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Application of Surface Active Agents to Pharmaceutical Preparations. XV.[1] Factors Affecting on the Preparation of Oil-in-Water Emulsion. (1). A New Determination of a Required HLB and an Adaptability of Surfactants to Oils[2]

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The present paper deals with a new method to determine a required HLB of oil and an adaptability of surfactants to oils.

Measurements were made of a continuous change of viscosity and electric conductivity during emulsification. The viscosity was measured with a torque meter equipped to the upper part of a stirring shaft.

There was found a characteristic change at the stage of phase inversion. Plotting the highest viscosity in a phase inversion *vs.* HLB of combined surfactants showed two peaks with a depressed junction. Temperature range for phase inversion showed a similar pattern in reference to HLB.

The middle HLB of the junction was assumed to be a required HLB. The required HLB was also confirmed with small and uniform particle size and good stability on aging at 30°.

And surfactants suitable for oils may be selected on the basis of relations between the highest viscosity during phase inversion and HLB of combined surfactants.

The present paper deals also with the phase inversion temperature in reference to HLB of combined surfactants.

It is generally accepted that many factors are related to the preparation of an emulsion. A required HLB of oil is one of the important factors. The required HLB has been usually determined only by microscopic observation on emulsions emulsified with combined surfactants. But this method has a disadvantage in the accuracy.

The present paper deals with a new method to determine a required HLB of oil and an adaptability of surfactants to oils.

Since the concept of HLB number of surfactants was introduced by Griffin,[4] many attempts have been made to study possible relations of this number to temperature of phase inversion,[5] to viscosity of emulsion,[6] to liquid-liquid distribution,[7] to interfacial tension[8] and *etc.*

The present paper deals also the temperature of phase inversion in reference to HLB of combined surfactants.

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[1] Part XIV: M. Aoki and T. Matsuzaki, *Yakugaku Zasshi*, **87**, 765 (1967).

[2] Part of the present report was presented at the 16th Anual Meeting of Kinki Branch, Pharmaceutical Society of Japan, November 1966.

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It is generally accepted that emulsification with nonionic surfactants results in a type of water-in-oil at higher temperature and when cooled the type inverses to an oil-in-water type at a certain temperature. This inversion is often applied in preparing oil-in-water emulsion. But changes of viscosity in emulsification with a decrease of temperature do not seem to have been investigated.

Presently measurements were made of a continuous change of viscosity and electric conductivity during emulsification. As result there was found a characteristic change at the stage of phase inversion in reference to HLB number of combined surfactants. Here, viscosity in emulsification is to be significantly taken up even in an emulsion containing many ionic substances. Then even a complicated emulsion may afford a valuable information of the applicability of surfactants to oil components.

Experimantal

Composition of Emulsion——Composition of emulsion under study is shown in Fig. 1. Surfactants were used in an amount of 13.2×10^{-3} moles which equals to the sum of Tween 60 and Arlacel 60 in combination at HLB 11.23 in 10 w/w% in the emulsion. The molecular weight of Tween 60 was calculated on the basis of chemical formula of polyoxyethylene (20 mole) sorbitan monostearate, *i.e.*, 1312 and Arlacel 60 as sorbitan monostearate, *i.e.*, 431.

Apparently non-ionic surfactant is a mixture of ethylene oxide condensation products containing unavoidable impurities. But mole ratio of combined surfactants seems to be important in comparing the characteristics of emulsions. Hence the present use of molarity instead of weight percent.

On calculation of HLB of combined surfactants, HLB numbers of 14.9 and 4.7 were adopted on the basis of the table issued from Atlas Powder Co. for Tween 60 (Lot No. 1003) and Arlacel 60 (Lot No. 1005) respectively.

In considering possible fluctuation of characteristics of surfactants in every manufacturing unit, Tween 60 of Lot No. 1003 and Arlacel 60 of Lot No. 1005 were conveniently set as a standard in a series of the present study.

Weight ratios of Tween 60 and Arlacel 60 in 13.2×10^{-3} moles at various HLB are shown in Table I. The characteristics of surfactants and mineral oil under study are shown in Table II.

