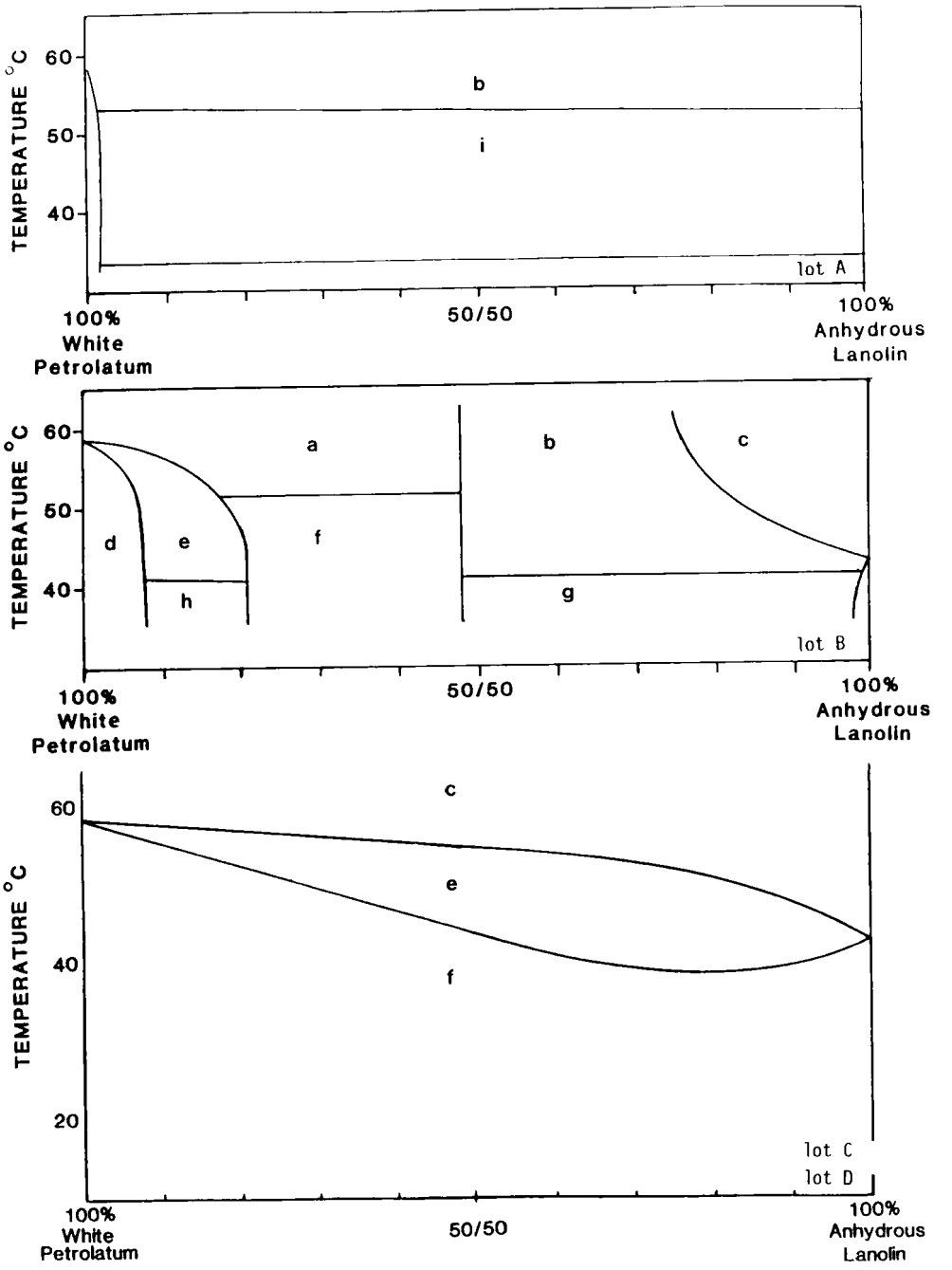
EXPERIMENTAL

Samples were prepared using laboratory robotics as previously described[6,7]. White petrolatum USP (Penreco, Butler, PA), mineral oil viscosity 180 (Penreco, Butler, PA), anhydrous lanolin USP (R.I.T.A., Crystal Lake, IL), and Softisan 649 (HULS of America Inc., Stony Point, NY) were within the manufacturer's specifications, and were used as received. Phase behavior was determined after storage and repeated mixing of the samples at 60°C. After checking the phase behavior characterized at 60°C, the temperature was lowered in 5°C increments for the binary systems or to the temperature specified for the ternary systems and the samples allowed to equilibrate without additional mixing. At least two days were allowed at each temperature for equilibrium to be established. All temperatures were controlled within $\pm$ 0.1 °C using an Espec LHU-112 Laboratory Chamber.

Rheology studies for the mineral oil/white petrolatum/lanolin mixtures were completed using a Ferranti Shirley cone and plate viscometer (Ferranti Electric, Inc., Commack NY) at 25°C with a 7 cm cone and 60 second sweep. For the mineral oil/white petrolatum/Softisan 649 mixtures viscosity was measured using a Brookfield Synchroelectric viscometer. Rheology samples were heated to 60°C and then vibromixed until complete solidification. The samples were then allowed to equilibrate at 25°C for 24 hours prior to rheology testing.

