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PHASE BEHAVIOR CHARACTERIZATION OF PROPYLENE GLYCOL, WHITE PETROLATUM, SURFACTANT OINTMENTS

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ABSTRACT

Ointment vehicles consisting of moderate amounts of propylene glycol (5-10%) and large amounts of white petrolatum (greater than 80%) were investigated by determining the ternary phase behavior between these two components and each of five surfactants exhibiting a range of physical properties. The commercial anionic surfactant Pationic SSL performed better as an emulsifier for propylene glycol and white petrolatum than did Lexamul 515, Lexamul AR, Arlacel 20, or Grilloten ZT 40. From this study a formulation consisting of 7% propylene glycol, 90% petrolatum, and 3% Pationic SSL was considered to be an optimized propylene glycol/white petrolatum ointment base.

INTRODUCTION

Vehicle composition can dramatically impact delivery of topical therapeutic agents, especially topical steroids (1). This has led to the development of optimized steroid vehicles in which biological equivalence is determined by vasoconstrictor assay rather than steroid concentration (2). The vasoconstrictor assay has shown good correlation with clinical effectiveness for steroids (3) with the most

TABLE I

Surfactant Properties

Name (synonyms)	HLB	m.p.
Lexamul 515[a] Glycerol Stearate Glycerol Monostearate	3.8	60°C
Lexamul AR[b] Glycerol Stearate Glycerol Monostearate	5.5	60°C
Pationic SSL[c] Sodium Stearoyl Lactylate	6.5	47-53°C
Arlacel 20 Span 20 Sorbitan Laurate	8.6	Liquid at Ambient Conditions
Grilloten ZT 40 Sucrose Ricinoleate	8-9	Liquid at Ambient Conditions

[a] Contains excess stearic acid (approx. 10%) and excess glycerol.
[b] Contains a cationic surfactant.
[c] Contains up to 40% stearic acid.

active preparations being optimized ointment vehicles containing propylene glycol and white petrolatum (4). Since white petrolatum and propylene glycol are immiscible, emulsifiers such as propylene glycol stearate (Diprolene® Ointment) and glycerol monostearate (Psorcon® Ointment) are added to the ointments to prevent phase separation. The clinical and commercial significance of these optimized ointments prompted a systematic investigation of the mutual solubilities and equilibrium of ointment vehicles containing propylene glycol, white petrolatum, and emulsifier.

One of the most useful representations of three component phase equilibrium is the ternary phase diagram. Traditionally, the completion of a ternary phase diagram required a considerable time commitment of the investigator due to the large number of samples that must be mixed. However, the recent introduction of laboratory robotics (5,6) for the determination of phase behavior has dramatically reduced the time required to construct a ternary phase diagram.

Since both the need for a systematic understanding of ointment vehicles, and the technique (laboratory robotics) to meet this need existed, the determination of the ternary phase behavior for a number of surfactants (Table I) exhibiting a range of physical properties was completed. Although HLB values for surfactants are only applicable to aqueous systems, this technique for quantifying surfactant properties was used as a guide for selecting surfactants.

EXPERIMENTAL

Samples were prepared using laboratory robotics as previously described (6). The materials used were white petrolatum (Penreco, Butler, PA), propylene glycol (Dow Haviland Products, Grand Rapids, MI), Lexamul 515 (Inolex, Philadelphia, PA), Lexamul AR (Inolex, Philadelphia, PA), Pationic SSL (RITA, Crystal Lake, IL) Arlacel 20 (ICI, Wilmington, DE), and Grilloten ZT 40 (RITA, Crystal Lake, IL). All materials were used as received. Phase behavior was determined after storage of not less than a week at the indicated temperature ±1°C. "Stressed" samples indicate that the samples were heated to 80-85°C for 15 minutes prior to being placed in the constant temperature oven. Otherwise, the samples were prepared under ambient conditions and then stored at the indicated temperature.

