The influence of formulation variables on phase inversion temperatures of emulsions as determined by a programmed viscometric technique*

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A programmed temperature rise viscometric technique has been used to examine the influence of formulation variables on the phase inversion temperatures (P.I.T.) of oil-in-water emulsions stabilized with mixed polyoxyethylene alcohol surfactants. Using a heating rate of $0.5°$ min^{-1}, the P.I.T. was defined either by a sharp change in apparent viscosity when recording shear stress-rate of shear rheograms for successive emulsion samples, or by the change in shear stress with time for a single emulsion sample. With an overall concentration of 6.00% w/w surfactant mixture of Brij 92 and Brij 96, the P.I.T. was found to rise in an approximately linear fashion as the HLB increased towards the optimum value. When the surfactant concentration was related to the aqueous or oil phase and these phase ratios varied, the P.I.T. changed in a complex manner. Water-soluble additives caused marked changes in the P.I.T. For example, 5.0% w/w sodium chloride depressed the P.I.T. by $17°$ and 5.0% w/w calcium chloride caused an $11°$ fall, whereas 2.0% w/w propylene glycol produced a $6°$ rise. These results followed the same trend as the cloud point of 1.0% w/w aqueous solutions of Brij 96 containing these additives. Linear correlations were obtained between the cloud point and P.I.T. data from which the effect of additives upon emulsion stability may be monitored.

Inversion of an emulsion, involving the sudden interchange of the continuous and disperse phases, can be detected by a number of methods. These include visual assessment of the emulsion in bulk (Shinoda & Arai, 1964; Matsumoto & Sherman, 1970), microscopic observation, and the dilution technique (Newman, 1914). Visual assessment is a subjective test, whilst both microscopical and dilution methods have a disadvantage in that they involve a dilution of the sample which may cause undetected phase reversion. The difference in electrical conductivity of oil-in-water (o/w) and water-in-oil (w/o) emulsions is the basis of a widely used technique for estimating inversion (Bhatnagar, 1920; Aoki & Matsuzaki, 1967a; Shimamoto, 1962). Unfortunately, the technique is not applicable to emulsion systems containing high concentrations of electrolytes. A differential thermal analysis procedure outlined by Matsumoto & Sherman (1970), and rheological measurements (Florence & Rogers, 1971; Lin & Lambrechts, 1969; Sherman, 1950) are more objective methods for monitoring phase inversion.

Emulsions of the o/w type stabilized by non-ionic surfactants may be inverted by raising the temperature. Shinoda (1967) has related this phenomenon to the curvature of the adsorbed interfacial layer of surfactant relative to the oil and water phases. The hydration forces between the hydrophilic portion of a surfactant and water molecules are stronger at lower temperatures. The adsorbed layer thus has a convex curvature towards water and gives rise to an o/w emulsion. As the temperature is raised the hydration forces decrease, the convex curvature changes gradually to concave, and inversion occurs. At some point, the phase inversion temperature (P.I.T.), the curvature is nearly zero, and this is considered to be the temperature at which the hydrophilic and lipophilic tendencies of the surfactant just balance.

The P.I.T. is a sensitive parameter that can be used to study the effects of various formulation variables upon the stability of emulsions prepared using non-ionic surfactants. Previous workers have demonstrated that the P.I.T. is influenced by the surfactant concentration (Aoki & Matsuzaki, 1967a; Mitsui, Machida & Harusawa, 1970; Shinoda & Takeda, 1970), the phase volume ratio, and the type of oil used in the emulsion (Shinoda & Arai, 1964, 1967). The relation between HLB and P.I.T. has frequently been reported to be linear for a variety of emulsion systems (Aoki, Kamada & Matsuzaki, 1963; Arai & Shinoda, 1967; Shinoda, 1968; and Mitsui, & others, 1970), although recently a more complex relationship was observed by Aoki, Yata & others (1970). Aoki & Matsuzaki (1967b) and Shinoda & Takeda (1970) have shown that the effect of salts upon the inversion temperatures can be correlated with their action upon aqueous solutions of non-ionic surfactants (Maclay, 1956; Schick, 1962; Becher, 1962; Shinoda, Yamaguchi & Hari, 1961; Doscher, Myers & Atkins, 1951).

