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Vibrational Test for Evaluation of Creams. I. The Effect of Vertical Vibration Imposed on O/W Creams[1]

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The steady flow behavior, dynamic characteristics and particle size (microscopical counting) of a semisolid O/W cream prepared with cetomacrogol and cetostearyl alcohol were studied. The continuous shear flow curve of this cream was in the form of an anti-clockwise hysteresis loop. Vertical vibration imposed on the cream, using a Sanki viscoelasto recorder, caused a first-order breakdown of viscoelastic structure formed in the cream at a rate of 10^{-5} s^{-1} for dynamic viscosity and 10^{-4} s^{-1} for dynamic modulus, while the vibration caused coalescence of the oil globules dispersed in the cream at a rate of 10^{-15} s^{-1}. The destruction of viscoelastic structure was much more rapid than the coalescence.

Keywords——O/W cream; vertical vibration; dynamic viscosity; viscoelastic structure; coalescence

The rheological evaluation of pharmaceutical semisolids is a useful technique.[2)] To support sensory assessments of consistency,[3)] spreadability,[4)] and stickiness[5)] of ointments and creams, viscoelastic measurements with a penetrometer,[6)] cone and plate viscometer,[4)] creep testing,[7)] and oscillatory testing,[8)] are useful in evaluating as well as the physical properties of ointments and creams. However, verical vibrational testing has not been applied to pharmaceutical ointments and creams for the estimation of viscoelastic properties.

Centrifugation[9)] is usually used as an accelerating method for the storage stability testing of creams. However, oil globules of O/W creams under centrifugal force behave very differently from those under normal gravitational force, so that centrifugation is not adequate to predict the storage stability of creams.[10)] In emulsions and creams, the solubility of emulsifiers changes with temperature. This change in solubility may not be the same for both phases, and consequently the hydrophilic-lipophilic balance (HLB) will be changed, so that it may be difficult to interpret or extrapolate date obtained in high temperature accelerated studies to room temperature conditions.[11)] Thus evaluation of possible shelf life at room temperature from the results of centrifuge tests or high temperature accelerated testing is very difficult. The aim of this study was to provide a basis for the establishment of an accelerated test to estimate the stability of creams for comparative screening in development studies. In this work, imposed vibrational stress was used to promote the destruction of viscoelastic structure in creams and to promote the coalescence of oil globules in O/W cream. A cream was examined at frequencies of 3 to 100 Hz using a viscoelasto recorder. If the response is linear, the time–temperature superposition principle may be applied. According to this principle, viscoelastic data obtained at one temperature may be transformed to another temperature by a simple multiplicative transformation of the time scale.[12)]

Experimental

Materials——Liquid paraffin, vaseline, and minor constituents used in this study were of J. P. grade. Cetostearyl

TABLE I. Compositions of the Creams (g)

Constituents	Sample (O/W type)	Cetomacrogol cream (B.P. Codex, O/W type)
Oils		
Solid (Cetostearyl alcohol)	12.5	7.2
Semisolid	5	15
Liquid	11	6
Water	57.865	69.9
Emulsifying agents (Cetomacrogol)	4.5	1.8
Minor constituents	9.135	0.1