RESULTS

The phase behavior of four different lots of lanolin was determined in combination with a single lot of white petrolatum and/or a single lot of mineral oil. As seen in figure 1, the phase behavior for the binary system white petrolatum and lanolin varies dramatically depending upon the lot of lanolin used. Lanolin lot A is essentially immiscible with white petrolatum (figure 1a), while Lanolin lots C and D are completely miscible (figure 1c). Lanolin lot B provides complex phase behavior when mixed with white petrolatum (figure 1b). Binary phase behavior for the mineral oil and lanolin mixtures



also indicate that lot to lot variability of the lanolin can significantly alter positioning of the solubility regions. When combined with mineral oil, lanolin lots A and B provide very similar phase behavior that is characterized by a large two phase region (figure 2a). For lanolin lots C and D both the width and temperature range over which this separation occurs is reduced (figure 2b). The binary phase behavior for mineral oil and white petrolatum is shown in figure 3, and is characteristic of mutually soluble solids of different melting points.

For the ternary system mineral oil/white petrolatum/lanolin it is found that mixtures of white petrolatum and lanolin can not incorporate as much mineral oil as can either white petrolatum or lanolin alone (figure 4). Furthermore, the maximum amount of mineral oil that will remain as a non-separated semisolid varies dramatically with the different lots of lanolin tested. As seen in figure 4, the 25:75 lanolin:white petrolatum weight ratio can incorporate 12, 17, 27, and 35 weight percent mineral oil for lanolin lots A, B, C, and D respectively. Note that for the specific ointment formulation 25/55/20 mineral oil/white petrolatum/lanolin, only lanolin lots C and D would provide a physically stable semisolid product.

To better correlate the phase boundary shown in figure 4 with product viscosity, a rheology study was completed. Compositions as shown on the phase diagram in figure 5 produced the series of rheograms shown in figure 6. Not only does the shear rate verses shear stress plots show that viscosity is

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Figure 1. Binary freezing point diagrams for lots A, B, C and D of lanolin when combined with white petrolatum. The phase regions were observed to have the following appearance: (a) single-phase, clear, colorless liquid; (b) two clear liquid phases, top colorless, bottom yellow; (c) single-phase clear yellow liquid; (d) white petrolatum with dissolved lanolin; (e) cloudy semisolid top phase, colorless clear liquid bottom phase; (f) homogeneous semisolid; (g) two semisolid phases, top white, bottom yellow; (h) two semisolid; and (i) multiple phases both liquid and semisolid. Lanolin lot A did not produce a homogeneous semisolid, while lots C and D resulted in phase behavior characteristic of two materials mutually miscible in both liquid and solid phases. Lanolin Lot C produced complex phase behavior best described as intermediate in appearance compared to completely miscible (lots C and D) and completely immiscible (lot A).