The work cited above, with the exception of studies concerning the influence of HLB, has been carried out with emulsions stabilized with a single surfactant. In the present investigation of factors affecting the P.I.T. of liquid paraffin emulsions, a mixed surfactant system has been used, since this is the situation more frequently encountered in pharmaceutical formulation. To determine the inversion temperatures of the emulsions, a technique has been used that combines a controlled heating rate (a prerequisite of the differential thermal analysis procedure) with a rheological measurement. To this end, a programmed temperature rise unit has been linked with a Ferranti-Shirley cone and plate viscometer. This type of viscometer has been used previously to detect phase transitions in emulsions (Barry & Saunders, 1970). The programmed viscometric technique for detecting the P.I.T. has the advantage that it also shows how changes in formulation and temperature influence the viscosity of the emulsion. This information can be important when such systems are processed on an industrial scale and are ultimately stored under variable temperature conditions.

MATERIALS AND METHODS

Materials

Liquid paraffin B.P. containing 0·01% w/w oil-soluble red dye.
Brij 92 (polyoxyethylene (2) oleyl ether, HLB 4·9) and Brij 96 (polyoxyethylene (10) oleyl ether, HLB 12·4) used in their commercially available form. (Honeywill and Stein Ltd. London). Sodium chloride and calcium chloride (dried) of Analar quality (BDH Chemicals Ltd. Poole). Propylene glycol of laboratory reagent grade (Fisons Scientific Apparatus Ltd. Loughborough).

Apparatus

A Transitrol Series 12–94 potentiometric program temperature controller (Ether Ltd., Stevenage, Herts), linked with a 1·5 kw heating element, was used to regulate the temperature of a water bath. Water from the bath was circulated to the plate of a Ferranti-Shirley cone and plate viscometer. The temperature of the plate was monitored by thermocouples embedded in its surface, and by thermometers ($\pm 0·1°$) placed in the water inlet and outlet of the plate. The viscometer was equipped with an automatic flow curve recorder unit and an automatic cone and plate setting unit. For all measurements a 7 cm diameter cone (cone angle 0·0063 radians) and a 600 g torque spring were fitted to the instrument. An anti-evaporation hood was placed over the cone to minimize evaporation effects.

During the initial experiments, a simple conductivity test circuit comprising two stainless steel electrodes connected in series with a 250V neon bulb and the electrical mains supply was also used to detect phase inversion and check the validity of the programmed viscometric technique.

Preparation of emulsions

Emulsions were prepared by mixing together at room temperature (20°) appropriate quantities of stock dispersions of the two surfactants in liquid paraffin and making up to the required weight with liquid paraffin. This mixture was then stirred into the appropriate weight of water and passed once through an Ormerod URF-2 hand homogenizer.

Determination of phase inversion temperatures

For this work a programmed temperature rise of 0·5° min^{-1} was adopted since Matsumoto & Sherman (1970) have reported that increased heating rates cause the phase inversion temperature to be less well defined and move slowly towards higher temperatures. The reduction in viscometer gap width caused by this temperature rise was automatically corrected for by the cone and plate setting unit. As an additional precaution, a manual check was made of the gap width after every 10° rise in temperature.

(i) *Phase inversion temperatures from shear stress-rate of shear studies.* The viscometer was used in the automatic mode with shear rate varying from 0 to 1660 s^{-1}. A sweep time of 60 s was selected as a compromise between possible evaporation effects and spurious results produced by cone inertial forces at shorter sweep times. Davis, Shotton & Warburton (1968) found no evaporation effects at 40° with o/w emulsions using this setting, and many of our studies were made in the region of 30–50°.