RESULTS

For the systems studied, only solubility regions appeared to be present. No liquid crystalline structures were encountered and, based on the shapes of the solubility regions, it seems unlikely that micellar association is occurring. First, the binary propylene glycol-surfactant phase behavior will be described as a function of HLB. Glycerol monostearate has the lowest HLB of the surfactants investigated (HLB = 3.8). At 70°C 34% propylene glycol is soluble in Lexamul 515, while Lexamul 515 is essentially insoluble in propylene glycol. As the HLB of the surfactant increases, i.e., as the hydrophilic nature of the surfactant increases, the solubility of propylene glycol in the surfactant generally increases. For Lexamul AR (HLB - 5.5) 43% propylene glycol is soluble in the surfactant, while Grilloten ZT 40 (HLB = 8.9) and Arlacel 20 (HLB = 8.6) can incorporate 48% and 60% propylene glycol respectively. Pationic SSL (HLB = 6.5) does not follow this trend. At 70°C more than 90% Pationic SSL is soluble in propylene glycol, while at 60°C the solubility of Pationic SSL in propylene glycol is between 50 and 55%. At room temperature, compositions above 5% Pationic SSL in propylene glycol contain crystalline surfactant.

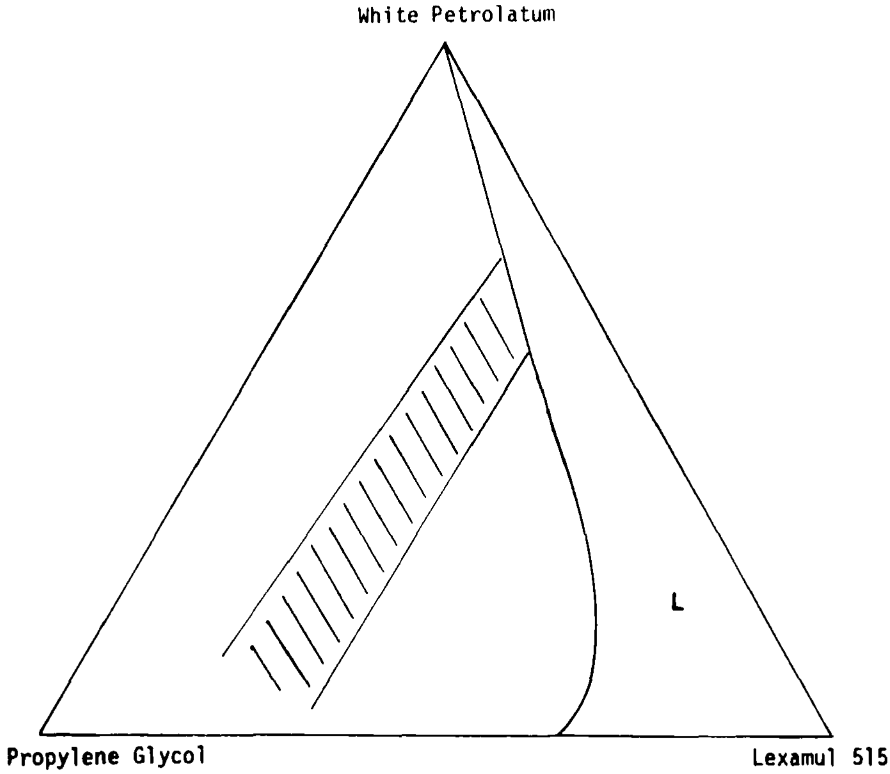

Figure 1 - Pseudo-ternary phase behavior for the Propylene Glycol/White Petrolatum/Lexamul 515 system at 70°C. Compositions within shaded region were three phases, all other compositions outside the single phase region (L) were two phases.