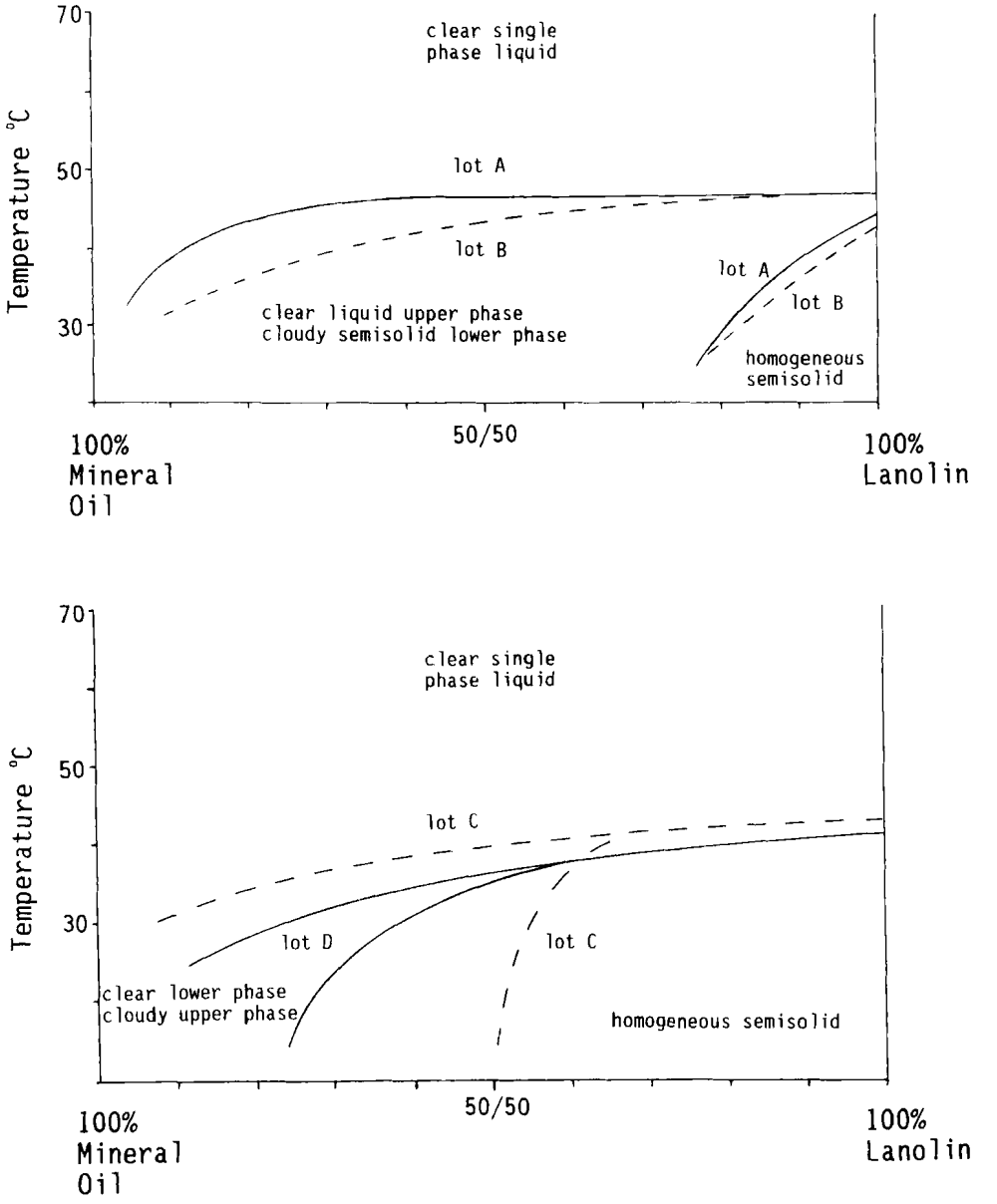

Figure 2. Binary freezing point diagrams for Lots A, B, C, and D of lanolin when combined with mineral oil. At high lanolin concentrations for lots C and D the two phase region was not discernable.

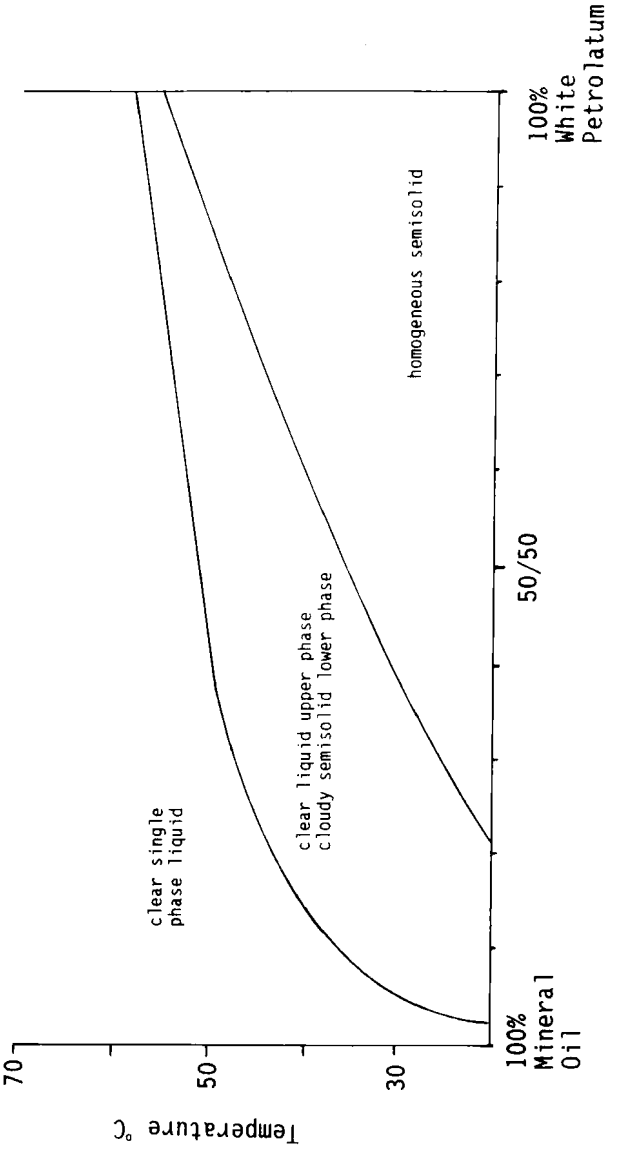

Figure 3. Binary freezing point diagram for mineral oil and white petrolatum.