The bulk emulsion sample was placed in the water bath at room temperature and the bath and viscometer were heated under programmed temperature rise conditions. At 4 min intervals, the emulsion was stirred and a sample transferred to the viscometer plate. The sample was allowed to equilibrate for 1 min and the shear stress-rate of shear rheogram was then obtained.

(ii) *Phase inversion temperatures from shear stress-time studies.* Using a constant shear rate of either 166 or 332 s^{-1}, a single emulsion sample was continuously analysed whilst undergoing programmed temperature rise by recording shear stress against time. These shear rates were selected to minimise any possible influence of shear

upon the temperature at which phase inversion occurred. A sweep time signal of 600 s was used to produce the time (Y) axis on the X-Y recorder.

Using either technique (i) or (ii), the phase inversion temperatures quoted in this work were mean values of four determinations.

Evaluation of formulation variables

For this work the shear stress-rate of shear technique was used to determine P.I.T.

(i) *Effect of HLB upon phase inversion temperature.* Emulsions of the following general formula were prepared: Brij 92 and Brij 96 together 6·00; liquid paraffin 44·00; distilled water 50·00% w/w.

The relative proportions of Brij 92 and 96 were varied as shown in Table 1 to produce emulsions containing surfactant blends ranging in HLB value from 6·2 to 7·0. The overall weight ratio of oil to water in these systems was assumed to be constant at 0·5 since both the Brij 92 (oil-soluble) and Brij 96 (self-dispersing) were incorporated in the oil phase.

The phase inversion temperatures were determined by electrical conductivity measurements of the bulk emulsion samples as well as by the viscometric technique.

(ii) *Effect of phase ratio upon phase inversion temperature.* Two series of emulsions containing a surfactant mixture of HLB 6·7 were prepared and examined. For the first series, the ratio of total surfactant concentration to oil concentration was held constant whilst the phase ratio of oil was varied as shown in Table 2. Table 3 shows the composition of the second series of emulsions where the ratio of total surfactant concentration to water concentration was kept constant whilst the phase ratio of water was varied. For the purposes of this work, the phase ratio was defined as the weight ratio of oil including surfactants, or of water, to the total emulsion weight.

(iii) *Effect of water-soluble additives upon phase inversion temperature.* A series of emulsions was prepared and examined in which the aqueous phase contained either

Table 1. *Relation between proportions of surfactants used and HLB value for emulsion system of oil phase ratio of 0·5 and surfactant concentration of 6·00% w/w.*

Concentration of surfactants % w/w		HLB values
Brij 92	Brij 96	
5·00	1·00	6·2
4·88	1·12	6·3
4·80	1·20	6·4
4·56	1·44	6·7
4·32	1·68	7·0

Table 2. *Compositions of emulsions used to determine the effect of oil phase ratio with constant oil: surfactant ratio of 7·33:1.*

Oil phase ratio	Concentrations % w/w		
	Oil	Water	Total surfactant
0·8	70·4	20·0	9·6
0·6	52·8	40·0	7·2
0·5	44·0	50·0	6·0
0·4	35·2	60·0	4·8
0·3	26·4	70·0	3·6
0·2	17·6	80·0	2·4

Table 3. *Compositions of emulsions used to determine the effect of aqueous phase ratio with constant water: surfactant ratio of 8·33:1.*

Water phase ratio	Concentrations % w/w		
	Oil	Water	Total surfactant
0·8	10·4	80·0	9·6
0·7	21·6	70·0	8·4
0·6	32·8	60·0	7·2
0·5	44·0	50·0	6·0
0·48	46·24	48·0	5·76
0·45	49·6	45·0	5·4
0·4	55·2	40·0	4·8
0·2	77·6	20·0	2·4

sodium chloride or calcium chloride in the concentration range 0 to 8·0% w/w, or propylene glycol in the range 0 to 2·0% w/w. The concentration of the surfactant mixture (HLB 6·7) was held constant at 6·00% w/w with respect to the total emulsion weight, and the oil phase ratio was 0·5.