The ternary behavior for the system propylene glycol/white petrolatum/lexamul 515 is given in Figures 1-3. Figure 1 shows the phase behavior for this system at 70°C. As seen, at this temperature white petrolatum and lexamul 515 are completely miscible in one another and a solubility area extends from the petrolatum corner to the propylene glycol in Lexamul 515 saturation point. Multiple phase behavior exists at the higher propylene glycol concentrations. The shaded region demonstrates three isotropic liquid phases in equilibrium, while the remainder of the diagram is two phases with the propylene glycol rich phase separating to the bottom of the container. Obviously, this is a pseudo-ternary diagram due to the component mixtures that comprise the commercial materials Lexamul 515 (contains stearic acid) and white petrolatum. The pseudo-ternary phase behavior for the propylene glycol/white petrolatum/Lexamul 515 is significantly different and more complex when the system is equilibrated to 60°C (Figure 2). At 60°C the surfactant has melted, but has a fluid, creamy white appearance. Lexamul

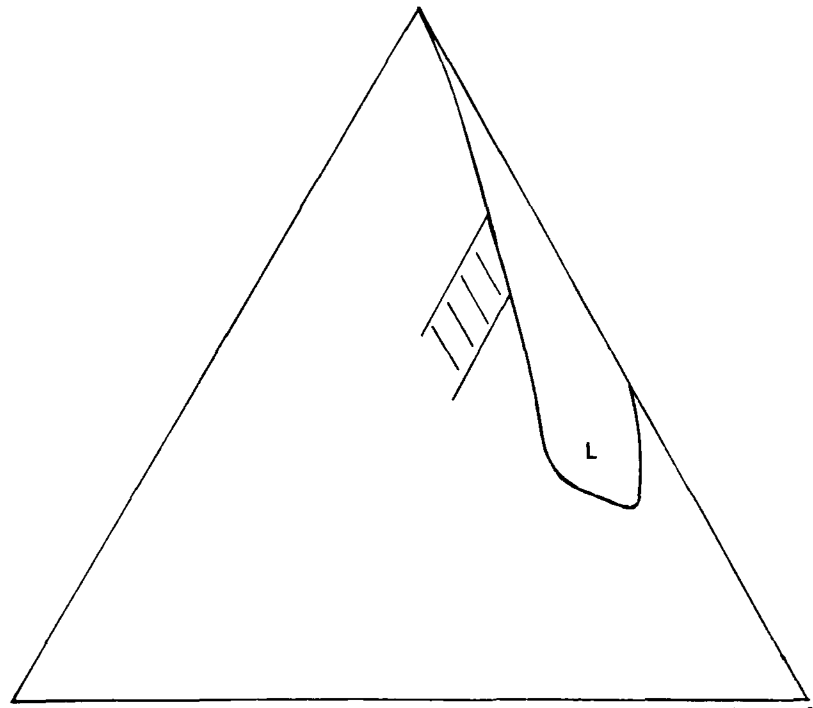

Figure 2 - Pseudo-ternary phase behavior for the Propylene Glycol/White Petrolatum/Lexamul 515 System at 60°C. Compositions within the shaded region were three phases. The single phase region (L) was in equilibrium with a propylene glycol rich phase left of the single phase boundary, and in equilibrium with partially melted surfactant at higher Lexamul 515 concentrations.

515 is no longer miscible with petrolatum, and the solubility of propylene glycol within the surfactant is difficult to establish because of the emulsion-like appearance of the partially melted Lexamul 515. A minimum amount of propylene glycol is actually necessary for the existence of a single phase system at high Lexamul 515 content. Figure 3 shows the result of initially stressing the system to 80-85°C for 15 minutes followed by slight agitation and prompt transfer to a 60°C oven. After five days the samples demonstrated phase behavior very similar to of the same system equilibrated to 70°C.

