Temperature Studies with Nonaqueous Emulsions

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Abstract □ Emulsions of glycerin and mineral oil were formed using anionic, cationic, and nonionic surfactants. Cetylpyridinium chloride and 2-amino-2-methyl-1,3-propanediol–linoleic acid combinations were employed to stabilize emulsions stored at four different temperatures for up to 120 days. Emulsions were prepared at three concentrations of each surfactant. The effects of temperature and aging on droplet size and viscosity were evaluated. The droplet size and viscosity checks were made at predetermined intervals throughout the study. The decrease in viscosity correlated well with droplet size growth. Only one cetylpyridinium chloride-stabilized emulsion showed positive signs of separation at the end of 120 days. All emulsions using 2-amino-2-methyl-1,3-propanediol separated at 45°, and the emulsion with the minimum 2-amino-2-methyl-1,3-propanediol concentration was also unstable at 35°.

Keyphrases □ Emulsions, nonaqueous—temperature dependency, glycerin–mineral oil emulsions with surfactants, droplet size and viscosity □ Surfactants, in glycerin–mineral oil emulsions—temperature dependency, viscosity and droplet size □ Stability, nonaqueous emulsions with surfactants effects of temperature, cetylpyridinium chloride and 2-amino-2-methyl-1,3-propanediol–linoleic acid as stabilizers □ Viscosity, glycerin–mineral oil emulsions with surfactants—effects of temperature

Previous publications from this laboratory (1–7) described the preparation and properties of some nonaqueous emulsions consisting of olive oil as the nonpolar phase and glycerin, propylene glycol, or polyethylene glycol 400 as the polar phase. The stability and viscosity changes of such nonaqueous emulsions over 120 days were reported (4); two anionic surfactants (condensation products of ammonia and of 2-amino-2-methyl-1,3-propanediol with the fatty acids available in olive oil) were used. Stable emulsions were obtained with concentrations of ammonia and 2-amino-2-methyl-1,3-propanediol as low as 0.0006 and 0.002%, respectively. The emulsifying effects of other anionic, cationic, and nonionic surfactants on the glycerin–olive oil system also were described (1, 2). In a study (5) on the effect of surfactant concentration on the interfacial viscosity of a glycerin–olive oil system, it was demonstrated that stability can be achieved in this type of emulsion with interfacial viscosities about 100 times lower than those considered necessary (8) in oil–water emulsions. When other glycols (polyols) were used in conjunction with olive oil, the emulsions with glycerin were found (6) to be more easily made and more stable than those from other polyols.

Although much work on emulsions is described in the literature, these cited studies constitute the majority of available references concerning nonaqueous emulsions. These publications made no reference to the effects of temperature on the nonaqueous emulsion system. The effects of temperature on emulsions with an aqueous phase have been reported (9–11), but information is needed regarding the effects of temperature on the stability of nonaqueous emulsions. For this reason, the present study was designed to explore the effects of temperature on selected nonaqueous emulsion systems. To broaden these studies, mineral oil was selected as the nonpolar phase instead of olive oil.

EXPERIMENTAL

The glycerin used had a purity of 99%[1], confirmed by its refractive index. The glycerin was heated to 180° and then sealed to ensure the absence of water. No further purification of any employed reagent was performed. When surfactant precursor amines were employed, 1% linoleic acid[2] was added to the mineral oil[3].

A phase volume of 0.5 was used in all experiments. The two methods employed for the mixing of reagents were described previously (1, 2). Briefly, Method I consisted of adding the surfactant or surfactant precursor (amine) to the glycerin. Then an equal volume of oil (with the linoleic acid, if needed) was added to the glycerin in a slow steady stream of about 1 ml./sec. while stirring in a blender[4]. The quantities of reagents and the procedure used in Method II were the same as in Method I, except the surfactant or surfactant precursor was added to the oil. Then the glycerin was added to the oil with stirring.

Emulsion stability was determined by close observation for 7 days. At the end of this period, the preparations were examined both macroscopically and microscopically for layer formation. If none was detected, the emulsion was termed "stable."

Two surfactants were selected to stabilize the emulsions for the extended time-temperature studies. The employed surfactant concentrations were determined as the lowest concentration producing stability for at least 30 days at room temperature, 10 times the lowest concentration, and a median concentration. Six solutions of the surfactants in glycerin were prepared. The surfactants used were 2-amino-2-methyl-1,3-propanediol (3, 20, and 30 mg./100 ml. emulsion) and cetylpyridinium chloride (40, 220, and 400 mg./100 ml.). Several sets of duplicate emulsions were prepared for data comparison. Extreme care had to be taken so emulsions would be as similar as possible.