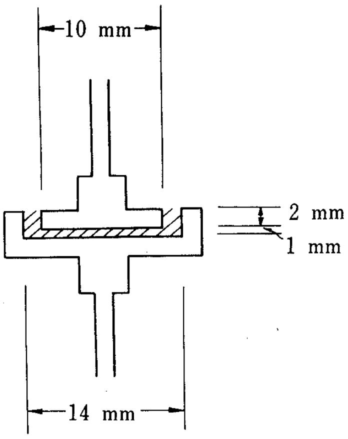

Fig. 1. Sample Cell of the Viscoelasto Recorder

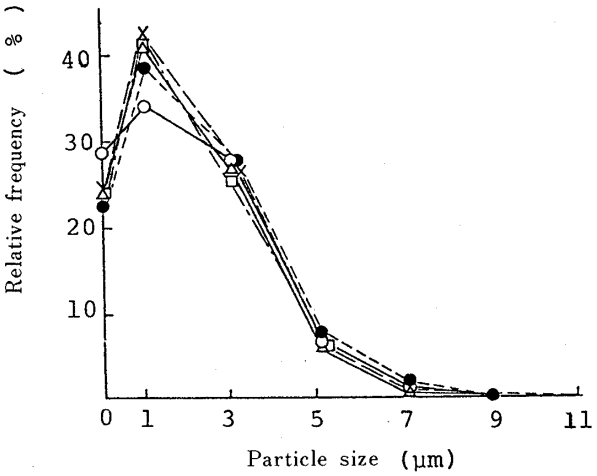

Fig. 2. Variation in Emulsion Particle Size Distribution with Mixing Time

—○—, 10 s; --●--, 15 s; --×--, 30 s; —△—, 45 s; ---□---, 60 s.

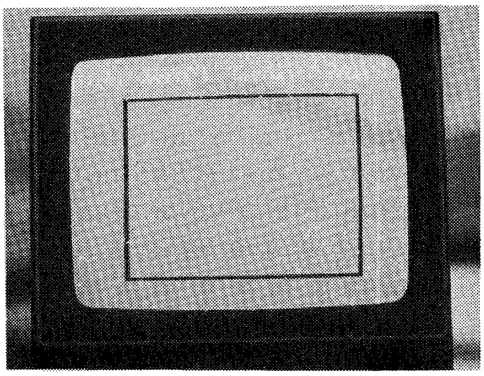

Fig. 3. An Example of the TV Image of the Oil Globules Dispersed in the Cream

alcohol and cetomacrogol were according to the Japanese Standards of Cosmetic Ingredients. Cetostearyl alcohol was a mixture of three parts of cetyl alcohol to two parts of stearyl alcohol. Sudan III dye of reagent grade was added to the oil phase in small quantities, 0.01% of the cream, to increase the contrast of oil globules for observation under a microscope.

Preparation of the Cream——The cream was prepared by a standardized procedure according to the formulas shown in Table I (modified from the cetomacrogol cream in B. P. Codex). Emulsification was carried out by adding the aqueous phase (90 °C) to the liquid oil phase (85 °C) and stirring the mixture untile the cream had cooled to 30 °C. Electroconductimetric data indicated that the cream was an oil-in-water emulsion.

Continuous Shear Test——A cone and plate viscometer (Isida high shear rheometer, model I) was used for continuous shear studies. It was connected with a flow curve recorder unit and an X–Y plotter. The apparatus constants had been obtained with standard liquids (JIS *Z*-8809) for calibrating viscometers.

Vertical Vibrational Test——After aging of the O/W cream for two weeks, the viscoelastic properties were measured at room temperature (in the vicinity of 20 °C) with a viscoelasto recorder (Sanki Engineering Co., VER-100), which was a vertical vibrating type apparatus. One ml of the cream was put in a cell (Fig. 1) of the viscoelasto recorder, and the gap between the inner and outer cells was set at 1.00 mm with an accuracy of 0.01 mm. The strain and stress under various vibrations imposed on the cream were obtained with strain gauges set on the holders of the inner and outer cells, for vibration over the frequency range from 3 to 100 Hz and amplitude of 50—250 μm. The stress/strain loop was obtained at the center on the oscilloscope of the viscoelasto meter every time by using the balancer of each strain gauge. Calibration constants of dynamic modulus G' and dynamic viscosity η' were obtained for the viscoelasto recorder by using an elasticity standard wired spring ($G=2.156\times10^5$ dyn/cm^2) and an oil viscosity standard (JIS *Z*-8809).

Particle Size Analysis of Oil Globules in the O/W Cream——The cream was diluted and particle size analysis was performed by using a particle size analyzer (Toyo Ink Co., Luzex 450 particle size analyzer), which consisted of a transistorized TV camera (Ikegami Tsushin Co., CTC-6000) set on a microscope (Nikon, Lur-Ke), and a TV set imaging the figures of oil globules, which were counted in terms of the size threshold. About one mg of the cream was taken periodically from the outer cell of the viscoelasto recorder into a test glass tube (18 cm length and 7.5 mm radius), and one ml of the aqueous phase of the cream (Table I) was added to the tube, then dispersed and diluted cream for observation under a microscope was obtained with a tube vibrator (Taiyo Co., Mixer 5F) operated for exactly 45 s. The relationship between the particle size distribution of the oil globules and the dispersing time with the tube vibrator is shown in Fig. 2. The particle size distribution was not constant at dispersion times between 10 and 30 s, but was constant over the dispersion time range from 30—60 s. The tube vibrator was usually used for 45 s. In Fig. 2, 0 μm particle size means a diameter of 1 μm and below of the globules, and 1 μm size means a diameter of 1 μm up to 3 μm. Figure 3 shows an example of the TV image of the globules, which were mainly spherical. The area of one observed microscope field was 3×10^5 μm^2, which contained about 300 globules in the O/W cream. It took less than two minutes to size and count these globules in a TV image at 2 μm intervals. Particle size analysis was base on about 2700 globules in 9 TV images.