Figure 4 shows the effect of replacing Lexamul 515 with Lexamul AR. Both of these surfactants are primarily glycerol monostearate, however the Lexamul AR contains a cationic surfactant that both raises the HLB and causes the material to be self-emulsifying in water. As seen, this substitution results

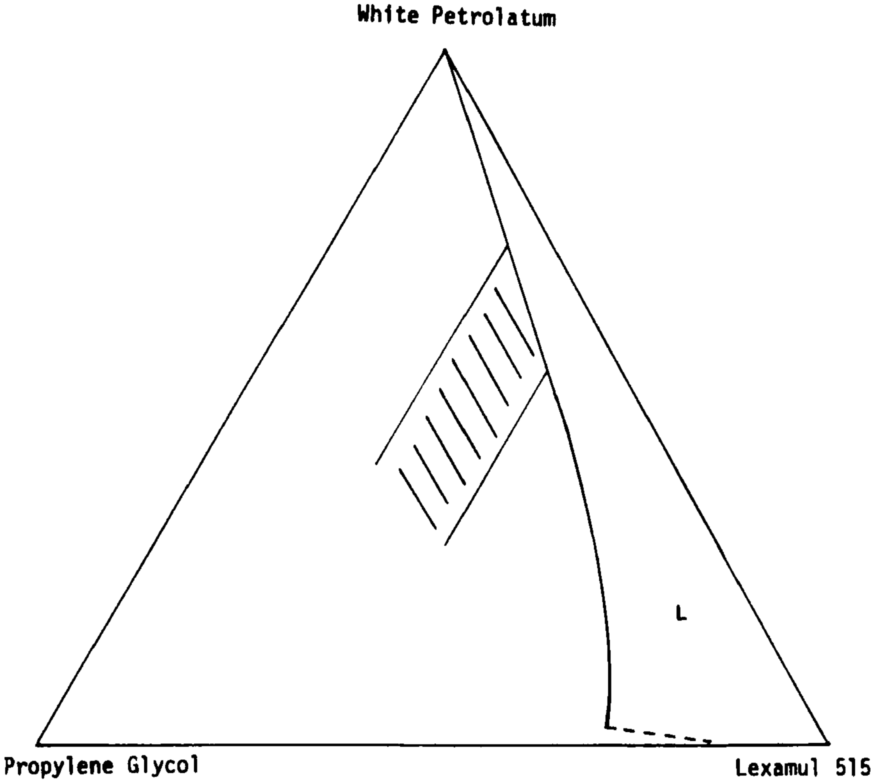

Figure 3 - Pseudo-ternary phase behavior for the Propylene Glycol/White Petrolatum/Lexamul 515 System at heating 80-85°C for 15 minutes prior to equilibration at 60°C. The single (L), two, and three (shaded) phase regions are similar to the same system at 70°C (Figure 1).

in the phase boundary moving toward the propylene glycol corner at lower petrolatum concentrations, while having no effect at higher petrolatum concentrations.

The ternary phase behavior for the anionic surfactant Pationic SSL system has the dramatic feature at 70°C of being miscible in both propylene glycol and white petrolatum (Figure 5). Despite this, very little propylene glycol is soluble at high petrolatum concentrations. As the temperature is dropped to 60°C after stressing (Figure 6), crystalline material from the surfactant forms. Since the melting range for Pationic SSL is given as 47-53°C, it is difficult to speculate as to the composition of the crystalline material.

Arlacel 20, i.e., sorbitan monolaurate, shows what happens upon further increase of the hydrophilic nature of the surfactant. Although more propylene glycol can be solubilized, the amount of