The temperatures involved were 0, 25, 35, and 45°. Three sets of emulsions were prepared to represent each temperature and surfactant concentration used in the study.

Particle-size studies were conducted by the use of oil-immersion, phase-contrast photomicrography, with light at 475 nm. and 730 × magnification. Photomicrographs were prepared at predetermined time intervals (Days 1, 2, 4, 7, 14, 30, and 60 of the study) and were made for each surfactant concentration and temperature involved. Droplet size change was followed by dividing the photomicrographs into areas measuring 3.0 cm.^{2}, selecting the squares at random, and counting the droplets at different size intervals.

The total volume of the droplets for each size interval was determined by using the formula:

$$T_v = (n)(0.523d^3) \qquad \text{(Eq. 1)}$$

where T_v = total volume of droplets within interval, n = total

[1] Colgate Palmolive Co.
[2] Fisher Scientific Co.
[3] Wastach Chemical Co.
[4] Waring model 702 BAW.

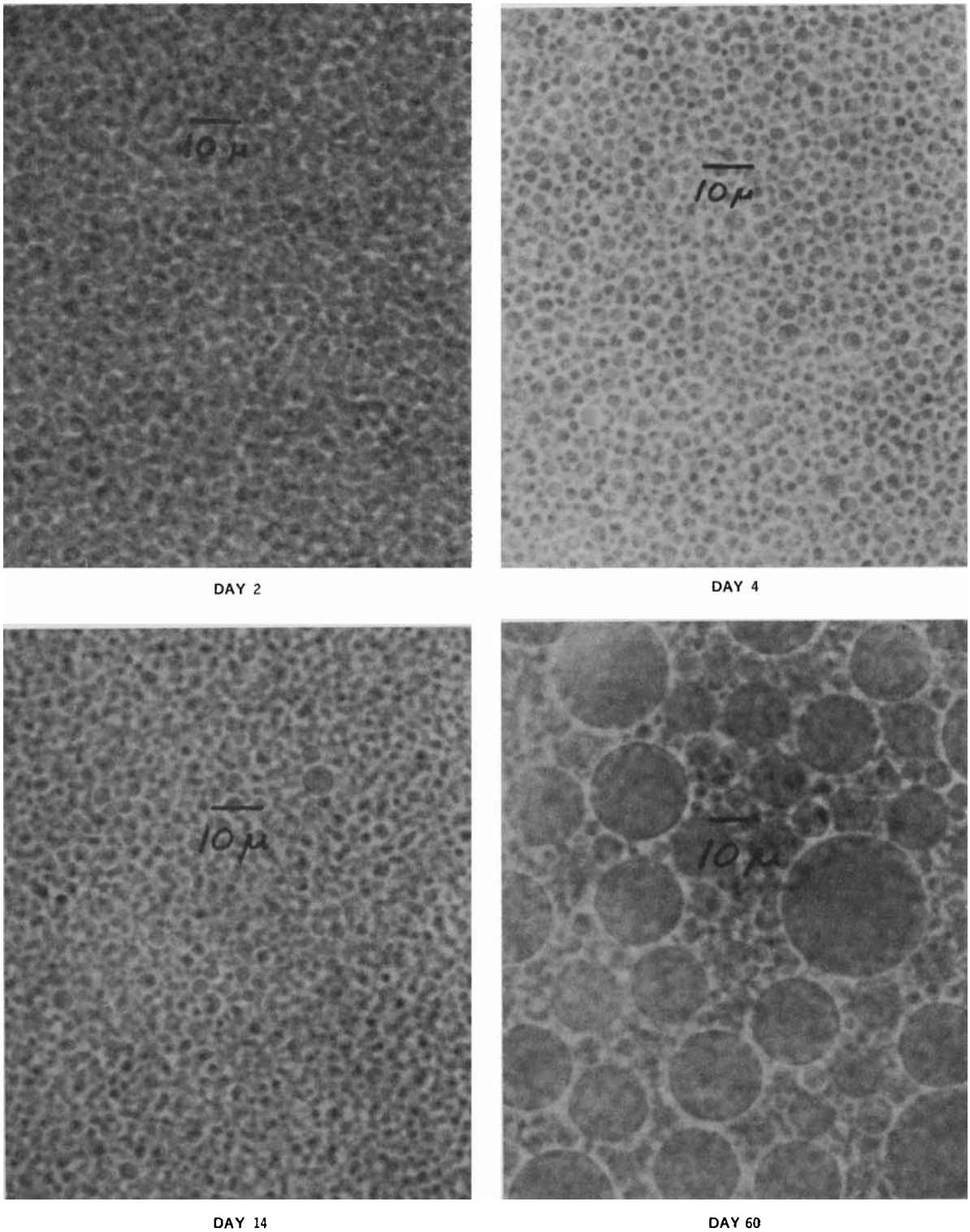

Figure 1—*Photomicrographs of emulsion stabilized with 3 mg. of 2-amino-2-methyl-1,3-propanediol and stored for 60 days at 25°.*

number of droplets within interval, d = mean droplet diameter of interval, and constant = $^1/_6\ \pi$.