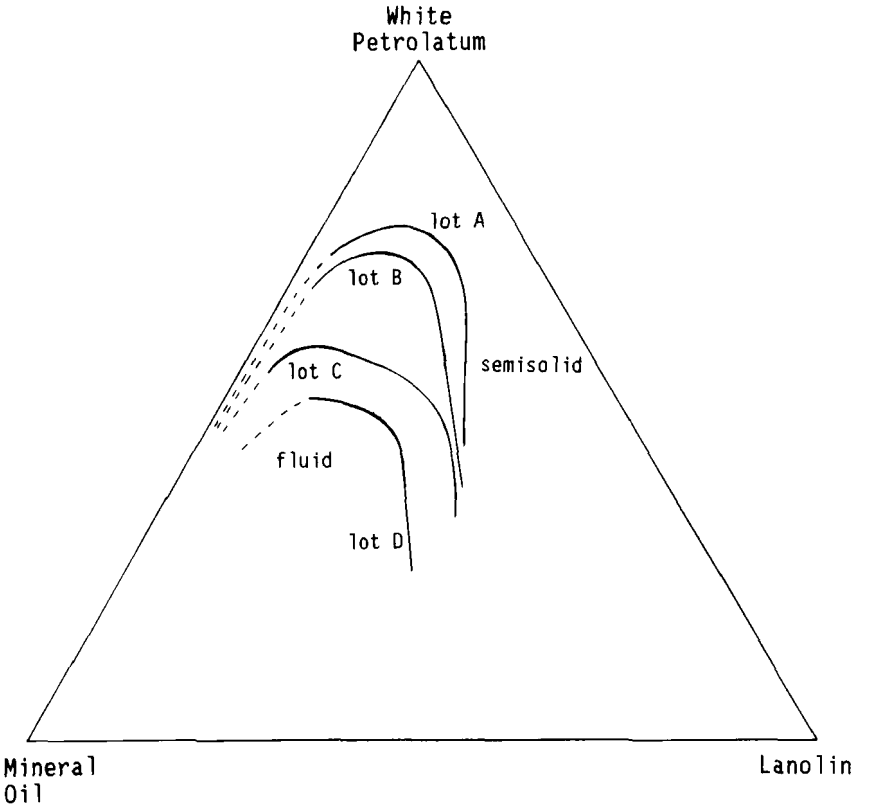

Figure 4. Pseudo-ternary phase behavior for lots A, B, C, and D of lanolin when combined with white petrolatum and mineral oil after mixing at 60°C and equilibration at 25°C. Lanolin lot D was able to incorporate the greatest amounts of mineral oil before changing from a semisolid to a more fluid mixture. The high mineral oil content side of this phase line was a fluid region that separated upon slow cooling (slower than 5°C/day) but remained physically stable for weeks after forced cooling.

significantly less for the formulations that phase separate upon standing, but also the hysteresis loop significantly changes. Virtually Newtonian behavior exists for the samples in the fluid region furthest from the proposed phase boundary. The thixotropic spur seen for rheology traces c and d of figure 6 were reproducible and characteristic of the semisolids having the highest white petrolatum concentrations, but were absent for the more viscous semisolids having higher lanolin concentrations, i.e. traces i and j of figure 6.

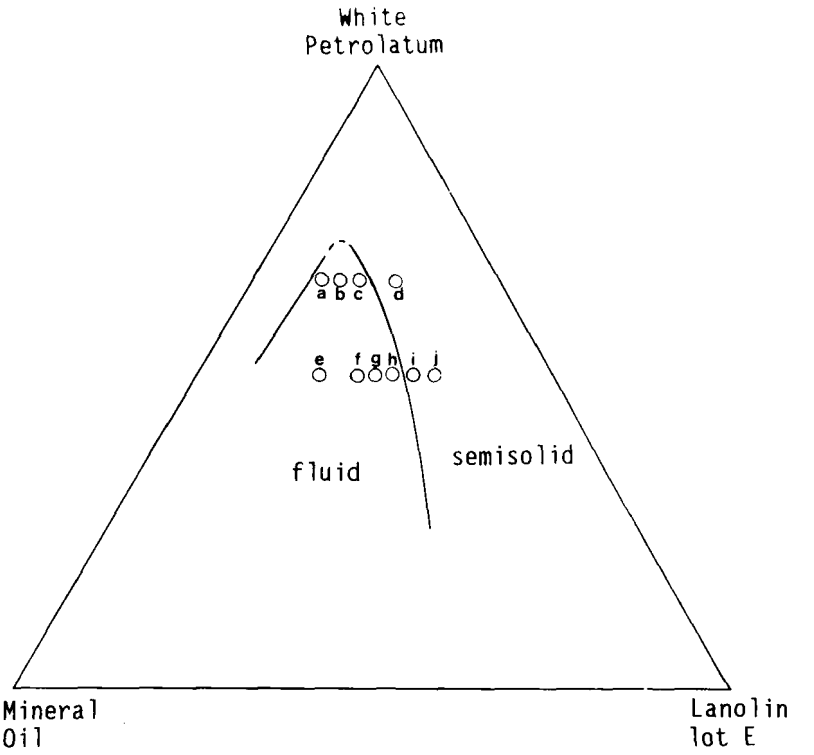

Figure 5. Detail of the compositions studied rheologically and the phase boundary for mixtures of mineral oil/white petrolatum/lanolin lot E. As in figure 4, compositions in the fluid region separated upon slow cooling (slower than 5°C/day) but did not readily separate when forced cooled from 60°C to 25°C.

Combination of white petrolatum and Softisan 649 results in rather complex, but very reproducible phase behavior. As seen in figure 7, at temperatures of 60°C and above a single phase clear liquid exists for mixtures of white petrolatum and Softisan 649 containing greater than 45% Softisan 649. Upon cooling, these mixtures appear to solidify as a homogeneous cloudy semisolid. Hcwever longer term storage (approximately one month) at temperatures between 45 and 55°C resulted in the composition containing greater than 60% Softisan 649 clouding at the top of the sample while the bottom of the sample remained clear. Distinct phase separations occurred for mixtures containing less than 40% Softisan 649. The binary phase behavior for mineral oil and Softisan 649 is shown in figure 8. While the phase behavior

