

pH, the polymer could be useful in preparing an orally administered wax matrix product which releases most of its drug content in the intestinal tract.

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Particle Size Analysis of Latex Suspensions and Microemulsions by Photon Correlation Spectroscopy

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Abstract □ The particle size in microemulsions and other highly dispersed systems was determined by means of photon correlation spectroscopy (PCS). As PCS cannot be applied to highly concentrated dispersed phases, the measurement accuracy was tested for its dependence on the particle concentration using latex suspensions. The data obtained by clipping and scaling were compared. The particle size determination was expected to provide information about the influence of the structure of the surfactant system on microemulsions, using a homologous alcohol series as cosurfactant and potassium oleate as surfactant. In this system the region of solubilization is characteristically divided from the region of microemulsification by a zone of instability. Furthermore, there are distinct differences in mean particle sizes between microemulsions (9-30 nm) and micellar solutions (4-6 nm).

Keyphrases □ Particle size analysis—photon correlation spectroscopy, latex suspensions, microemulsions □ Photon correlation spectroscopy—particle size analysis, latex suspensions, microemulsions □ Microemulsions—particle size analysis, photon correlation spectroscopy, latex suspensions

Microemulsions appear as monophasic, more or less stable and transparent or slightly translucent, systems. They have been defined as dispersed liquid-liquid systems in which the particle size of the dispersed phase is <2000 Å. Shinoda and Friberg (1) assumed the existence of discrete micelles (oil-in-water) and reverse micelles (water-in-oil). According to the emulsion theory of Prince and co-workers (2, 3), these systems can be described as emulsions with highly dispersed internal phases. This definition includes the premise that there are essential differences between the microemulsion and the solubilization regions. The description of the structure of microemulsions as droplets is only valid for low concentrations of the internal phase. For high concentrations, Scriven (4)

postulates bicontinuous microstructures. This bicoherence of microemulsions was confirmed by Lindman *et al.* (5).

These are of interest since drugs applied topically are liberated more efficiently from microemulsions than from ointments composed of the same ingredients (6). Up to now most of the known microemulsions were made with toxic surfactants or with surfactants in very high concentrations, precluding pharmaceutical use. Therefore, an attempt is made herein to determine the dependence of microemulsion formation on the structure of the emulsifier system and on other such factors, in order to find suitable excipients in suitable concentrations.

THEORETICAL SECTION

Light-scattering techniques are used extensively when testing microemulsions (7-12). In the following, the mean particle diameter was determined by photon correlation spectroscopy (PCS) (13, 14). A laser beam is sent through a sample and the scattered light is detected by a photomultiplier at a certain angle. The time-dependent periodical fluctuations of the scattered light are analyzed. Smaller particles diffuse faster than larger ones and, thus, cause a more rapid fluctuation of the intensity of the scattered light. The signal received by the photomultiplier is evaluated by a correlation function $C_{(t)} = e^{-t/\tau}$, where τ stands for the time and t for the correlation coefficient that describes the decay of this correlation function. The correlation coefficient is related to the diffusion coefficient D by $t\tau = 1/2DK^2$, where K is the absolute value of the scattering vector. As $t\tau$ and K can be calculated, the diffusion constant D can be obtained; this is related to the particle radius by the Einstein relationship:

$$\bar{r} = \frac{k \cdot T}{6 \pi D \eta}$$

Table I—Particle Radii of Latex Suspensions (19 nm)

Particle Conc., µg/L	Radius, nm ^a	Measuring Error, %
0.05	19.3	1.6
0.1	19.2	1.1
0.25	19.4	2.1
0.5	18.9	-0.5
1	18.7	-1.6
2.5	17.8	-6.3
5	17.2	-9.5
10	16.4	-13.7
25	15.3	-19.5
50	13.8	-27.4

^a Determined by photon correlation spectroscopy.

Table II—Particle Radii of Latex Suspensions (54 nm)

Particle Conc., µg/L	Radius, nm ^a	Measuring Error, %
0.1	62	14.8
1	51	-5.6
5	50	-7.4
10	50	-7.4
20	49	-9.3
50	49	-9.3
100	50	-7.4
250	46	-14.8
500	46	-14.8
1000	44	-18.5
2500	32	-40.7

^a Determined by photon correlation spectroscopy.