The percent of the total volume within each interval for each day and temperature was determined by using the formula:

$$\%T_{va} = \frac{T_{va} \times 100}{(T_{va} + T_{vb} \cdots + T_{vn})} \qquad \text{(Eq. 2)}$$

where $\%T_{va}$ = percent of total volume of droplets represented for each size interval for a given day and temperature, and $T_{va,vb\cdots vn}$ = designation assigned to size intervals.

A Coulter counter[5] was also used to determine the droplet size. Droplet counts were made immediately after mixing the emulsion with saline electrolyte (0.9% aqueous solution of sodium chloride). The results of the experiments using the Coulter counter were then compared with the results of the visual counting of the photomicrographs. The Coulter counter was used to determine droplet size of all duplicate emulsions.

Viscosities[6] of the emulsions were measured on the same days that

[5] Model B with plotter model J.
[6] Brookfield viscometer, model LVT, using spindles Nos. 3 and 4.

Table I Emulsifying Effect of Various Surfactants on Equal Volumes of Glycerin and Mineral Oil[a]

Agent	Percent	Method I[b]	Method II[b]	Emulsion Appearance
Anionic:				
Tetrasodium *N*-(1,2-dicarboxyethyl)-*N*-octadecyl sulfosuccinamate[c]	0.3	Separation	—	—
	0.5	Emulsification	—	Opaque
	5.0	Emulsification	—	Opaque, semisolid
Dioctyl sodium sulfosuccinate[d]	0.5	Separation	—	—
	1.0	Emulsification	—	Opaque, white
	5.0	Emulsification	Separation	Opaque, white
Diamyl sodium sulfosuccinate[e]	5.0	Separation	Separation	—
Sodium lauryl ether sulfate[f]	0.5	Separation	—	—
	1.0	Emulsification	—	Opaque, white, viscous
	5.0	Emulsification	Separation	Opaque, white, very viscous
Sodium lauryl sulfate	1.0	Separation	—	—
	2.0	Emulsification	—	Opaque
	5.0	Emulsification	Separation	Opaque, semisolid
Sodium stearate	0.25	Separation	—	—
	0.5	Emulsification	Separation	Opaque
	2.0	Emulsification	Emulsification[g]	Opaque, semisolid
Calcium stearate	1.0	—	Separation	—
	2.0	Separation	Emulsification[g]	Opaque
	5.0	Separation	Emulsification[g]	Opaque
2-Amino-2-methyl-1,3-propanediol	0.002	Separation[h]	—	—
	0.003	Emulsification	Separation	White, cloudy
	5.0	Emulsification	Separation	Opaque, white, solid
Ethanolamine	1.0	Separation	—	—
	2.0	Emulsification	—	Cloudy
	10.0	Emulsification	Separation	Cloudy
Triethanolamine	0.2	Separation	—	—
	0.25	Emulsification	—	Opaque
	5.0	Emulsification	Separation	Opaque, very viscous
2,2-Diethyl-1,3-propanediol[i]	0.5	Separation	—	—
	1.0	Emulsification	Separation	Clear
	5.0	Emulsification	Separation	Clear
Tromethamine[j]	0.25	Separation	—	—
	0.5	Emulsification	Separation	Clear
	5.0	Emulsification	Separation	Clear
Ammonia[k]	0.005	Separation	—	—
	0.01	Emulsification	Separation	Clear
	1.0	Emulsification	Separation	Clear
Cationic:				
Benzalkonium chloride[l]	0.05	Separation	—	—
	0.1	Emulsification	—	Clear
	10.0	Emulsification	Separation	Clear
Lauryltrimethylammonium bromide[m]	0.5	Separation	—	—
	1.0	Emulsification	—	Opaque
	5.0	Emulsification	Separation	Opaque
Cetylpyridinium chloride[m]	0.025	Separation	—	—
	0.040	Emulsification	Separation	Opaque
	5.0	Emulsification	Emulsification	Opaque
Stearyltrimethylammonium chloride[m]	0.5	Separation	—	—
	1.0	Emulsification	Separation	Opaque, viscous
	5.0	Emulsification	Emulsification	Opaque, viscous
Stearyldimethylbenzylammonium chloride[m]	0.5	Separation	—	—
	1.0	Emulsification	—	Opaque
	5.0	Emulsification	Separation	Opaque, semisolid
Laurylpyridinium chloride[m]	5.0	Separation	Separation	—
Nonionic:				
Polyoxyethylene sorbitan esters:				
Monolaurate (polysorbate 20)[n]	6.0	Separation	Separation	—
Monopalmitate (polysorbate 40)[o]	6.0	Separation	Separation	—
Monostearate (polysorbate 60)[p]	6.0	Separation	Separation	—
Monooleate (polysorbate 80)[q]	6.0	Separation	Separation	—
Sorbitan fatty acid esters:				
Monolaurate[r]	6.0	Separation	Separation	—
Monopalmitate[s]	6.0	Separation	Separation	Insoluble[t]
Monostearate[u]	6.0	Separation	Separation	Insoluble[t]
Monooleate[v]	6.0	Separation	Separation	Insoluble[t]
Trioleate[w]	6.0	Separation	Separation	Insoluble[t]
Monooleate[v] (in oil)	2.0	Emulsification	—	Opaque
	4.0	Emulsification	Separation	Opaque
Trioleate[w]	4.0	Emulsification	Separation	Opaque
	6.0	Emulsification	Separation	Opaque
Glyceryl monostearate, self-emulsifying[x]	2.0	Separation	Separation	—
	5.0	Emulsification	Emulsification[g]	Opaque