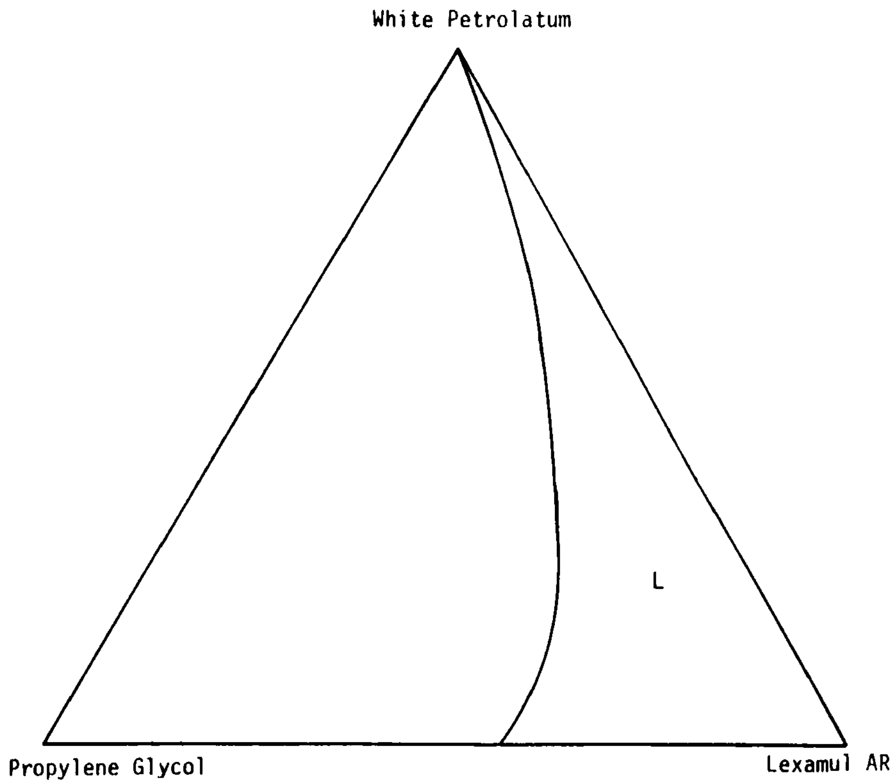

FIGURE 4 - Pseudo-ternary phase behavior for the Propylene Glycol/White Petrolatum/Lexamul AR System at 70°C. The single phase region is denoted by L.

white petrolatum that is soluble in the surfactant decreases. As seen in Figure 7 this decreases the possibility of obtaining a stable ointment vehicle using Arlacel 20. A similar, but even more dramatic, example of using a surfactant that is too polar is shown in Figure 8. Obviously, Grilloten ZT 40 is an unacceptable choice for stabilizing a propylene glycol/petrolatum ointment base.

DISCUSSION

From Figures 1-3 it is seen that high white petrolatum (>80%) containing vehicles cannot incorporate more than approximately 3% propylene glycol and will immediately separate into a propylene

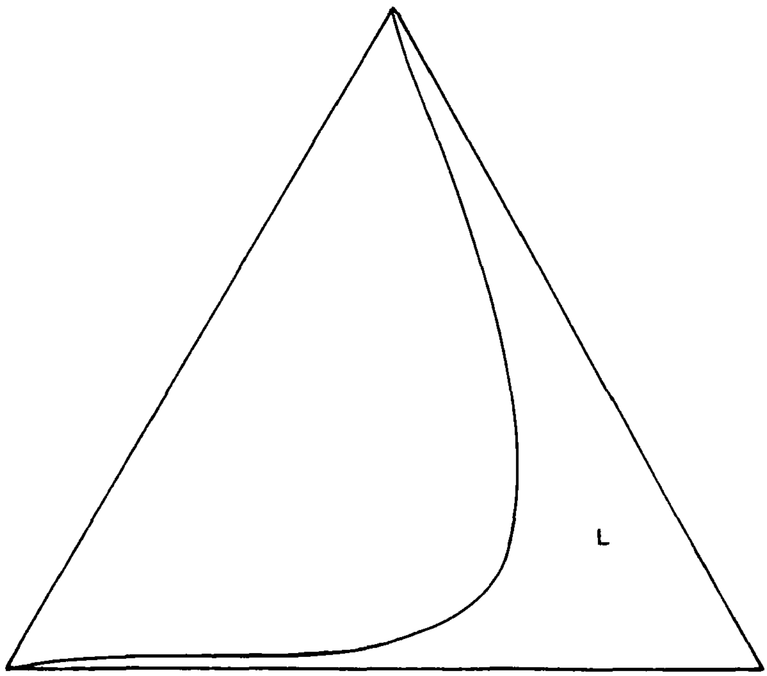

FIGURE 5 - Pseudo-ternary diagram for the Propylene Glycol/White Petrolatum/Pationic SSL System at 70°C. The mutually miscible solubility area is denoted by L.