Table III—Particle Radii of Latex Suspensions (110 nm)

Particle Conc., μg/L	Radius, nm ^a	
	Clipping Mode	Scaling Mode
0.1	181	—
1	128	139
10	113	112
50	115	113
100	109	113
500	103	104

^a Determined by photon correlation spectroscopy.

Table IV—Particle Radii of Latex Suspensions

Particle Conc., μg/L	Radius, nm ^a	
	Clipping Mode	Scaling Mode
1	228	259
10	229	226
50	235	244
100	222	225
500	209	213
1000	95	84

^a Determined by photon correlation spectroscopy.

where k is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the external medium, and \bar{r} is the mean hydrodynamic radius.

EXPERIMENTAL SECTION

Materials—To determine the functional capacity of the measuring apparatus, monodispersed latex suspensions¹ (10% dry weight) were used which had particles of the following diameters ($\pm SD$): 0.038 (± 0.0075) μm , 0.109 (± 0.0027) μm , 0.220 (± 0.0065) μm , 0.497 (± 0.0059) μm . The quantity of particles was $1.37 \times 10^{14}/\text{mL}$ for the 109-nm suspension. The stock suspensions were diluted with fresh twice-distilled water. To eliminate dust, the samples were purified using membrane filters² (0.22–0.8 μm), which were attached to 10-mL disposable syringes. The microemulsions were prepared using twice-distilled water, potassium oleate³, liquid paraffin oil⁴, and pentanol⁵, hexanol⁵, or heptanol⁵. The potassium oleate was taken from one homogeneous batch. The alcohols were used without further purification.

Apparatus—The measuring apparatus consisted of an argon laser⁶, a temperature-stabilized measuring cell, and a photomultiplier⁷. This setup was fitted on an optical bank, which was stabilized against vibrations by placement on a slab of marble buffered with special shock absorbers. The sample was tempered (± 0.05 K) by means of a matching fluid, regulated by a temperature controller. To eliminate the vibrations of the elastic-tube pump, the matching fluid flowed through a collecting vessel before it was returned to the measuring cell. The photomultiplier detected the scattered light to an angle of 90° .

On the basis of the photomultiplier signals the correlation function was calculated in a correlator⁸. If necessary a clipping counter⁹ was added. The correlator data were analyzed in a computer¹⁰ and simultaneously stored in a data logger. The data were transferred from the correlator to the computer using an interface constructed specifically for this purpose. This interface was connected between the punch-outlet of the correlator and the computer input terminal. This not only allowed the data transfer, but also permitted the computer to control the correlator functions.

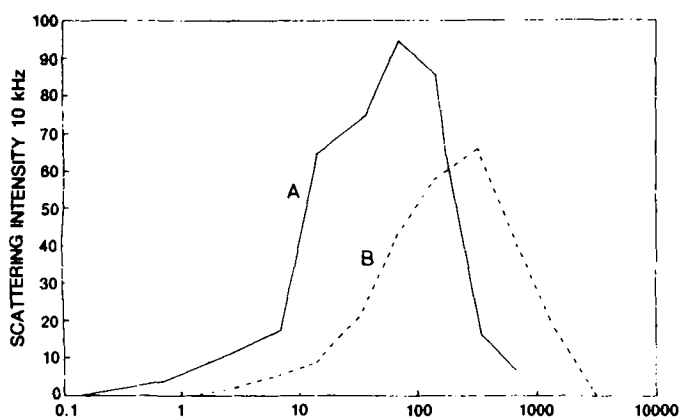


Figure 1—Scattering intensity in dependence on the concentration of the particles. Key: (A) 55 nm; (B) 19 nm; A, units are $\times 10^{10}/\text{mL}$; B, units are $\times 10^{12}/\text{mL}$.