Table I—(*Continued*)

Agent	Percent	Method I[b]	Method II[b]	Emulsion Appearance
Glyceryl monostearate, nonself-emulsifying[u]	2.0	Separation	Separation	—
	5.0	Emulsification	Emulsification[a]	Opaque
Polyoxyethylene derivatives:				
Polyoxyethylene (4) lauryl ether[s]	5.0	Separation	Separation	—
Polyoxyethylene stearate[aa]	2.0	Separation	—	—
	5.0	Emulsification	Separation	Opaque, very viscous
	10.0	Emulsification	Emulsification	Opaque, very viscous
Polyol fatty acid ester[bb]	8.0	Separation	Separation	—
Polypropylene oxide[cc]	8.0	Separation	Separation	—

[a] Representative results shown generally indicate minimum percent of surfactant effecting emulsification. (*Note:* Numerous combinations of Arlacels and Tweens were attempted with varying percentages of surfactants up to 8.0% surfactant. All were unsuccessful.) [b] See text. [c] Aerosol 22, American Cyanamid Co. [d] Aerosol OT, American Cyanamid Co. [e] Aerosol AY, American Cyanamid Co. [f] Sipon ES, American Alcolac Corp. [g] Glycerin-in-oil emulsions. All others were oil-in-glycerin. [h] Macroscopic examination indicated emulsification, but separation was noted within 7 days. [i] Carbide and Carbon Chemicals Co. [j] Commercial Solvents Corp. [k] Liquid ammonia obtained from condensation of ammonia gas. [l] Benzalkonium chloride (Zephiran Chloride, Winthrop Lab.) was obtained by evaporation of a 12.8% aqueous solution and a 92.7% semisolid. The results shown are from the 92.7% preparation. The other produced unstable emulsions below the 5% level. [m] K & K Laboratories. [n] Tween 20, Atlas Chemical Industries. [o] Tween 50, Atlas Chemical Industries. [p] Tween 60, Atlas Chemical Industries. [q] Tween 80, Atlas Chemical Industries. [r] Arlacel 20, Atlas Chemical Industries. [s] Arlacel 40, Atlas Chemical Industries. [t] Surfactants indicated were insoluble in glycerin and/or mineral oil. [u] Arlacel 60, Atlas Chemical Industries. [v] Arlacel 80, Atlas Chemical Industries. [w] Arlacel 85, Atlas Chemical Industries. [x] Arlacel 165, Atlas Chemical Industries. [y] Arlacel 169, Atlas Chemical Industries. [z] Brij 30, Atlas Chemical Industries. [aa] Myrj 52, Atlas Chemical Industries. [bb] Arlatone T, Atlas Chemical Industries. [cc] Pluronic (PPO F-68), Wyandotte Chemical Corp.

the photomicrographs were prepared. Four speeds were used: 0.6, 1.5, 3.0, and 6.0 r.p.m. Viscosity measurements of the emulsions were made at the same temperature at which the samples had been stored. Temperature-controlled rooms provided the environment for 0 and 25°. The containers with the samples stored at 35 and 45° were placed in oil baths to maintain a constant temperature throughout the viscosity determination. The readings were first taken from the lowest revolutions per minute to the highest. Then a