TABLE I. Weight Ratios of Tween 60 and Arlacel 60 in 13.2×10^{-3} moles at various HLB[a)]

HLB	Surfactant (g) Tween 60	Surfactant (g) Arlacel 60	HLB	Surfactant (g) Tween 60	Surfactant (g) Arlacel 60
11.48	6.85	3.45	10.33	5.00	4.05
11.30	6.50	3.55	10.25	4.90	4.10
11.23	6.40	3.60	10.17	4.80	4.15
11.10	6.20	3.65	10.06	4.60	4.15
10.96	5.95	3.75	9.95	4.45	4.20
10.82	5.70	3.80	9.89	4.40	4.25
10.69	5.55	3.90	9.80	4.30	4.30
10.54	5.30	3.95	9.71	4.15	4.30
10.42	5.10	4.00			

a) HLB of combined surfactants was calculated with HLB of 14.9 and 4.7 for Tween and Arlacel, respectively.

Emulsification——An apparatus shown in Fig. 2a was employed in the present study. Surfactants are mixed with oil in a glass beaker equipped with a water jacket and heated up to 100° and boiling water is poured at one time into the beaker and the mixture is stirred at a rate of 150 rpm with a stirring blade made of the Teflon (Fig. 2b).

Immediately viscosity and electric conductivity are measured with a decrease of temperature. The temperature decreased at a rate of 0.5°/min.

Table II. Characteristics of Surfactants and Mineral Oil

Surfactants	Moisture content, (%)[a]	Free fatty acid content, (%)[b]	Na^+ content, (%)[c]
Tween 60	3.42	0.82	0.033
Tween 20	—	0.61	0.044
Arlacel 60	3.35	0.64	0.097
Span 40	—	8.45	0.107
Mineral Oil (Carnation Oil #70, Sonnebone Co.)			
Specific Gravity	0.844	Aniline Point	105.0°C

a) Determined by the Karl Fischer method.
b) Determined by colorimetrically (Y. Iwayama, *Yakugaku Zasshi* 79, 552 (1958)).
c) Determined by flamephotometrically.

Mineral oil (carnation, # 70)	40 g
Surfactants (Tween 60+Arlacel 60)	13.2×10^{-3} moles
Water	50 g

Fig. 1. Composition of Emulsion

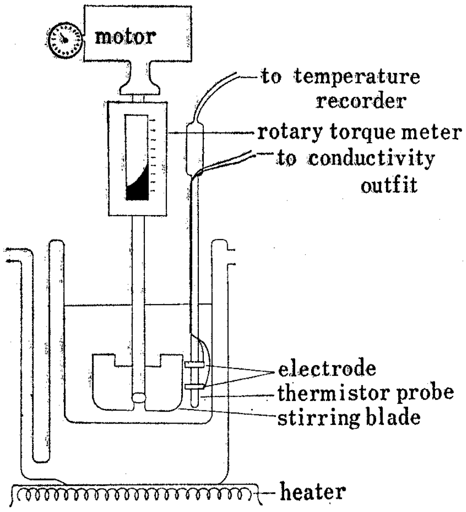

Fig. 2a. Apparatus

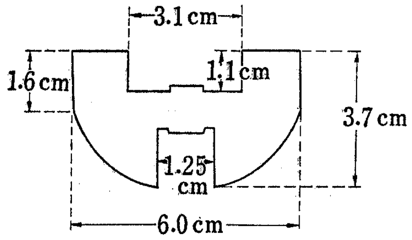

Fig. 2b. Stirring Blade

Here it is important to watch a decreasing rate of temperature so that equilibriation of surfactants at the interface of oil and water may be established at any temperature. The decreasing rate should be kept at a minimal level as possible. A rate of less than 0.5°/min seems enough for equilibriation.

Measurement of Viscosity——A rotary torque meter (Yamazaki Seiki, Kyoto, Japan) was equipped to the upper part of a stirring shaft (Fig. 2a). Torques of 0—0.2 kg-cm can be measured successively within accuracy of 0.005 kg-cm by this meter.

Considering a rate of stirring and shape of a stirring blade responsible for the readings, a stirring blade as shown in Fig. 2b was used at rate of 150 rpm in the present study.

Measurement of Electric Conductivity——A pair of brass rings was used as electrodes. It was fixed at the lower part of a thermister probe at a distance of 1.1 cm (Fig. 2a). The electrode were immersed into a test solution. Electric conductivity was measured with the Yanagimoto conductivity out fit Model MY-6. The use of brass instead of platinum-black as electrodes was found to be acceptable in measuring relative changes of electric conductivity.