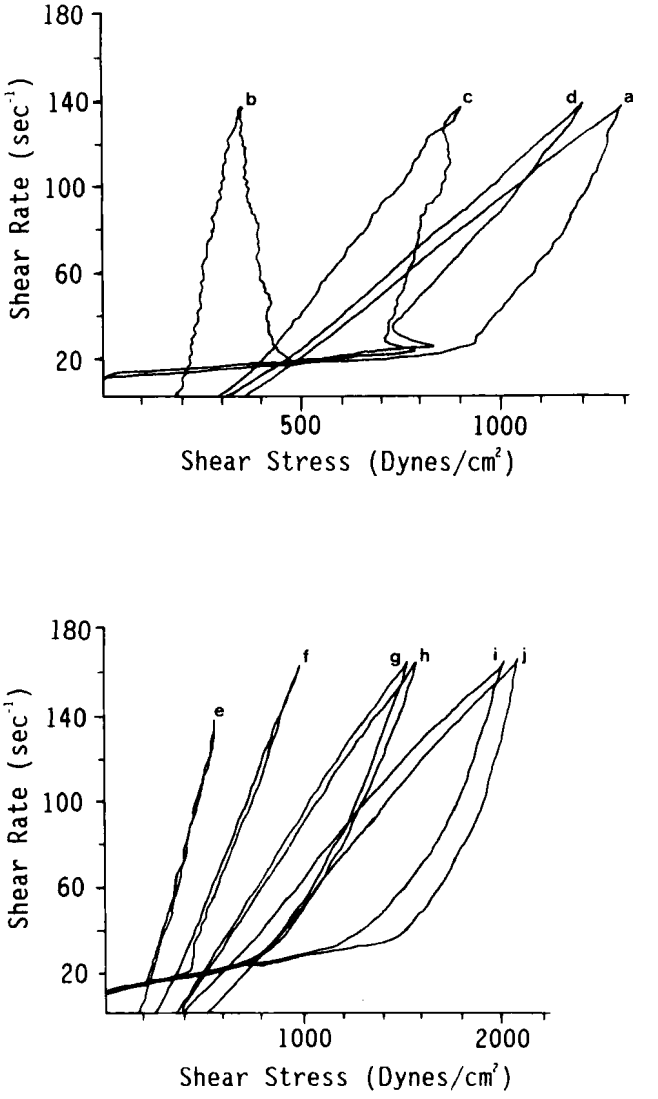

Figure 6. Rheology traces at 25°C for the compositions shown on the ternary diagram in figure 5. Rheology measurements were made after mixing the samples at 60°C and equilibrating for 24 hours at 25°C. Note different scales for the shear stress axis. Apparent viscosities in Poise were as follows: a) 9.6 P, b) 2.5 P, c) 8.6 P, e) 4.0 P, f) 6.0 P, g) 9.2 P, h) 9.4 P i) 12.2 P and j) 12.6 P

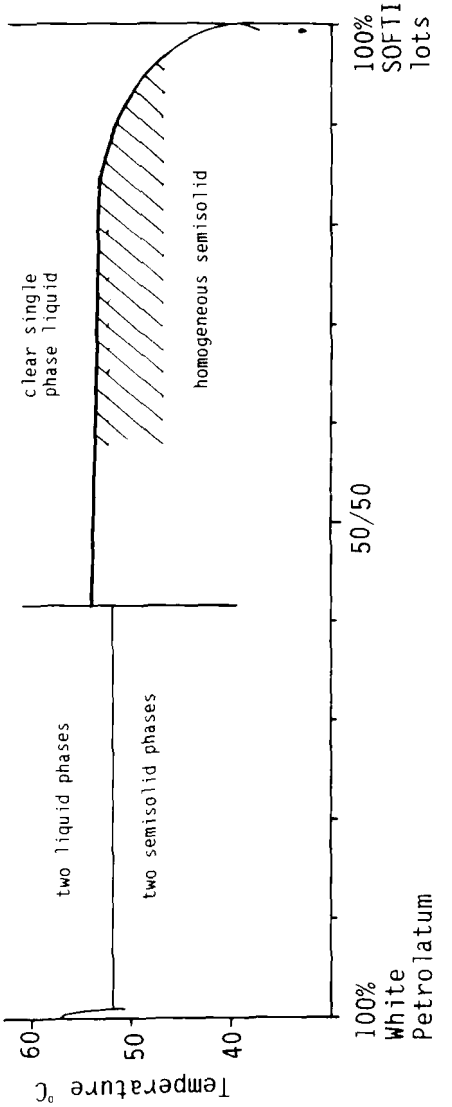

Figure 7. Binary freezing point diagram for lots A and B of Softisan 649 when combined with white petrolatum. The shaded region slightly clouded at the top of the sample but did not appear to phase separate.