Results and Discussion

Continuous Shear Test

The continuous shear flow curve for the cream was in the form of an anticlockwise hysteresis loop, as shown in Fig. 4. Yield value and apparent viscosity at the apex of the hysteresis loop were 250 dyn/cm^2 and 0.5 poise (obtained from Fig. 4). Yield values usually reflect structural networks extending throughout an entire system. To break such a network

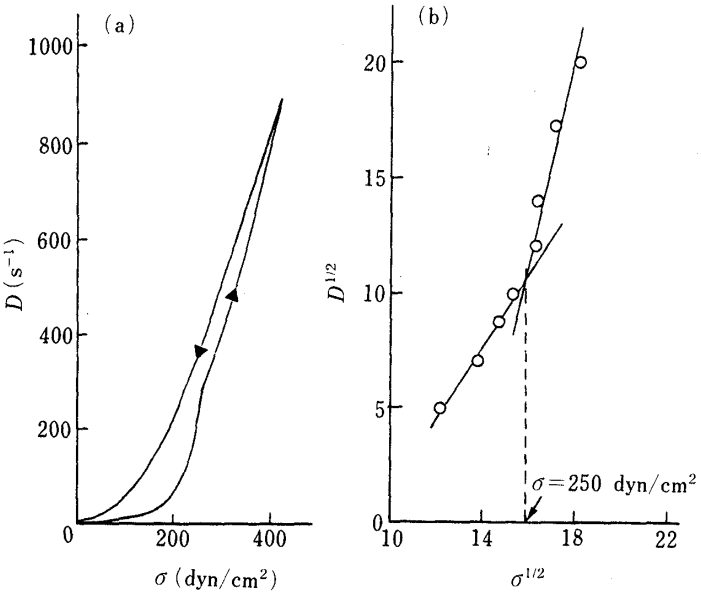

Fig. 4. (a) Flow Curve of Shear Rate, D (s^{-1}), *versus* Shear Stress, σ (dyn/cm^2), Obtained on a Cone-Plate Viscometer, and (b) Casson's Plot of $D^{1/2}$ *versus* $\sigma^{1/2}$ Obtained from the Up Curve of (a)

A yield value of 250 dyn/cm^2 was obtained from the inflection point in Casson's plot (b).

requires stresses equal to or exceeding the yield value. When the yield value is exceeded, the network is partly ruptured and flow occurs.

Vertical Vibrational Test

Dynamic modulus, G' and dynamic viscosity, η' of the cream were obtained with a vibrational viscoelasto recorder at an amplitude of 200 μm and frequencies of 3, 10, and 30 Hz for 20 min continuously as shown in Figs. 5 and 6. At the frequency of 100 Hz values of G' and η' were not reproducible. G' and η' decreased rapidly at the beginning of vibration in Figs. 5 and 6, because the vibration was started from the stationary state with the on–off switch of the apparatus. G' and η' behaved steadily after about 10 min. As shown in Fig. 5, the values of dynamic modulus, G', at 10 min were 5×10^5 dyn/cm^2 at the frequency of 3 Hz, 5.8×10^5 at 10 Hz, and 25×10^5 at 30 Hz. A positive correlation between G' and the frequency was observed. The dynamic viscosity, η' at 10 min (Fig. 6) was 145 P at a frequency of 3 Hz, 170 P at 10 Hz, and 46 P at 30 Hz. On the other hand, apparent viscosity determined by the continuous shear method was 0.5 P. The value of 46 P at 30 Hz is equal to the viscosity at the shear rate of 1.7 s^{-1} obtained from the plot of shear stress and shear rate (the up curve) in Fig. 4. This discrepancy in the value of viscosity may be due to the difference of methodology (static method with a cone-plate viscometer and dynamic method with a viscoelasto recorder). Figure 7 shows the relation of frequency to G', η', and loss modulus, G'', taken from Figs. 5