Stability of Emulsions on Ageing——Emulsions stabilized with combined surfactants following the above emulsifying technique were filled in a 100 ml glass stoppered volumetric flask and were stored in a incubator.

Ageing was carried out at 30° over 400 days. Changes of their appearance based on any phase separation were checked at frequent intervals.

As a index of stability, days when emulsions could be stored without any phase separation were taken up.

Results and Discussion

Viscosity during emulsification did not change significantly till a certain temperature, below which it changed markedly.

For instance, viscosities of an emulsion emulsified with combined surfactants of Tween 60 and Arlacel 60 having HLB of 10.96 began to increase markedly at 80°, reaching a maximum at 72.5°, followed by the decrease to the initial level and then gradual increase due to a decrease of temperature (Fig. 3). The above marked increase in viscosity is subjected to change in phase from water-in-oil to oil-in-water.

Electric conductivity changed similarly with viscosity (Fig. 3). At a maximum viscosity, electric conductivity proved to be maximum. So significant changes of viscosity reflect a phase inversion (W/O to O/W).

Such marked increase in viscosity was found at all HLB studied. But the appearance on temperature and the magnitude of such increase were different depending upon a combination of surfactants (Fig. 4 and Fig. 5). The higher the HLB, the higher the temperature. But this relationship does not exist between HLB and the highest viscosity in a phase inversion.

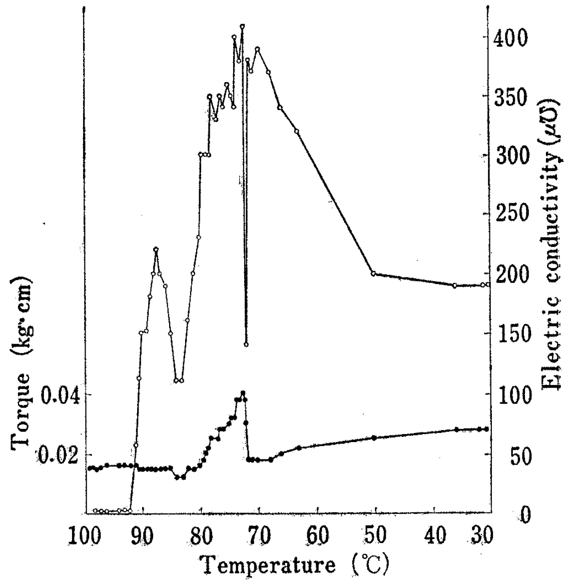

Fig. 3. Changes of Viscosity and Electric Conductivity during Emulsification at HLB 10.96

—●—: viscosity, —○—: electric conductivity

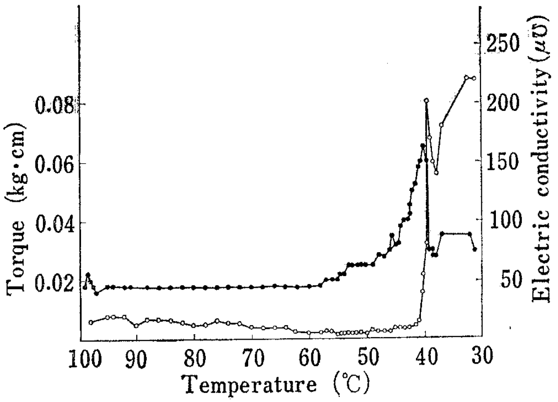

Fig. 4. Changes of Viscosity and Electric Conductivity during Emulsification at HLB 9.8

—●—: viscosity, —○—: electric conductivity

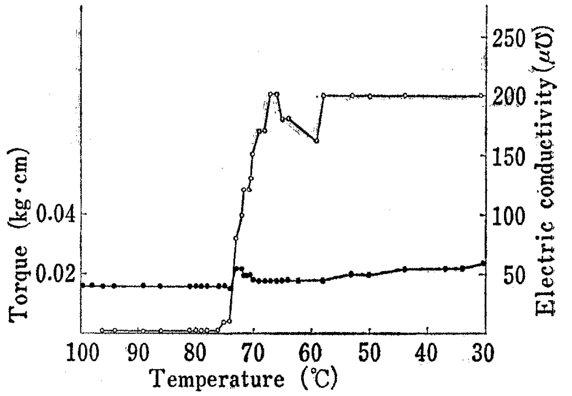

Fig. 5. Changes of Viscosity and Electric Conductivity during Emulsification at HLB 10.33

—●—: viscosity, —○—: electric conductivity

Plotting the highest viscosity in a phase inversion *vs.* HLB of combined surfactants, showed interesting relations as shown in Fig. 6.