Table II—Effect of Age and Temperature on Droplet Volume of Selected Emulsions[a]

Diameter Range, μ	Days 1	2	4	7	14	30	60
3 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol at 0°							
0.5-1.0	7.7	1.5	1.2	1.1	1.0	1.0	0.8
1.0-2.0	72.4	24.9	20.5	19.0	18.5	17.4	14.5
2.0-3.0	19.9	33.0	38.6	35.8	35.1	36.4	32.9
3.0-4.0	—	39.3	39.7	42.0	43.3	45.3	50.2
4.0-5.0	—	1.3	—	2.1	2.0	—	1.7
20 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol at 25°							
0.0-0.5	3.1	3.6	2.0	1.8	1.4	1.0	—[b]
0.5-1.0	70.4	80.2	48.4	47.9	44.4	40.2	—
1.0-2.0	12.7	8.4	6.1	6.4	6.7	6.6	—
2.0-3.0	13.8	7.8	16.5	18.2	18.5	16.2	—
3.0-4.0	—	—	12.9	12.5	17.0	14.9	—
4.0-5.0	—	—	13.7	13.3	12.0	21.0	—
400 mg./100 ml. Cetylpyridinium Chloride at 25°							
0.0-0.5	100	100	100	74.1	63.5	64.0	62.1
0.5-1.0	—	—	—	9.6	11.8	14.6	16.9
1.0-2.0	—	—	—	16.2	24.6	21.4	21.0
3 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol at 35°							
0.5-1.0	7.7	0.9	—	—	—	—	—
1.0-2.0	72.4	23.3	13.2	5.8	—[c]	—	—
2.0-3.0	19.9	73.9	53.4	37.8	—	—	—
3.0-4.0	—	0.6	23.2	38.9	—	—	—
4.0-5.0	—	1.3	10.2	17.7	—	—	—
220 mg./100 ml. Cetylpyridinium Chloride at 45°							
0.0-0.5	7.2	1.9	1.7	0.9	0.3	—	—[b]
0.5-1.0	91.0	37.0	34.0	21.4	12.2	8.0	—
1.0-2.0	1.2	16.3	11.1	12.4	11.3	9.9	—
2.0-3.0	—	17.5	33.7	37.1	30.6	23.7	—
3.0-4.0	—	16.0	19.5	21.6	27.4	32.5	—
4.0-5.0	—	11.3	—	6.6	18.2	23.0	—
30 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol at 45°							
0.0-0.5	8.6	1.9	1.5	0.1	—	—[c]	—
0.5-1.0	90.2	35.0	36.9	6.3	3.3	—	—
1.0-2.0	1.2	12.9	20.4	23.0	18.7	—	—
2.0-3.0	—	29.8	36.0	46.4	37.7	—	—
3.0-4.0	—	20.4	5.2	17.0	15.8	—	—
4.0-5.0	—	—	—	7.2	24.4	—	—

[a] Distribution is represented as percent of total droplet volume measured in each group. [b] Slide damaged, reliable readings impossible. [c] Demulsification observed.

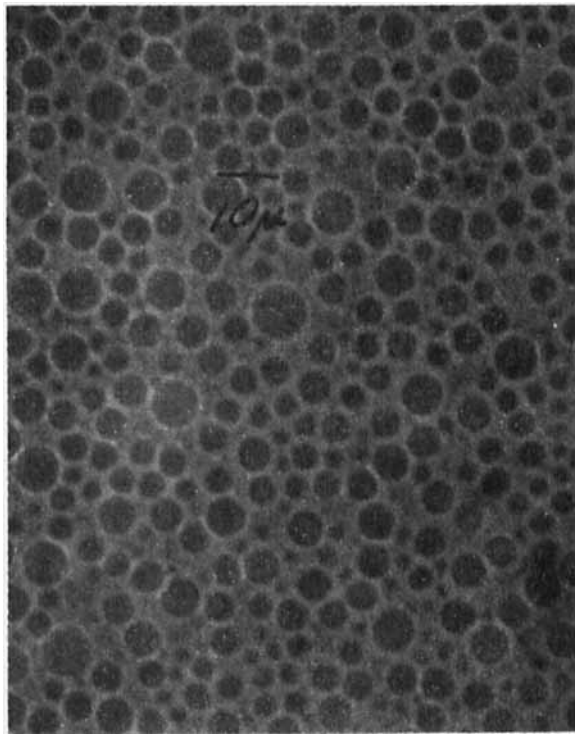

Figure 2—*Photomicrograph of emulsion (30 mg./100 ml. 2-amino-2-methyl-1,3-propanediol) stored at 45° for 14 days.*