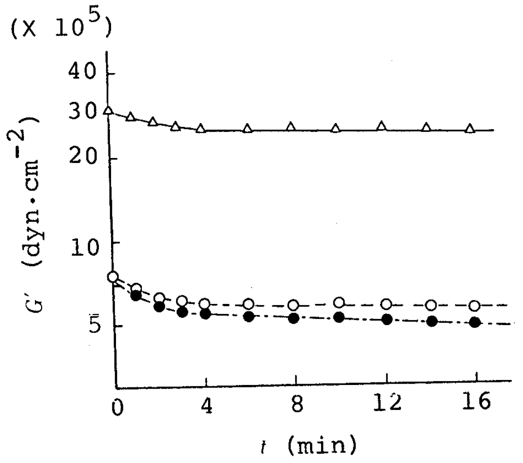

Fig. 5. Dynamic Modulus Data Obtained by the Vibrational Test Method

—△—, 30 Hz; --○--, 10 Hz; ---●---, 3 Hz.

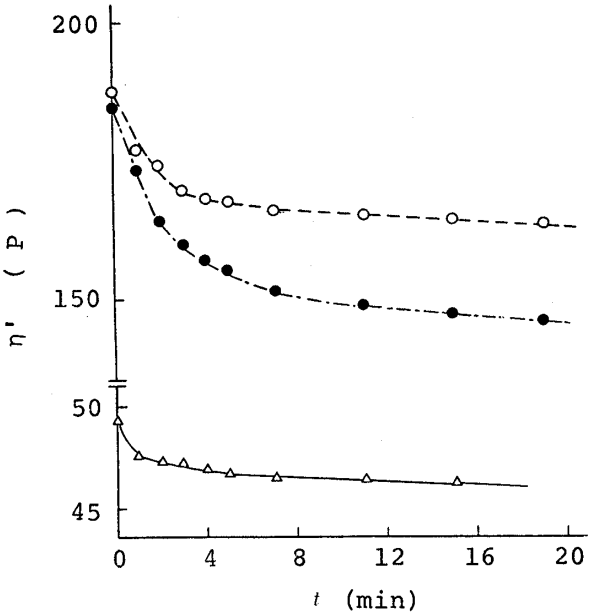

Fig. 6. Dynamic Viscosity Data Obtained by the Vibrational Test Method

—△—, 30 Hz; --○--, 10 Hz; ---●---, 3 Hz.

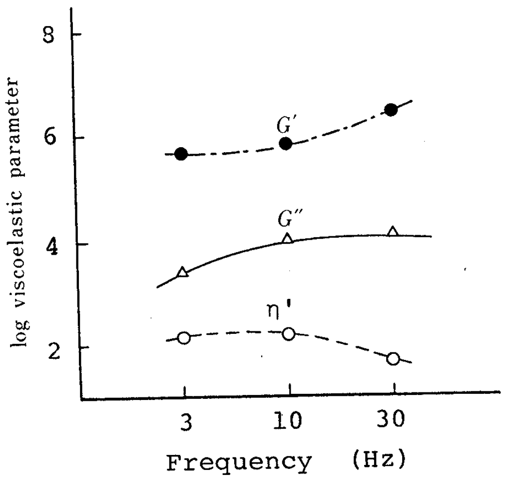

Fig. 7. Dynamic Viscoelastic Data Obtained from Figs. 5 and 6 at 10 min Vibration Time

Table II. Effect of Input Frequency on the Rate Constant for Breakdown of Viscoelastic Structure

Input frequency ν (Hz)	Rate constant k (s^{-1})	$t_{1/2}$ (min)	k/ν
G' 3	2.2×10^{-4}	52	7.4×10^{-5}
10	1.1×10^{-4}	102	1.1×10^{-5}
30	1.4×10^{-4}	82	4.7×10^{-6}
η' 3	9.0×10^{-5}	128	3.0×10^{-5}
10	4.2×10^{-5}	275	4.2×10^{-6}
30	3.6×10^{-5}	324	1.2×10^{-6}