The cloud points of 1·0% w/w aqueous solutions of Brij 96 in the presence of various concentrations of these additives were determined as follows. The solutions were placed in 10 ml sealed phials and warmed in a water bath until they became distinctly cloudy. The bath was then allowed to cool slowly, and the cloud point of each solution was taken to be the temperature at which the liquid became clear.

RESULTS AND DISCUSSION

Evaluation of viscometric technique for determining phase inversion temperature

Rheograms of the o/w emulsions obtained under isothermal conditions (25°) showed pseudoplastic flow properties, and microscopic observation confirmed that the oil globules were flocculated. In the determination of the P.I.T. of an emulsion by the shear stress-rate of shear technique, the rheograms showed a small hysteresis loop because of the 1° rise in temperature during the course of the measurement. An example of the results obtained with this technique is shown in Fig. 1A in the form of a plot of apparent viscosity at 1000 s^{-1} against temperature. The data refer to an emulsion of oil phase ratio of 0·5 containing 6·00% w/w of surfactant mixture of HLB 6·7 (see Table 1 for relative proportions of Brij 92 and 96). It can be seen that successive samples of the emulsion produced rheograms that showed a decreased apparent viscosity with temperature until 35° was reached. Subsequently, there was a slight increase in apparent viscosity followed by a sudden and dramatic increase in apparent viscosity. This break in the trend occurred at 46·5° and was taken to be the P.I.T. Conductivity tests and visual observation of the emulsion carried out concurrently confirmed this result. Once inversion had occurred, further analysis of samples of higher temperatures resulted in rheograms showing a gradual decrease in apparent viscosity from that obtained at inversion.

Fig. 1B is an example of the results of a shear stress-time study, using a shear rate of 332 s^{-1}, for a single emulsion sample of the same formula detailed above to which 4·0% w/w sodium chloride had been added. It is evident that an abrupt change in shear stress occurs after 16 min shearing. Since the initial sample temperature was 24°, and the programmed temperature rise was $0·5° \text{ min}^{-1}$, this corresponded to a P.I.T. of 32°.

It is possible to account for the sequence of change in apparent viscosity with rise in temperature shown in Fig. 1A in the following manner. The initial decrease in
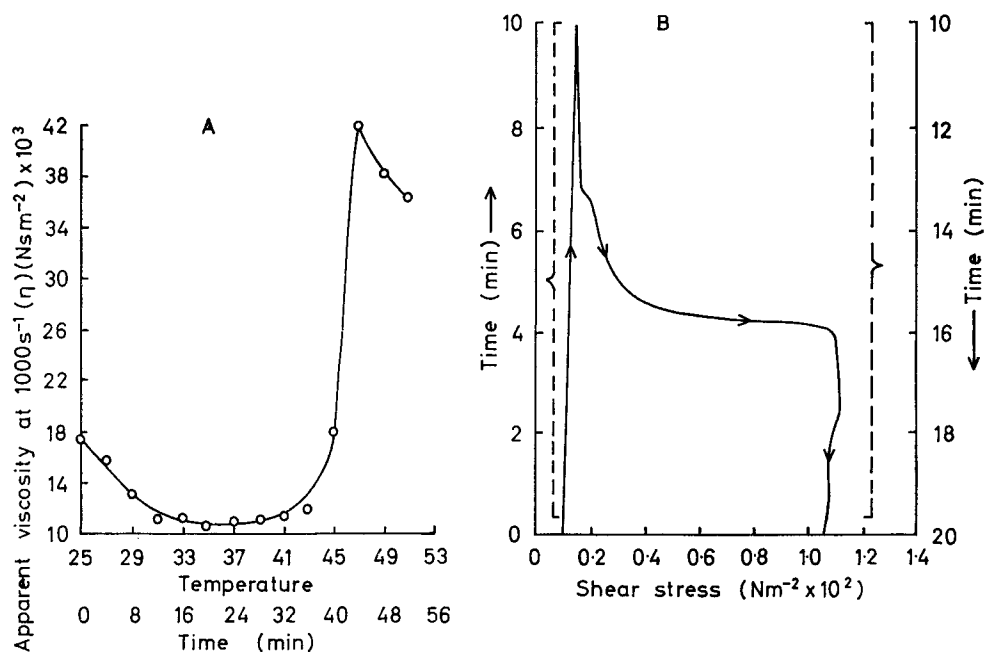
FIG. 1. A. Relation between apparent viscosity at 1000 s^{-1} and temperature for emulsion of oil phase ratio 0·5 containing 6·00% w/w of a surfactant mixture of HLB 6·7.