glycol rich phase and a petrolatum rich phase at temperatures above 60°C. Since the phase boundary actually recedes from the propylene glycol corner upon lowering the temperature from 70°C to 60°, it follows that the solubility of propylene glycol in the white petrolatum/Lexamul 515 mix decreases as the temperature decreases. This implies that optimized ointment vehicles containing large amounts of white petrolatum are thermodynamically unstable, and that the product stability is totally dependent upon the kinetic stabilization caused by the increase in viscosity of the vehicle upon solidification of the white petrolatum/Lexamul 515 mixture. If this ointment base is allowed to stand without mixing at high temperatures, the vehicle will spontaneously separate into multiple phases. Since a steroid is primarily solubilized in the propylene glycol component of the ointment, separation at high temperatures either before or after packaging will result in content uniformity problems. By increasing the Lexamul 515 content sufficiently to incorporate 7% propylene glycol into the single phase region (25% minimum), the

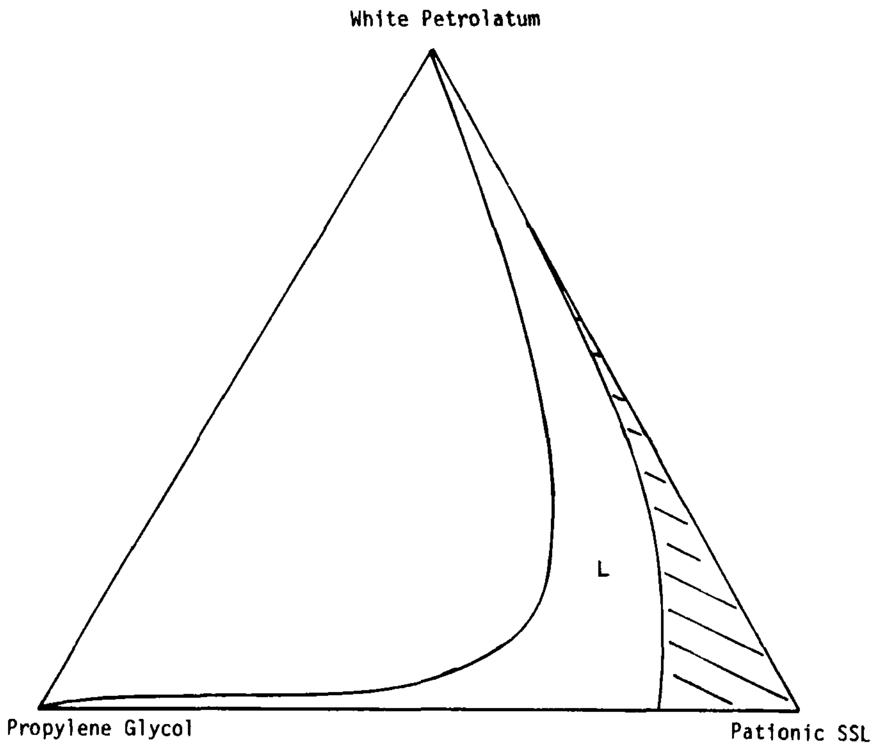

FIGURE 6 - Pseudo-ternary diagram for the Propylene Glycol/White Petrolatum/Pationic SSL System equilibrated to °C after initial heating to 80-85°C for 15 minutes. Shaded region denotes single phase samples (L) that precipitated crystalline material upon cooling to 60°C.

system became unacceptably viscous upon cooling. It is also evident that heating of the surfactant past its approximately 60°C melting point is important to establish reproducible phase behavior. If heated to only 60°C, complex multiple phase behavior occurs.