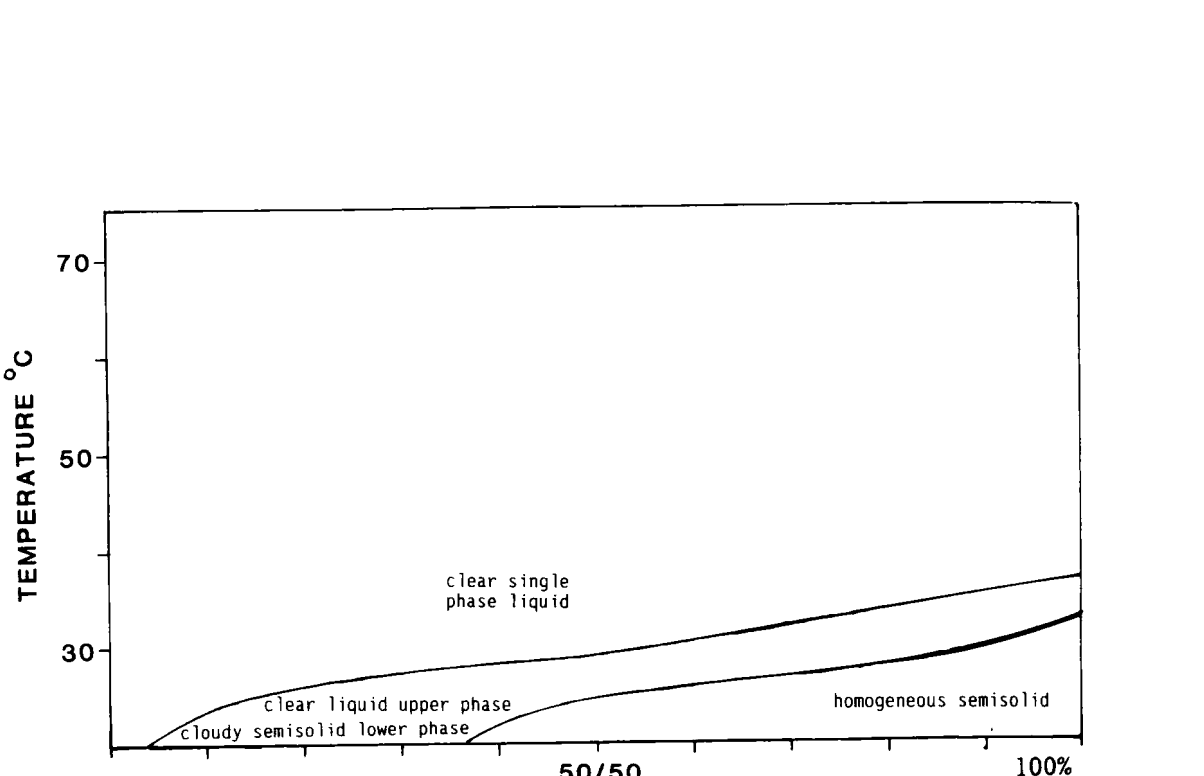

Figure 8. Binary freezing point diagram for mineral oil and Softisan 649 lots A and B.

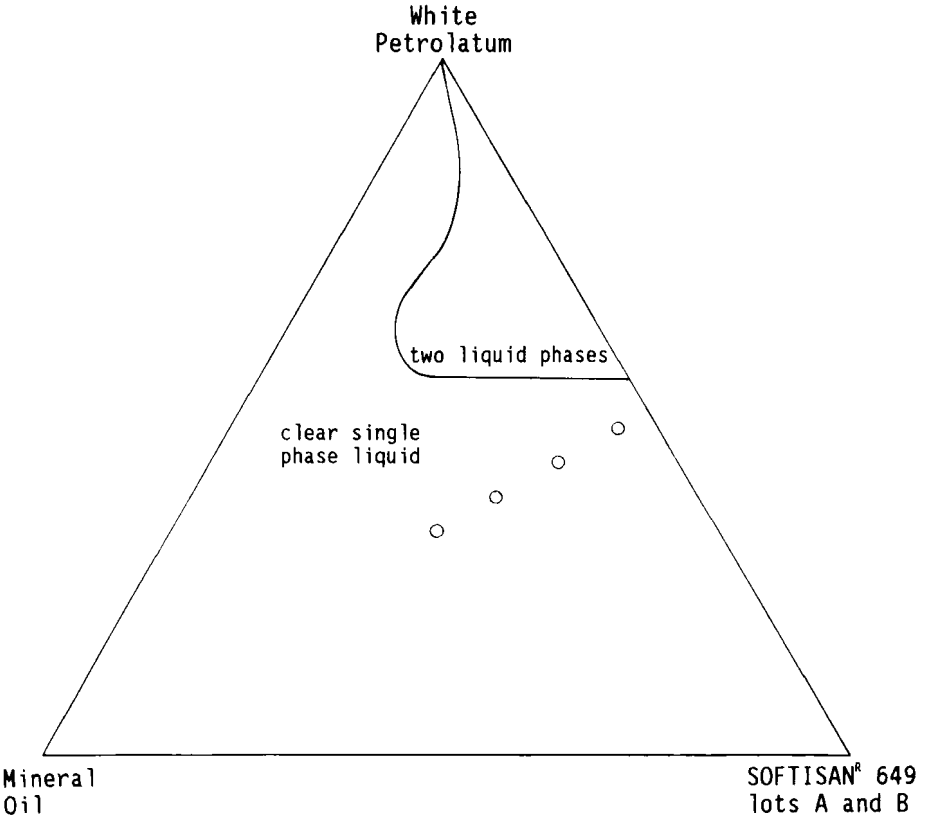

Figure 9. Pseudo-ternary phase behavior for lots A and B of Softisan 649 when combined with white petrolatum and mineral oil at 60°C. Viscosities were determined for the compositions circled in the single phase region (Table 1).

is once again typical of mutually soluble solids, solidification does not occur until the temperature is below 30°C. While only one lot of white petrolatum and mineral oil were used for all of these studies, two different lots/batches of Softisan 649 were used with the result of indistinguishable phase behavior. For the ternary system mineral oil/white petrolatum/Softisan 649, the phase behavior was simple (figure 9). Except for a range of concentrations extending from the two phase region at greater than 55 weight percent white petrolatum, the three materials form physically stable ointment bases. As with the binary Softisan 649 phase behavior, indistinguishable differences in phase behavior was found for the two different lots of Softisan

Table 1

Viscosities in Poise as Determined Using a Brookfield Synchroelectric Viscometer on 1:1 Weight Ratios of White Petrolatum:Softisan 649 Containing the Indicated Weight Percent of Mineral Oil.