B. Shear stress-time relation for emulsion of oil phase ratio 0·5 containing 6·00% w/w of a surfactant mixture of HLB 6·7 and 4·0% w/w sodium chloride. Shear rate 332 s^{-1}.

viscosity was due to the usual decrease in viscosity of the continuous phase of the emulsion. The subsequent gradual increase in viscosity could be due to the change in degree of hydration of the ethylene oxide units, and, because of the extension of the polyoxyethylene chains, an increase in the radius of micelles present in the continuous phase (Beresnev, Fermor & Smernev 1966; Elworthy & McDonald, 1964; Greenwald & Brown, 1954). The further sudden and considerable increase in viscosity may be attributed to the aqueous continuous phase of relatively low viscosity being replaced by the much more viscous oil phase. These results could not have been due to either changes in the viscometer gap width or evaporation effects. The gap width was continuously controlled with the automatic cone and plate setting unit, and a fresh emulsion sample was used to obtain each successive rheogram.

The precision of both the shear stress-rate of shear and shear stress-time methods of determining P.I.T. was about ±0·5°. Coupled with an error of ±0·5° introduced when interpreting the rheograms, the maximum error of the technique was ±1·0°. This compares favourably with the results published by Shinoda & Arai (1964) of ±2° and Mitsui & others (1970) of ±1°. The rates of shear applied to the emulsions during analysis did not appear to affect the inversion temperatures since there was close agreement with the values obtained by conductivity measurements and visual observation (see also Fig. 2).

Either form of the viscometric technique outlined may be used for determining P.I.T., but the shear stress-rate of shear method is more suitable for the range from 20° to approximately 75°. Experiments made with o/w emulsions which did not invert in this temperature range confirmed that there were no significant evaporation effects compared with the results of Davis & others (1968), or with the changes in
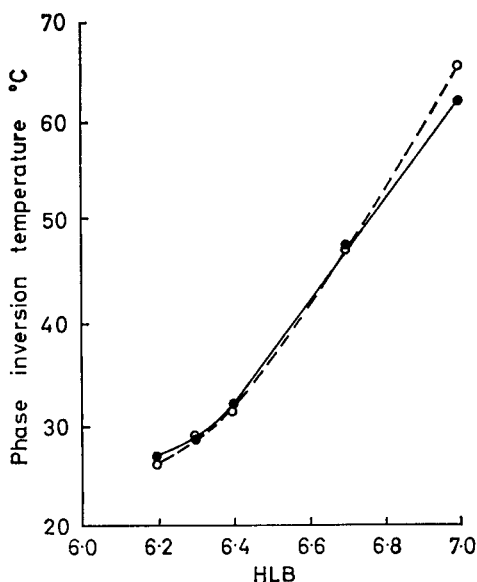
FIG. 2. Relation between HLB and P.I.T. for emulsion with oil phase ratio of 0·5 and total surfactant concentration of 6·00% w/w. ○ Results obtained by conductivity measurements. ● Results obtained by viscometry.

viscosity occurring at the point of emulsion inversion. Above 75°, the probability of evaporation resulting in alteration of the emulsion composition could produce erroneous results.