The replacement of Lexamul 515 with Lexamul AR had little effect on the phase behavior of the propylene glycol-white petrolatum ointment base. The slightly greater solubility of propylene glycol in the surfactant does not correspond to greater solubility of propylene glycol at higher petrolatum concentrations, and can be readily explained by the increase of hydrophilicity of Lexamul AR compared with Lexamul 515. This insignificant increase in HLB of the surfactant is contrasted with Arlacel 20 and Gillotin ZT 40, both of which are too hydrophilic. From this investigation, an HLB value above 8 results in no stabilization of the propylene glycol/white petrolatum system at greater than 50% white petrolatum.

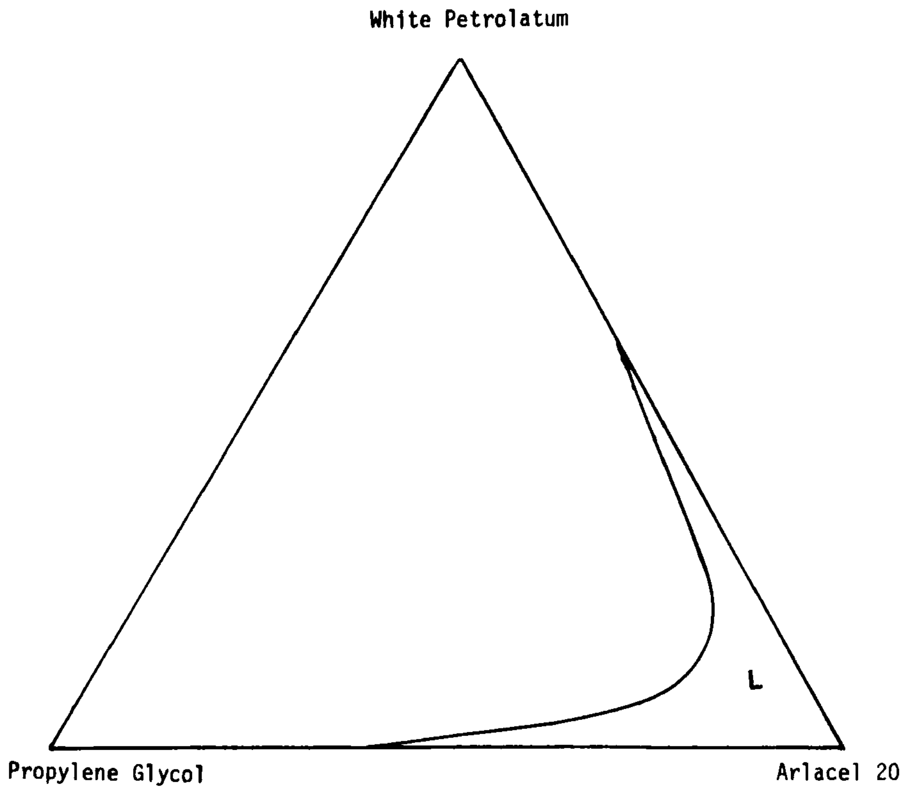

FIGURE 7 - Pseudo-ternary phase behavior for the system Propylene Glycol/White Petrolatum/Arlacel 20 at 70°C where the L denotes a single phase region.