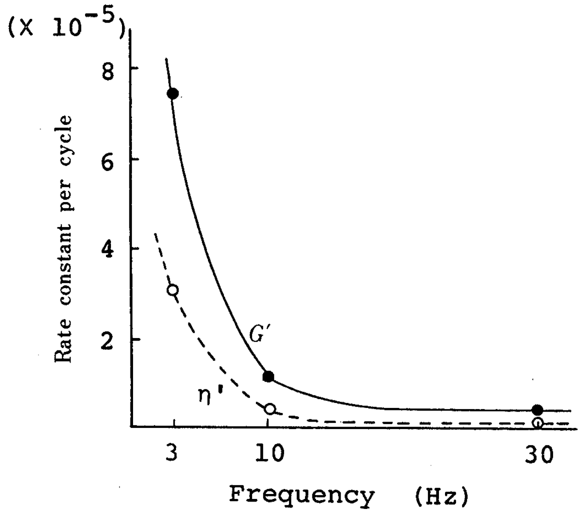

Fig. 8. Rate Constant per Cycle

—●—, dynamic modulus G'; --○--, dynamic viscosity η'.

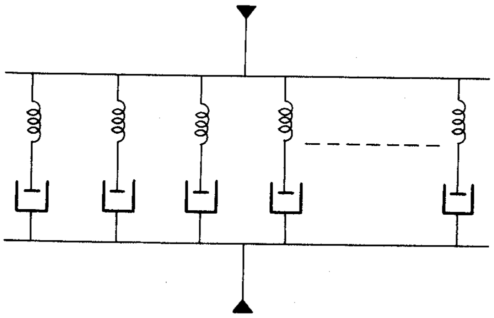

Fig. 9. Generalized Maxwell Model Representing the Behavior of a Viscoelastic Material

and 6 at 10 min. In the present experimental range of frequencies, the order, $G' > G'' > \eta'$ was obtained, as was found in an aqueous cream by Davis.8) This cream and the aqueous cream have similar formulations based on surfactant-long chain alcohol complexes, which give a self-boding action.13) It is known that a viscoelastic gel network links the emulsion droplets and entraps the continuous phase, thereby forming the highly elastic component.8,13)

G' and η' are plotted on a log scale against time in Figs. 5 and 6. After 7 min, these values decreased with time in a linear fashion. The rate constant, k, taken from the linear portion and the half-life period, $t_{1/2}$, as shown in Table II were calculated from a first-order representation. Frequency dependence of the rate constants was not observed for G', but was observed for the dynamic viscosity, η'. In the aqueous cream described by Davis,8) the rate constant of breakdown of viscoelastic structure (first-order representation) was $2.0 \times 10^{-3}\,s^{-1}$ at 7.9×10^{-3} Hz imposed oscillator frequency, although Davis did not divide the breakdown into viscosity and elasticity components. In the frequency range from 3 to 30 Hz, the breakdown of the elastic elements in the structure of the cream was shown to be around tenfold faster than that of viscous elements. If the same destructive process occurred at different frequencies, the amount of breakdown per cycle should be constant. The results in Fig. 8 show that the rate constants per cycle, $k_{G'}$ and $k_{\eta'}$, fall as frequency increases. That is, less structure is broken down per cycle at high frequency than at low; the mechanisms of breakdown are not frequency-independent.

The viscoelastic behavior of a semisolid material such as the cream used in this study may be considered, as described by Davis,$^{8)}$ in terms of a mechanical model made up of a combination of springs (elastic elements) and dashpots (viscous elements) as shown in Fig. 9. At high frequency, the springs can elongate and contract under imposed vertical vibration but the dashopts have very little time to move. The breakdown of the elastic elements, as shown in Table II, proceeded faster than that of the viscous elements.