Evaluation of influence of formulation variables

(i) *Effect of HLB on phase inversion temperature.* Fig. 2 shows the relation between HLB and P.I.T. obtained using both electrical conductivity and programmed viscometric methods. Within the HLB range studied, there was an approximately linear rise in P.I.T. with increase in HLB of the surfactant mixture. The findings are similar to those obtained by Mitsui & others (1970), using polyoxyethylene stearyl ether surfactants (HLB values 8·5 to 11) to emulsify liquid paraffin. Such an effect is to be expected since the P.I.T. is a measure of emulsion stability, which will increase as the HLB moves towards the optimal region (9–10) for emulsification of liquid paraffin (Atlas, 1963a). Unfortunately, since the upper limit of P.I.T. that could be examined was 75°, it was not possible to extend the HLB values to this region. However, the data obtained are sufficient to indicate that surfactant mixtures with HLB values greater than 6·8 should produce stable emulsions. This prediction is based on the concept of Shinoda & Saito (1969) that emulsions with inversion temperatures from 25 to 70° above storage temperature will be satisfactorily stable.

The change in emulsion viscosity at inversion was found to be less marked towards higher HLB values as was found by Aoki & others (1970). It is also interesting to note that at low HLB values the P.I.T. obtained by electrical conductivity measurements was slightly lower than obtained by programmed viscometry, whereas the reverse was true at higher HLB values. This may be due to the complex changes in electrical conductivity that occur with change in HLB of the surfactant mixture. Aoki & others (1970) have shown that at HLB values removed from the optimum

there is not such an abrupt and distinct change in conductivity upon inversion of the emulsion.

(ii) *Effect of phase ratio on phase inversion temperature*. With emulsions stabilized with a single surfactant, it is only possible to isolate the effect of the phase ratio upon the P.I.T. when the concentration of surfactant is held constant with respect to the phase in which it is preferentially soluble. If the surfactant concentration is held constant with respect to the total emulsion bulk then, as the phase ratio varies, the concentration of surfactant in the phase in which it is soluble will vary, and this in itself will influence the P.I.T. The effect of phase ratio cannot be examined in isolation with mixed surfactant systems, since it is not possible to hold both the water-soluble and oil-soluble surfactant concentrations constant with respect to their phases and also maintain the same HLB as the phase ratio is varied. The approach adopted in this work was to use a surfactant mixture of constant composition (HLB 6·7) and prepare one emulsion series in which the total surfactant concentration was constant relative to the oil phase, and a second series in which the total emulgent concentration was constant with respect to the aqueous phase.

Fig. 3 shows the results for these two emulsion systems. With the total surfactant
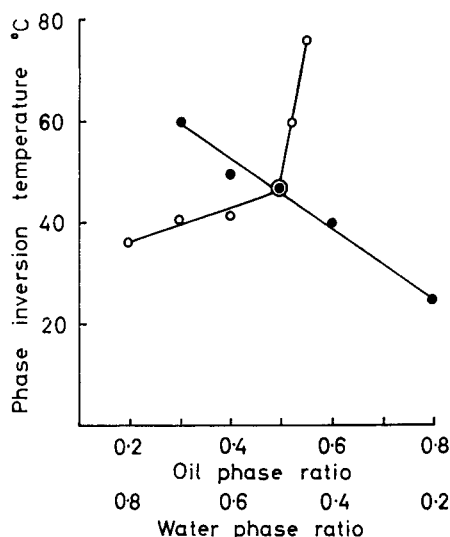

FIG. 3. Relations between phase ratio of emulsion and P.I.T. with HLB of surfactant mixture held constant at 6·7. ● Total surfactant concentration related to oil phase. ○ Total surfactant concentration related to aqueous phase.

concentration related to the oil phase, it can be seen that as the phase ratio of oil was increased the P.I.T. decreased. The phenomenon could be merely due to the increasing number of oil droplets causing an increase in probability of collision and coalescence with consequent reduction in emulsion stability. However, as the oil phase ratio was increased, the surfactant concentration relative to the overall bulk of emulsion and also to the aqueous phase increased. Mitsui & others (1970) have shown with a single emulgent system, that under these circumstances the P.I.T. will decrease. Friberg & Wilton (1970) and Friberg & Mandell (1970) indicated that an increase in surfactant concentration above the critical micelle concentration, with consequen

increase in the number of micelles in the aqueous phase, can alter the distribution of surfactants between the phases and adversely affect emulsion stability.   This would be reflected in a reduction in the P.I.T.