% Mineral Oil	Apparent Viscosity Using Spindle 4 (P)	Apparent Viscosity Using Spindle TF (P)
35	180	230
25	370	410
15	680	7,000
5	900	>25,000

649. Viscosities for a series of compositions having a 1:1 ratio of white petrolatum:Softisan 649 are given in Table 1.

DISCUSSION

A standard and very useful method of qualitatively predicting the mutual solubilities of materials is to consider their Hildebrand solubility parameters[8]. Compounds that have solubility parameters within two units of each other are usually miscible[9]. As solubility parameters become progressively dissimilar, the likelihood of even limited solubility of one in the other becomes progressively less likely. For two materials having solubility parameters varying by four units, the addition of a liquid having an intermediate solubility parameter may produce a mutually soluble blend of the three materials. The material having the intermediate solubility parameter is called the co-solvent, and this approach has been thoroughly exploited in the pharmaceutical industry[10]. Since solubility parameters of mineral oil, white petrolatum and lanolin are 7.1, 7.3, and 7.5-8 respectively[9,11] these three components should be mutually miscible. Thus, the binary phase behavior should be similar to figure 10 which is the idealized phase behavior for two components of different melting temperatures that are completely miscible in both the solid and the liquid phases.

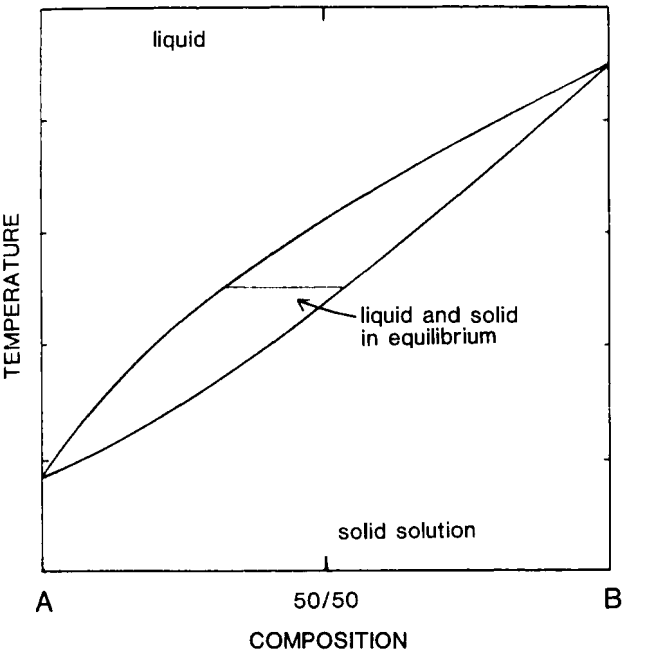

Figure 10. Idealized binary diagram for a two-component system in which the components are miscible in both the liquid and solid phases but having different melting points.

As seen in figure 1, lanolin lots C and D are completely miscible with white petrolatum both as liquids and semisolids, and the experimental phase behavior is ideal. In stark contrast is the equally ideal phase behavior of two completely immiscible materials that results when white petrolatum is mixed with lanolin lot A. Equally disconcerting is the complex phase behavior seen in figure 1 for white petrolatum and lanolin lot B. This complete range of phase behavior emphasizes that white petrolatum and lanolin are complex, potentially highly variable mixtures of components. As stated in the introduction, lanolin is a complex mixture of esters, diesters, and hydroxy esters of aliphatic alcohols/sterols (C_{12}-C_{36}) and normal, iso, anteiso, and hydroxy acids[1]. Depending upon the processing method utilized, a large amount of oxidized material may be present in anhydrous material, i.e. high levels of free acidity. Note that each of these many and chemically diverse components will have a corresponding Hildebrand solubility parameter. The Hildebrand

solubility parameter value of 7.5-8 stated above represents the weighted average value for the many components that make up lanolin. Since a diversity of components is anticipated, components of intermediate polarity will serve as cosolvents for the more polar and more non-polar components. Addition of significant amounts of a more non-polar material could overwhelm the cosolvancy ability of the components of intermediate polarity. Thus, a non-separated lanolin raw material may exist that will phase separate upon addition of significant amounts of a more non-polar material such as white petrolatum or mineral oil. Alternatively, lanolin consisting of components having a narrow range of polarity centered around Hildebrand values of 7.5 to 8 will be completely miscible with white petrolatum or mineral oil and exhibit ideal phase behavior (see figure 10). This description emphasizes that while these highly variable mixtures may at times exhibit phase behavior indistinguishable from ideal pure components, reproducible phase behavior from lot to lot of raw material will not occur.