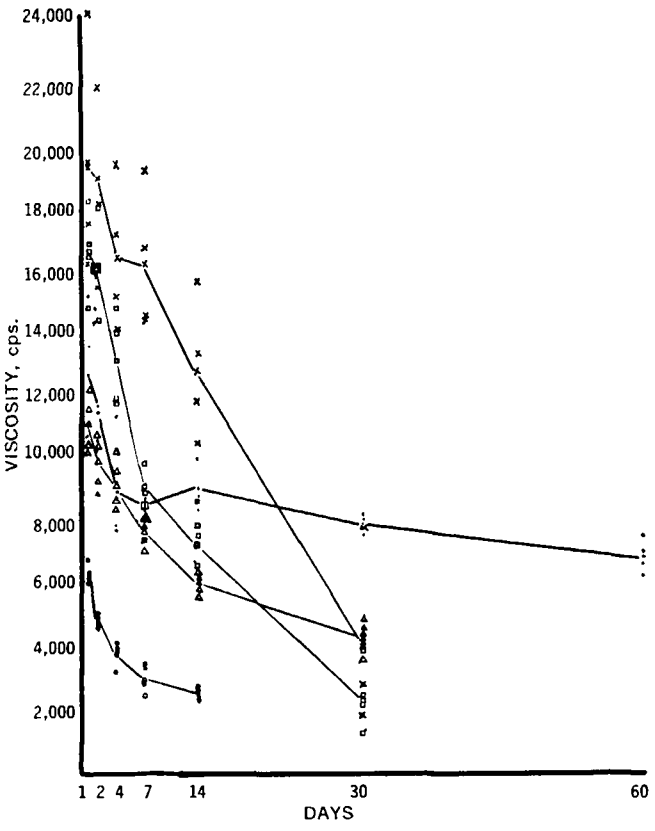

Figure 3—*Comparison of average viscosity change of selected emulsions stored at different temperatures. Key: 2-amino-2-methyl-1,3-propanediol, 3 mg./100 ml. emulsion, 25°, —·—; 2-amino-2-methyl-1,3-propanediol, 20 mg./100 ml., 35°, —Δ—; 2-amino-2-methyl-1,3-propanediol, 3 mg./100 ml., 35°, —○—; 2-amino-2-methyl-1,3-propanediol, 30 mg./100 ml., 45°, —□—; and cetylpyridinium chloride, 40 mg./100 ml., 45°, —×—.*

revolutions per minute of 60 was applied for 10 min., and the viscosity was recorded as the revolutions per minute was decreased from 6.0 to 0.6. Thixotropy was demonstrated when the up (or increasing revolutions per minute) readings exceeded the down readings.

To check the validity of this work, duplicate emulsions of the same concentrations were prepared. The viscosities of these emulsions were recorded for 7 days and compared with those of the test emulsions.

Emulsion type was determined by both the phase dilution method and visual observation. The addition of methylene blue to the glycerin phase allowed sufficient observation with the use of an ordinary microscope to determine emulsion type.

RESULTS AND DISCUSSION

The effects of various anionic, cationic, and nonionic surfactants on glycerin-mineral oil systems are given in Table I. All emulsions were of the oil-in-glycerin type with four exceptions. These surfactants or surfactant precursors were all stearate esters or salts. Similar results were reported previously with glycerin olive oil systems (1, 2).

Although linoleic acid was added to the mineral oil when precursor amines were employed, stearic acid and palmitic acid also produced satisfactory results but required high concentrations. Further studies with stearic acid added to the mineral oil are presently being conducted in an effort to produce other glycerin-in-oil emulsions.

The photomicrographs produced a record of droplet size growth (Fig. 1). This was clearly seen when lower surfactant concentrations were employed. No droplet size change was apparent in emulsions prepared with high surfactant concentrations and stored at 0°, while other emulsions exhibited droplets of various sizes (Fig. 2).

Methods of particle-size analysis (12, 13) have been described, as have the problems of photomicrography (12). The use of oil-immersion, phase-contrast photomicrography eliminated many problems. The slides from which the photomicrographs were made were prepared several hours in advance to reduce particle movement. This procedure proved to be very satisfactory. Even at the high degree of magnification employed, droplets below 1 μ in diameter were difficult to resolve. Despite these limitations, the photomicrographs provided a reliable method from which droplet size data were obtained.

The Coulter counter instrument was used to confirm the data obtained from the photomicrographs. In almost every case, the data from the two methods were comparable and were in almost exact agreement in several instances.