When the total surfactant concentration was held constant relative to the aqueous phase, the P.I.T. was found to decrease with increasing aqueous phase ratio.   Since the number of oil droplets was decreasing as the aqueous phase ratio increased, then this effect must have been almost entirely due to the fact that the surfactant concentration was increasing relative to the oil phase and the total bulk of the emulsion. Above an aqueous phase ratio of 0·5, the fall in P.I.T. was less marked.   This change of slope may indicate that, at aqueous phase ratios of less than 0·5, the lower concentrations of the oil-soluble Brij 92 were not as effective in stabilizing the w/o emulsion produced upon inversion.   Another possible cause is that the increase in emulsion stability below an aqueous phase ratio of 0·5 was produced by the formation of a liquid crystalline phase or ordered layer at the oil-water interface (Friberg & Wilton, 1970; Friberg & Mandell, 1970).

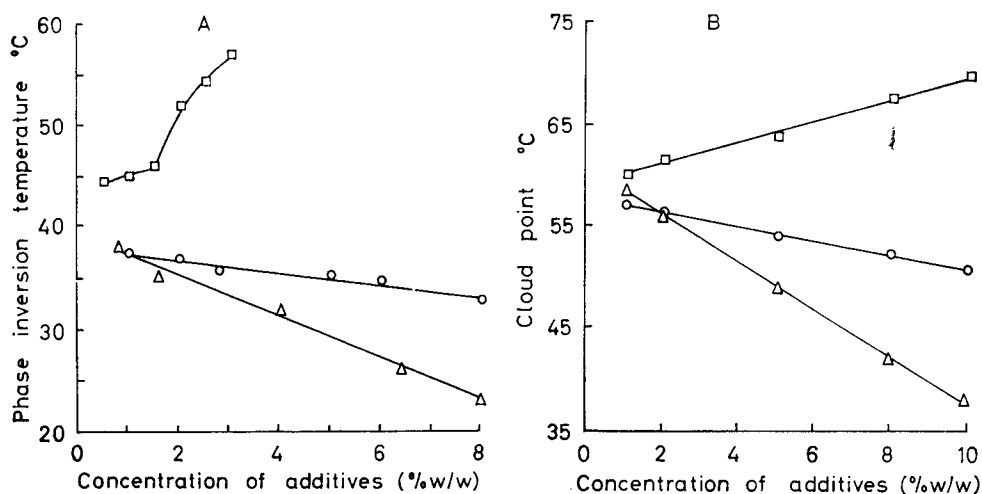(iii) *Effect of water-soluble additives on the phase inversion temperature.*   Fig. 4A

FIG. 4.   A. Effect of water-soluble additives upon P.I.T. of an emulsion of oil phase ratio of 0·5 and total surfactant concentration of 6·00% w/w (HLB 6·7).
   B. Relation between cloud point of 1·0% w/w aqueous solutions of Brij 96 and concentrations of water-soluble additives.   □ Propylene glycol.   ○ Calcium chloride.   △ Sodium chloride.

shows that the increasing addition of sodium chloride to the emulsion system having an oil phase ratio of 0·5 and total surfactant concentration of 6·00% w/w (HLB 6·7) resulted in a linear decrease in P.I.T.   The effect was considerable, for example, addition of 5·0% w/w sodium chloride produced a 17° fall in P.I.T.   With calcium chloride the effect was not so pronounced, 5·0% w/w caused an 11° reduction.   Aoki & Matsuzaki (1967b), Shinoda (1968) and Shinoda & Takeda (1970) have reported similar trends for the addition of salts to emulsions stabilized with single non-ionic surfactants.