In a region of HLB showing a depressed junction between two peaks of the highest viscosity, the particle size of emulsion was the smallest and showed a minimum distribution on microscopy. So the middle HLB of the region, *i.e.*, 10.3 is assumed to be a required HLB for the mineral oil employed in the present study.

Here, measurement of viscosity during emulsification will offer a significant method to determine the required HLB. In this case it must be noticed that the two peaks are found at both sides of a required HLB.

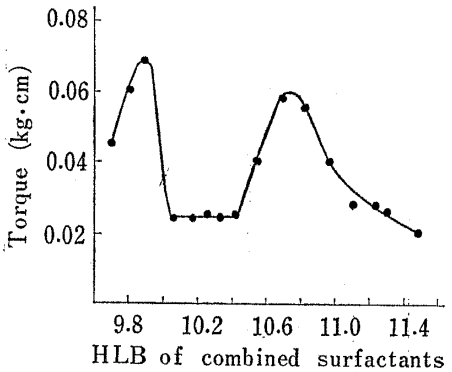

Fig. 6. Relations between the Highest Viscosity in a Phase Inversion and HLB

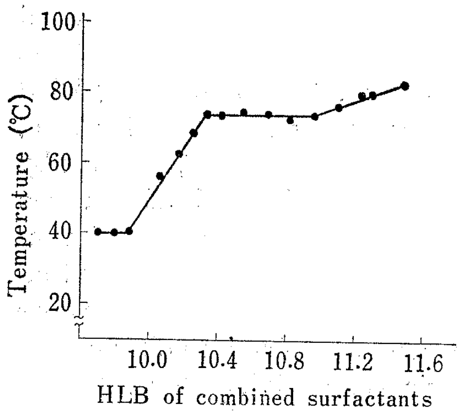

Fig. 7. Relations between Phase Inversion Temperature and HLB

Ohba[6] studied the viscosity of emulsion and reported that when surfactants were used in combination of a required HLB for oil, viscosity of the resulting emulsion decreased more than in other combinations of surfactants.

In the present study it was found that features in viscosity during emulsification at a required HLB were similar to those reported by Ohba following emulsification.

The temperature showing the highest viscosity (tentatively designated as the phase inversion temperature) changed with HLB as shown in Fig. 7.

In emulsification of cosmetic materials, stress has generally been given to the rate of stirring and of cooling. As a result processing hazards could not be detected during emulsification but after processing. If a viscosity-temperature relationship is studied previously and if a viscosity measuring device is applied during manufacturing process, emulsification can be checked up, not after, in the process.

Assuming a range of temperature at a significant change of viscosity as temperature range for phase inversion, relations between such range and HLB are presented in Fig. 8.

At the required HLB or in the neighborhood, a range of temperature of phase inversion became more narrow than at any HLB.

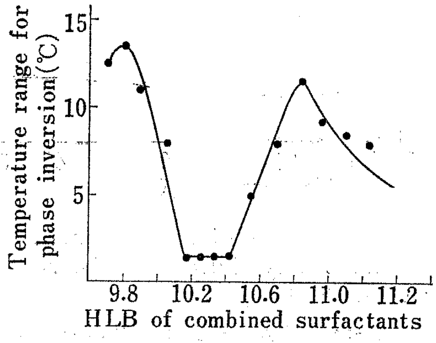

Fig. 8. Relations between Temperature Range for Phase Inversion and HLB

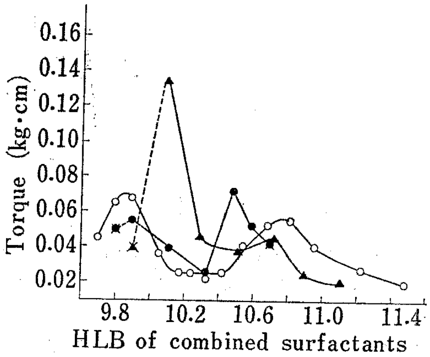

Fig. 9. Relations between the Highest Viscosity in a Phase Inversion and HLB in reference to various Combination of Tweens and Arlacels

—○—: Tween 60 and Arlacel 60
—▲—: Tween 60 and Span 40
—●—: Tween 20 and Span 40
Symbols marked with × represent no emulsions were formed at the HLB.