The anionic surfactant Pationic SSL gives the phase behavior most suitable for the physical stabilization of a propylene glycol/white petrolatum ointment base. Although incorporation of 7% propylene glycol is not possible at higher than 65% white petrolatum, Pationic SSL is miscible with both propylene glycol and white petrolatum at 70°C. This implies that the surfactant is appropriately balanced between the hydrophilic and lipophilic components. This should be the most favorable condition for the formation of a stable propylene glycol/white petrolatum 70°C emulsion. Indeed, compositions that fall in the two phase region of the diagram above 80% white petrolatum form emulsions that require a few hours to separate at 60°C. Samples in this two phase region have an additional stabilizing effect due to the ability of Pationic SSL to gel propylene glycol (7). Thus, for these two phase systems both the white petrolatum and the propylene glycol solidify upon cooling. From these observations, an ointment

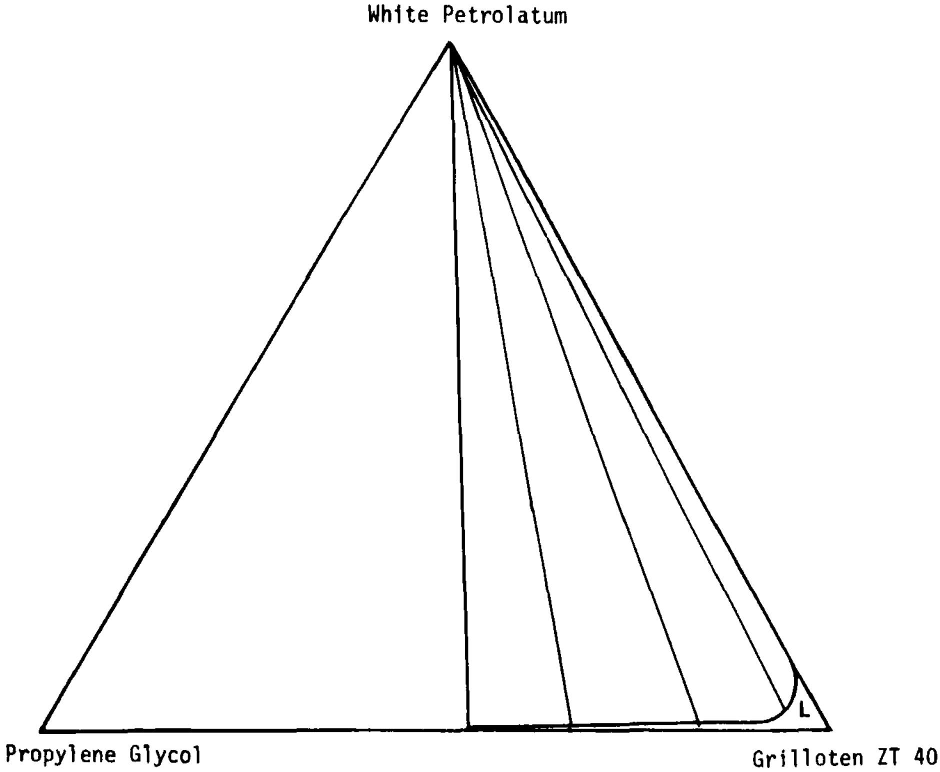

FIGURE 8 - Pseudo-ternary phase behavior for the system Propylene Glycol/White Petrolatum/Gilloten ZT 40 at 70°C where the L denotes a single phase region.

formulation of 7% propylene glycol, 90% petrolatum, and 3% Pationic SSL is recommended to be considered when evaluating ointment bases that contain propylene glycol.

CONCLUSIONS

Formulation of an ointment base using moderate amounts of propylene glycol (5-10%) and large amounts of petrolatum (greater than 80%) requires careful selection of a surfactant. This study indicates that best results will be obtained using surfactants with HLB values within the range 6-7. A formulation that is recommended for evaluation with a drug of interest is 7% propylene glycol, 90% white petrolatum, and 3% Pationic SSL. This formulation will produce a briefly stable (hours) emulsion at

60°C in which both the petrolatum and the propylene glycol will solidify upon cooling. Since this is a kinetically stabilized formulation, product quality will depend upon processing. Thus, mixing, immediately followed by a force cooling technique is recommended for this propylene glycol/petrolatum formulation.

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