Particle Size Analysis

The particle size analysis was difficult to perform. This was because the usual method is to dilute the emulsion so that there are approximately 500 oil globules in the field of view and then to rapidly size and count them (in less than 10 min).$^{14)}$ In this study, about 300 oil globules in the field of one TV image were sized and counted in less than 2 min using a particle size analyzer. The number of globules observed for one analysis were approximate 2700 globules in 9 TV image field. Typical particle size distributions are shown in Fig. 10; these were obtained from the cream under a vertical vibration at 10 Hz frequency and 200 μm amplitude. Although the cream was vibrated over 210 min, globules larger than 20 μm were not observed in this study. It was assumed that the density of this cream was 1.0 and that the volume of the dispersed oil phase was equal to that of the outer continuous phase. The average volume, surface area, and numbers of particles of oil globules in the cream were calculated, and the variations with time are shown in Figs. 11 and 12, respectively. It was found that the average volume of the globules in the cream increased with vibration time, while the interfacial area of the globules decreased, so the numbers of oil globules in one ml of the O/W cream decreased. These results can be interpreted as follows; network structure formed in the cream was destroyed by the imposed vibration. Owing to the coalescence of oil globules in the cream, the globules became larger with time.

The correlation between the number of globules in the cream and time in the frequency range of 10—100 Hz is shown in Fig. 12. At each frequency, the particle concentration, N (numbers/ml), decreased with time, t. According to Smoluchowski's theory,$^{15)}$ the particle concentration, N and vibration time, t have the following relation:

$$1/N = Kt + 1/N_0 \qquad (1)$$

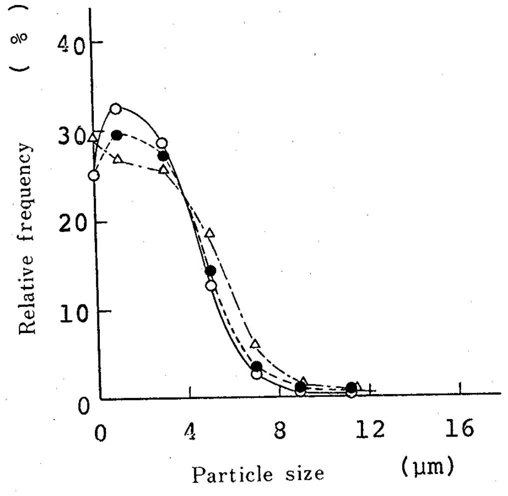

Fig. 10. Variation in Emulsion Particle Size Distribution with Time, $\nu = 10$ Hz, Strain Amplitude = 200 μm

—○—, 30 min; --●--, 120 min; ---△---, 210 min.

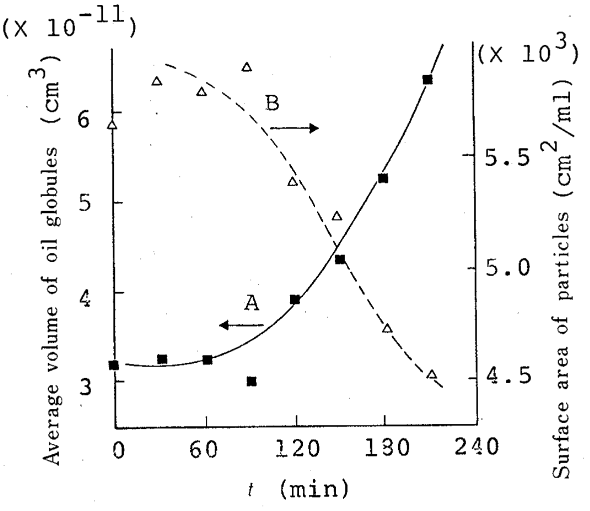

Fig. 11. Variation of Average Volume (A) and Surface Area (B) of Oil Globules with Vibration Time, Frequency = 10 Hz, Strain Amplitude = 200 μm

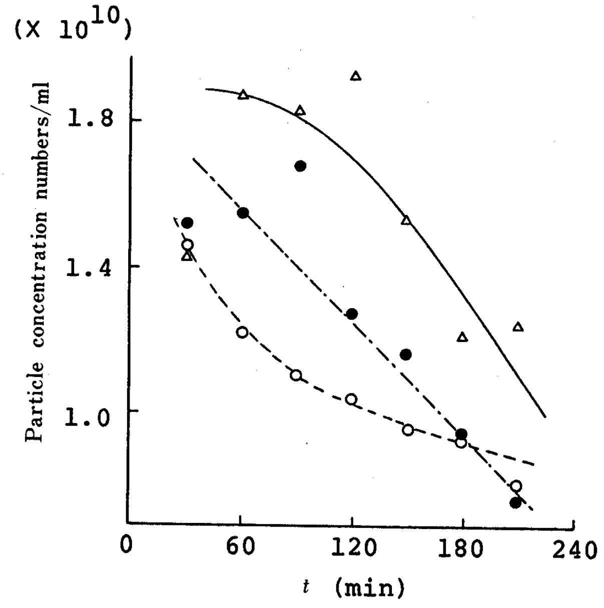

Fig. 12. Rate of Decrease in Particle Concentration with Time

—△—, 100 Hz; --○--, 30 Hz; ---●---, 10 Hz.