It means that the phase of emulsion inverses smoothly at the required HLB. This is reflected on the change of electric conductivity (Fig. 5). Near the required HLB electric conductivity increased abruptly as soon as the viscosity decreased, and the conductivity kept the same level subsequently. Those patterns of electric conductivity were observed at HLB of 10.25 and 10.33. At other HLB, complicated changes were observed in electric conductivity.

At a required HLB, the ratio of Tween 60 and Arlacel 60 on molecular level seems to be optimum for emulsification. Therefore electric conductivity keeps the same level after phase inversion.

But at a higher HLB, Tween 60 seems to be excess. After a marked increase, electric conductivity decreases with a decrease of temperature (Fig. 3). This decrease is supposed to be subjected to the formation of mixed micelles consisting of excess Tween 60 and fatty acid soap in aqueous phase of the emulsion. The fatty acid soap is considered to be present in Tween 60 as an unavoidable impurity and be possible responsible for the presence of electric conductivity in the aqueous solution of Tween 60. Similar results were obtained at HLB of 10.45—11.23.

At a lower HLB, electric conductivity decreased sharply, immedeately followed by another increase (Fig. 4). This seems to be subjected to less Tween 60. Considering fatty acid soap distributed once to the oil-water interface with Tween 60 and Arlacel 60 is squeezed out because of its less affinity for oil, changes of electric conductivity may be explained. Similar results were obtained at HLB of 10.17—9.7.

As descibed above, measurement of viscosity during emulsification is useful for the determination of the required HLB. And this also will afford a clue to the selection of suitable surfactants for oil. Few reports have been made on the adaptability of surfactants to oils. Surfactants suitable for oils have been empirically selected being based on solubility of surfactants in oils or water.

In combination of Tween 60 and Arlacel 60, relations between the highest viscosity during phase inversion and HLB were presented by two peaks at both sides of the required HLB. When other Tweens and Arlacels were used in combination, emulsion was formed only in a region close to the required HLB and the resultant emulsions were more coarser and less stable than emulsions emulsified with Tween 60 and Arlacel 60 (Fig. 9).

In combination of Tween 20 and Span 40, a fine curve which should have developed between the above two peaks, was not obtained and no emulsions were formed at higher HLB than 10.7 and at lower HLB than 9.81.

TABLE III. Stability of Emulsions emulsified with Some Combination of Tweens and Arlacels

HLB	Days, stored in stable at 30°
Tween 60–Arlacel 60	
11.48	60
11.23	159
10.96	159
10.69	>400
10.54	>400
10.42	>400
10.33	>400
10.25	>400
10.17	>400
10.06	>400
9.80	150
9.71	130
Tween 60–Span 40	
11.10	108
10.90	79
10.72	30
10.51	270
10.29	>400
10.09	30
9.90	unemulsified
Tween 20–Span40	
10.70	unemulsified
10.59	30
10.48	48
10.32	51
10.11	49
9.89	40
9.81	unemulsified
Tween 20–Arlacel 60	
10.70	6
10.52	5
10.30	5

In combination of Tween 60 and Span 40, emulsions were not formed in a lower HLB region than 9.9.

Those results seem to reflect the adaptability of surfactants for mineral oil used. A combination of Tween 60 and Arlacel 60 seems to be more suitable for mineral oil than a combination of Tween 20 and Span 40 or Tween 60 and Span 40.

Indeed emulsions emulsified with Tween 20 and Span 40 or Tween 60 and Span 40 or Tween 20 and Arlacel 60 showed less stability than emulsions emulsified with Tween 60 and Arlacel 60 (Table III).

Here, significant information on the adaptability of surfactants to an oil will be obtained from the relations between the highest viscosity in phase inversion and HLB of combined surfactants.

In this paper only Tweens and Arlacels were used in combination. The use of ether type will also afford results similar to what is described above provided they are purified so as not to overlap each other in terms of the distribution of ethylene oxide condensations.