This study indicates that variation in phase behavior directly relates to unacceptably low product viscosities for mineral oil/white petrolatum/lanolin ointments. As seen in figure 4, separation of the ointment semisolid occurs for mixtures that are cooled slowly. This separation can be attributed to the same mechanism as described above for the phase behavior of the white petrolatum-lanolin or mineral oil-lanolin binary mixtures. As either the mineral oil or white petrolatum is added to lanolin, separation of the more polar lanolin components can occur. The amount of mineral oil and white petrolatum that can be incorporated is dependent upon the range in polarities of the components present in the lanolin. To strengthen the link between the compositions that will separate upon slowly cooling after heating to 60°C and the ointment production batches that had unacceptably low product viscosity, the rheology study summarized in figure 5 was completed. Multiple samples were prepared and the phase behavior for lanolin lot E was determined as before, i.e. heated to 60°C, slowly cooled. Selected samples were then heated to 60°C and then vibromixed until solidification. These "forced cooled" samples were then allowed to equilibrate at 25°C for 24 hours prior to

testing. For the compositions shown in figure 5 all of the samples were non-separated at the time of testing. The forced cooled with mixing compositions tested showed that product viscosity significantly increases as the equilibrated phase boundary is approached. Since this boundary shifts significantly from lot to lot of lanolin, only certain lots of lanolin will result in acceptable product for the 25/55/20 mineral oil/white petrolatum/lanolin ointment. It should be emphasized that the rheology results do not indicate that these are sharp boundaries. Rather, the transitions occur over a few weight percent as expected for a complex mixture of esters, fatty alcohols, and fatty sterols having a range of chain lengths.

The rheology traces of figure 6 provide both viscosity information and an indication of microcrystalline structure. Petrolatum consists of both solid and liquid hydrocarbons having a structure in which the three dimensional crystalline hydrocarbons enclose and immobilize the hydrocarbons to form a shear sensitive gel (12). While the apparent viscosity provides a convenient comparison between compositions, the thixotropic area indicates the degree of microcrystalline structure. For systems that have microcrystalline structure, the application of shear sufficient to disrupt this structure results in shear-induced reduction of viscosity. Rapid structural breakdown at a low rate of shear produces the thixotropic spur noted in traces c and d of figure 6. The greater the shear-induced reduction in viscosity the greater the thixotropic area. This infers that the greater the thixotropic area the greater the original microcrystalline structure. As seen in figures 5 and 6 the hysteresis loops for compositions furthest from the "equilibrium" phase boundary (samples e and f) have low apparent viscosities and essentially no thixotropic area, while compositions within the "equilibrium" single phase boundary have the highest apparent viscosities and greatest thixotropic areas (samples i and j). Thus, those compositions with the highest apparent viscosities also have the greatest microcrystalline structure and correspond well with the compositions that are single phase upon "equilibration." Remember that none of the rheology samples specified in figures 5 and 6 showed any indication of phase separation at the time the rheological study was

completed, i.e. 24 hours after forced cooling from 60°C with mixing. However, the differences in the resulting hysteresis loops would undoubtedly result in significant changes in skin feel.[13,14]

As shown above, the lot to lot variability of lanolin causes unacceptable variability in the attributes of ointment products. Natural lanolin may contain skin sensitizing contaminants that have been attributed to pesticides/herbicides ingested by the sheep prior to shearing of the wool[1]. Aliphatic alcohols contained within the lanolin have also been identified as a source of skin sensitization[15]. Considering these difficulties with formulation of topical products containing lanolin, the use of the lanolin substitute Softisan 649 was investigated. As seen in figure 7, the binary phase behavior of white petrolatum and Softisan 649 cannot be described as ideal, but is very reproducible between the two lots studied. The two phase region that exists for the binary system at high white petrolatum concentrations remains upon addition of mineral oil, and extends significantly into the ternary diagram for ratios of white petrolatum:Softisan 649 between 85:15 and 65:35. It is apparent that the ternary phase behavior for the mineral oil/white petrolatum/Softisan 649 system (figure 9) is not equivalent to the mineral oil/white petrolatum/anhydrous lanolin phase behavior shown in figures 4 and 5. However very reproducible homogeneous semisolid preparations can be formed upon force cooling the compositions within the large single phase region at 60°C shown in figure 9. In an attempt to verify a range of suitable compositions for a topical ointment containing white petrolatum, mineral oil and the lanolin substitute Softisan 649, the viscosity of a series of compositions was determined. As seen in Table I, a range of viscosities are possible with the compositions having the greatest amount of mineral oil being of the lowest apparent viscosity. Each of the compositions clouded uniformly upon cooling and initially appeared to be homogeneous ointment preparations. Slight syneresis was noted for the samples continuing 15 and 25% mineral oil after ambient storage for one month.

In summary, the viscosity variation for ointments consisting of mineral oil, white petrolatum, and anhydrous lanolin can be related to lot to lot

variability of the lanolin in this ointment base. These viscosity variations correspond to definite changes in the "equilibrated" phase behavior of the system. It is proposed that the lanolin contains materials having a wide range of polarities that are balanced with regard to their solubility parameter values to form a multicomponent co-solvent system. Addition of the relatively non-polar mineral oil or white petrolatum disrupts this co-solvent balance for a lot of lanolin that contains high amounts of polar material and phase separation results. Lots of lanolin containing lower amounts of polar material remain sufficiently balanced with regard to solubility parameters even after addition of mineral oil or white petrolatum and result in phase behavior characteristic of ideally miscible materials. Both the problems of lot to lot variability and skin sensitization associated with lanolin can be avoided by the use of Softisan 649. While this is not a direct replacement for lanolin from a phase behavior perspective, Softisan 649 formulation properties are very reproducible and products of similar aesthetics should be obtainable after suitable compositional changes.

ACKNOWLEDGEMENTS

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