One problem encountered with the Coulter counter was that of aggregation after the addition of the electrolyte solution. This became more marked with time, as reported previously (14, 15). It has been observed (16) that the Coulter counter is ideal for investigating aggregation phenomena. Count loss has also been reported (17).

Because of the occurrence of aggregation, the droplets of the emulsion samples were counted immediately after the introduction of the saline electrolyte. This sharply reduced aggregation and, as stated previously, gave results that were in agreement with those from the photomicrographs.

The droplets were counted from the photomicrograph in size intervals of 1 μ. The intervals used were: <0.05–1, 1–2, 2–3, 3–4, 4–5, and >5 μ. Very few droplets with a diameter >5 μ were present in the stable emulsions. However, some larger droplets were seen in some emulsions prior to demulsification. As close to 100% of the droplets as possible were represented in the calculations.

All diol–linoleic acid-stabilized emulsions stored at 45° were unstable. The preparations with a surfactant concentration (2-amino-2-methyl-1,3-propanediol) of 3 and 20 mg./100 ml. of emulsion were also unstable at 35°. Only one quaternary amine- (cetylpyridinium chloride) stabilized emulsion showed positive signs of separation. This emulsion, stored at 45°, had a quaternary amine concentration of 40 mg./100 ml. Although some inherent error was introduced, the droplets were assumed spherical and the mean diameter was determined by using the midpoints of the respective intervals. This procedure gave a parameter by which the change in droplet volume of the various emulsions could be compared (Table II). As the size of the droplet increases, a small number of droplets

can exert a great influence on the total combined volume of the droplets. The total volume of the internal phase generally increased throughout the test period.

Droplet size data obtained from duplicate emulsions were generally within 5% of the data of the test emulsions. Viscosity data correlation was more difficult, although results generally agreed within 10%. Exceptions were found in both cases, however. Care in emulsion preparation was extremely important in obtaining closely correlated data.

Representative examples of viscosity changes are found in Fig. 3. Viscosities of emulsions stored at high temperatures decreased more rapidly than those of emulsions of the same surfactant concentrations stored at a lower temperature. A decrease in viscosity generally corresponded with droplet size growth. This was very evident just prior to demulsification of the unstable emulsions. As expected, the viscosities of the emulsions stored at 0° were extremely high and appeared very stable. The emulsion viscosities increased with increasing surfactant concentration, a property described previously (18).

Thixotropy was exhibited after the 14th day of the study. The hysteresis loop can be drawn for a large number of the emulsions at all temperatures involved (Table III). Some emulsions of high surfactant concentration stored at the higher temperatures formed gels and exhibited erratic viscosity readings. Thixotropic properties have been shown to exist with other nonaqueous emulsion systems (4).

SUMMARY

Emulsions of glycerin and mineral oil were prepared using a number of different surfactants. Emulsions of the glycerin-in-oil type were produced only with the use of stearate salt or stearate ester surfactants.

Emulsions with 3, 20, and 30 mg./100 ml. of 2-amino-2-methyl-1,-3-propanediol and 40, 220, and 400 mg./100 ml. of cetylpyridinium chloride were prepared for temperature studies. The emulsions were stored at 0, 25, 35, and 45°. Emulsion stability, droplet size, and