The present work also showed that addition of these salts caused a marked increase in viscosity at inversion, and that the higher the salt concentration the greater the effect became.   This phenomenon is in all probablity due to the increasing partition of the Brij 96 from the aqueous to the oil phase with a consequent increase in viscosity

of the oil continuous phase produced upon inversion.   Fig. 4B shows that the lowering of the cloud point of 1 % w/w aqueous solutions of Brij 96 upon the addition of the salts followed the same trend as the emulsion inversion temperatures.   Doscher & others (1951), Maclay (1956), Schick (1962) and Kuriyama (1962) have found similar effects for the addition of salts to solutions of non-ionic surfactants.   It follows that the stability of this emulsion system in the presence of salts was governed by the solubility of the water-soluble component of the surfactant mixture.

Doscher & others (1951) believe that the mechanism by which calcium chloride reduces the aqueous solubility of non-ionic surfactants differs from that occurring with sodium chloride.   They postulated that the action of sodium chloride was to "salt out" the surfactants by reducing the hydration of the ether linkages because of the increased ion concentration.   Calcium chloride had a "salting in" effect which involved the complexing of hydrated calcium ions with the ethereal oxygens of the polyoxyethylene chain.   The observed difference in the linear relations obtained with sodium and calcium chloride shown in Figs 4A & B, which occurs even when electrolyte concentration is expressed in terms of normality, molality or ionic strength, also points to a difference in mechanism of action of the two salts.

Addition of propylene glycol to the aqueous phase resulted in a significant increase in P.I.T. (Fig. 4A).   Again, the cloud point of 1% w/w Brij 96 solutions in the presence of propylene glycol followed the same trend (Fig. 4B).   These results can be explained by the increased solubility of the surfactants in the mixed solvent (Atlas, 1963b).   The curvilinear nature of the P.I.T. relationship (Fig. 4A) may be due to the increasing partitioning of the Brij 92 from the oil to the aqueous phase.

The correlation between P.I.T. of the emulsion and cloud point of Brij 96 in the presence of water-soluble additives is shown in Fig. 5.   The plot has been obtained by interpolation of the data in Fig. 4A & B.   In this instance, because of the low water-solubility of liquid paraffin, the correlation was achieved without prior saturation of the aqueous solution with the oil phase.   The different relation of greater slope exhibited by the propylene glycol systems (Fig. 5), indicating more effective
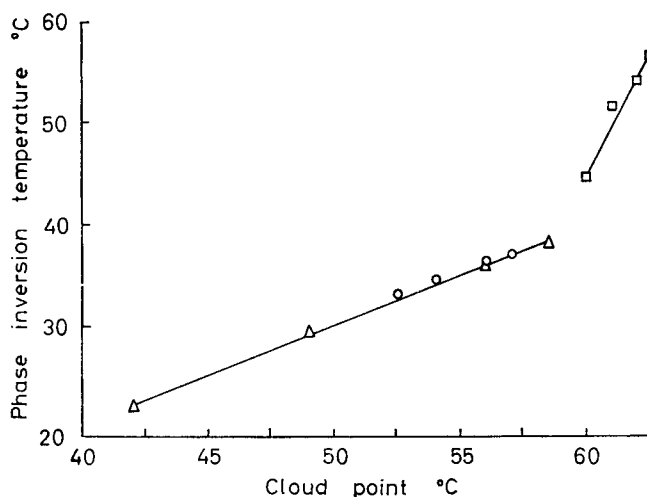
FIG. 5.   Correlation between P.I.T. and cloud point of 1·0% w/w aqueous solutions of Brij 96 for emulsion of oil phase ratio of 0·5 and total surfactant concentration of 6·00% w/w (HLB 6·7).   □ Propylene glycol.   ○ Calcium chloride.   △ Sodium chloride.

emulsion stabilization, probably reflects the partitioning of the Brij 92 into the aqueous phase.

The effect of the water-soluble additives is to alter the HLB of the surfactant mixture, and thus this presents the possibility of achieving optimum stabilization, when using non-ionic surfactants, either by careful initial selection of the HLB of the mixed surfactants, or the use of such water-soluble additives to achieve the desired effect.

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