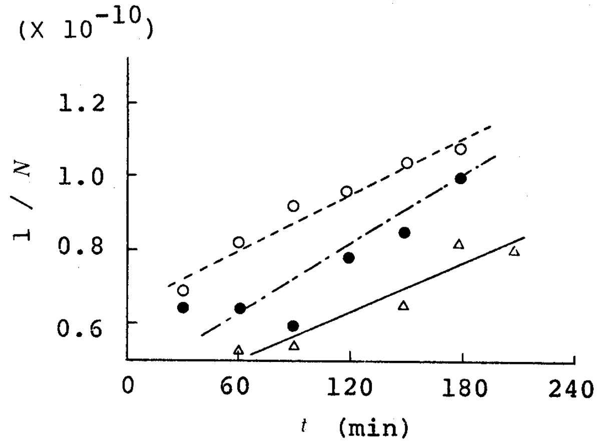

Fig. 13. Rate of Decrease in Particle Concentration as a Function of Time, Based on Eq. (1)

—△—, 100 Hz; --○--, 30 Hz; ---●---, 10 Hz.

Table III. Effect of Imposed Frequency on the Rate Constants, K, for Coalescence of Oil Globules Dispersed in the Cream

Input frequency (Hz)	K (s^{-1})	$t_{1/2}$ (h)
3	4.1×10^{-15}	4.2
10	4.5×10^{-15}	2.9
30	3.6×10^{-15}	5.5
100	3.5×10^{-15}	3.1

where K is the rate constant and N_0 is the particle concentration at the initial stage. Plots of $1/N$ against time, t, are shown in Fig. 13. The standard deviation (S.D.) and the coefficient of variation (C.V.) of the mean particle concentration N_0 in 9 TV images at the initial stage were $0.16 \times 10^{10}\ ml^{-1}$ and 8.7%. Despite inevitable errors in the particle size analysis of oil globules in O/W cream by microscopy, the plots of $1/N$ against time, t, were generally linear as shown in Fig. 13, although some deviations were observed. The slope of the regression line is the rate constant, K of coalescence in equation (1). The half-life period, $t_{1/2}$, was calculated by using the rate constant obtained from the equation (Table III). The values of K and $t_{1/2}$ of coalescence in the cream under vibration were 3.5×10^{-15} to $4.5 \times 10^{-15}\ s^{-1}$ and 2.9 to 5.5 h, respectively. It was clear that the vertical vibration imposed on the O/W cream caused coalescence of the oil globules in the cream at a rate of approximately $4 \times 10^{-15}\ s^{-1}$. When these results are compared with the breakdown of the viscoelastic structure in the cream, the rate of coalescence was slower than the rate of destruction of elastic elements (of the order of $10^{-4}\ s^{-1}$), or that of viscous elements (of the order of $10^{-5}\ s^{-1}$) of the cream by the imposed vibration.

Conclusions

Vartical vibration imposed on an O/W cream caused the breakdown of viscoelastic structure in the cream. The rate of destruction was of the order of $10^{-5}\,s^{-1}$ for viscosity, and $10^{-4}\,s^{-1}$ for elasticity, obeying a first-order representation. On the other hand, the coalescence of the oil globules dispersed in the cream occurred at a rate of $10^{-15}\,s^{-1}$. The breakdown of the viscoelastic structure was much more rapid than the coalescence. It is clear that vertical vibration imposed on an O/W cream accelerates the breakdown of the viscoelastic structure and the coalescence of the oil globules dispersed in the cream.

It is expected that this vibrational testing method will be useful to estimate the stability of O/W creams in comparative screening during development studies.

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References and Notes

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