Table III—Effect of Shear Rate and Age on Viscosity of Selected Emulsions

Sample	Shear Rate (Spindle Speed), r.p.m.	Viscosity, cps.[a] Day 1	Day 2	Day 4	Day 7	Day 14	Day 30	Day 60
3 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol, 0°	0.6	29,000	42,000	47,000	50,000	51,000	49,000[b]	50,000
							47,000	46,000
	1.5	23,600	28,400	30,000	47,600	58,800	46,000	47,200
							41,600	42,000
	3.0	26,200	27,800	29,200	39,000	54,400	45,000	45,800
							37,400	37,200
	6.0	23,700	24,400	25,500	33,400	48,800	42,000	43,800
							34,200	33,200
20 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol, 25°	0.6	11,200	10,200	9,200	9,400	7,600	7,000	7,000
							5,800	5,400
	1.5	10,560	9,920	8,720	8,720	7,040	6,160	6,240
							4,320	4,280
	3.0	10,400	9,600	8,240	7,840	6,880	6,320	6,400
							3,720	3,640
	6.0	9,100	8,760	7,400	7,320	6,120	5,720	5,920
							3,220	3,260
400 mg./100 ml. Cetylpyridinium chloride, 25°	0.6	56,000	50,000	42,000	36,000	34,000	32,000	28,000
							35,000[c]	31,000
	1.5	45,600	34,600	40,000	32,000	24,800	25,200	23,600
							20,200	18,000
	3.0	43,000	40,800	37,400	29,200	21,200	20,200	20,800
							27,200	24,400
	5.0	38,300	36,100	33,600	24,700	16,000	14,900	14,700
							19,200	17,600
40 mg./100 ml. Cetylpyridinium chloride, 35°	0.6	15,200	13,400	12,600	8,400	7,800	5,800	5,200
								4,700
	1.5	14,080	12,720	11,920	7,840	6,600	6,400	6,400
							5,880	4,400
	3.0	11,840	10,840	10,520	7,200	5,200	4,880	4,800
							3,640	
	6.0	10,400	9,600	9,349	6,400	4,420	4,240	4,200
							3,940	3,960
30 mg./100 ml. 2-Amino-2-methyl-1,3-propanediol, 45°	0.6	18,200	18,000	14,000	9,800	8,600	—[d]	—
	1.5	16,800	16,000	14,800	9,120	7,840	—	—
	3.0	16,400	16,000	11,920	8,560	7,240	—	—
	6.0	14,800	14,400	11,760	7,420	6,500	—	—
220 mg./100 ml. Cetylpyridinium chloride, 45°	0.6	103,000	92,000	81,000	74,000	69,000	52,000	18,000
							39,000	8,000
	1.5	70,400	63,600	56,800	44,400	49,600	28,400	8,800
							17,200	4,400
	3.0	59,200	54,000	43,200	39,400	34,400	17,200	5,600
							11,200	4,400
	6.0	39,200	35,100	30,700	28,300	25,800	11,100	4,200
							7,800	3,600

[a] Measured with a Brookfield viscometer using spindle No. 4 for all 0° and 220-mg./100 ml. and 400-mg./100 ml. cetylpyridinium chloride readings. All other readings were with a No. 3 spindle. [b] Thixotropy demonstrated by two figures. The upper figure represents viscosities at the increasing spindle speed. The lower figure represents the viscosities at the decreasing spindle speed. [c] Erratic readings noted with many of the cetylpyridinium chloride emulsions since gels were formed with aging. [d] Demulsification had occurred.

viscosity were studied on Days 1, 2, 4, 7, 14, 30, and 60. Day 1 corresponded to the day the emulsions were prepared.

When stored at high comparable temperatures for the study period, emulsions stabilized by a quaternary amine (cetylpyridinium chloride) were more stable than those stabilized by a surfactant precursor amine (2-amino-2-methyl-1,3-propanediol) and linoleic acid. All emulsions stored at room temperature (25°) and at 0° were stable.

Photomicrographs were used to study droplet size change. High surfactant concentrations retarded droplet size growth. A sudden increase of droplet size preceded demulsification, as was very evident at high temperatures.

A rapid decrease in viscosity preceded demulsification. At high temperatures, the cetylpyridinium chloride-stabilized emulsions formed loose gels and exhibited erratic readings.

Thixotropy was demonstrated as the emulsions were allowed to age at least 2–4 weeks. It was manifested by the change in viscosity readings as the stress was increased from 0.6 to 6.0 r.p.m. and then reversed from 6.0 to 0.6 r.p.m.

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Preformulation Studies II: Stability of Drug Substances in Solid Pharmaceutical Systems

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Abstract □ The stability of drug substances in solid pharmaceutical systems is discussed. Theoretical models for various situations are proposed and their practical implications are considered.

Keyphrases □ Preformulation theory—stability of drug substances in solid pharmaceutical systems □ Drug stability in solid pharmaceutical systems—theory, preformulation □ Solid drug systems—stability of drug substance, theory

The stability of drug substances in solid pharmaceutical systems has been discussed in some detail previously (1–11 and the references cited therein). However, further treatment of the subject seems desirable for the following reasons.

1. In spite of the importance of solid dosage forms, there are relatively few quantitative reports on their chemical stability, primarily because of the complexities and difficulties involved.

2. This paper presents a somewhat different point of view than those of most references cited previously.

3. Some theoretical concepts need further clarification and application to practical stability studies.

DISCUSSION

Quantitative chemical stability studies on drug substances in solid dosage forms are difficult to perform for two primary reasons. First, analytical results tend to have more scatter because tablets and capsules are distinct dosage units rather than the true aliquots encountered with stability studies on drug substances in solution. Second, tablets and capsules are heterogeneous and discontinuous systems involving gas (air and water vapor), liquid (*e.g.*, adsorbed water), and solid phases, all of which can vary in concentration during an experiment.

Analytical error can be minimized by ensuring that content uniformity is satisfactory before initiating stability studies. The problems arising from the heterogeneity associated with these systems are more difficult to overcome, but the primary prerequisites for dealing with them are an awareness of their existence, an under-