RESULTS AND DISCUSSION

The mean radii of the particles were determined by photon correlation spectroscopy (PCS) on the basis of the diffusion coefficients. This required an unhindered diffusion. Higher particle concentrations resulted in measuring faults because of an interaction between the particles on the one hand and the multiple scattering on the other. The use of a structure factor should correct for these errors (15–19). While the interactions between the particles leads to lower diffusion constants, the multiple scattering produces a higher fluctuation of scattered light intensity. The described effects result in a stronger decaying correlation function together with a higher diffusion constant and a smaller particle radius. Therefore, the determination of highly concentrated suspensions and emulsions is difficult. To determine the dependence of the measurements on the particle concentration, latex suspensions with different particle sizes were measured in a dilution series (Tables I–IV). The measuring errors obtained in the clipping and scaling modes are also compared (Tables III and IV).

In the latex suspensions of 19-nm particles (Table I) the particle radii were almost constant over a wide range of concentrations (50–1000 $\mu\text{g/L}$). In higher concentrations, the measured value was markedly low. Comparable results were obtained for the other particle sizes (Tables II–IV). In some cases, measuring errors of $>60\%$ were observed. Hence, from the standpoint of accuracy of measurement, the results of some reports (20) which neglect this effect for microemulsions are in doubt. The observed error is less in emulsions than in suspensions, but in certain concentrations, errors result whereby the data is $>50\%$ too low. If Nichol森 *et al.* (20) measure a particle radius of 2–3 nm in their microemulsions, the consideration that the micelle diameter must be at least twice the molecule length of the surfactant plus the diameter of the aqueous (oily) core reveals that their value must be too low. Moreover, the PCS determines the hydrodynamic diameter, which means that higher values are more probable.

If the scattering intensity is plotted against the particle concentration, the curves show a maximum of the scattered light (Fig. 1). When this maximum is exceeded, back-scattering predominates and the measuring error increases. The reproducibility of the experimental results is dependent on the scattering quality of the sample. It decreases when the scattering intensity, *i.e.*, the signal–noise ratio, is low. With low particle concentrations, the relative standard deviation of the results was ~ 1 –3%. If the measuring conditions were good, a reproducibility of $\pm 0.5\%$ could be obtained. At a measuring angle of 90° , an optimal reproducibility within a wide concentration range of latex particles was observed.

Table V—Particle Sizes of Microemulsions Prepared with the Same Molar Concentrations of Different Alcohols^a

Potassium Oleate, %	Alcohol, mol/L	Particle diameter, Å		
		Pentanol	Hexanol	Heptanol
1.5	0.964		225	155
	0.803		205	121
	1.852	228	130	
2.5	0.482		211	110
	0.642		198	102
	0.803		128	102
	0.964		112	97
	1.124		105	108
3.0	1.482	220	95	
	1.666	164	95	
	0.642		141	92
	0.803		127	88
	0.964		108	85
	1.124		97	89
	1.296	135	101	

^a Measured by photon correlation spectroscopy shortly after production; water content 3.6%.

¹ Dow Chemical.
² Millipore Corp.
³ Depuratum grade; Roth, Karlsruhe, FRG.
⁴ Pharmacoepia quality DAB 8.
⁵ Merck, FRG.
⁶ Model 162-03, maximum output 18 mW, air cooled; Spectra-Physics.
⁷ Malvern, U.K.
⁸ Model K 7023 with a connected memory; Malvern, U.K.
⁹ Model R 95; Malvern, U.K.
¹⁰ Tektronix 4052.

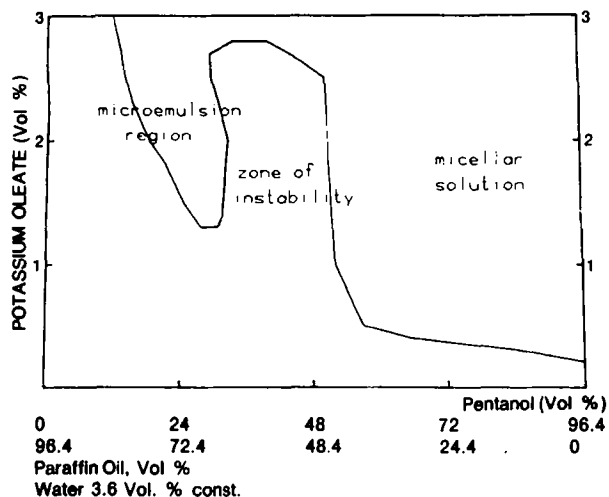


Figure 2—Component diagram with pentanol.

To eliminate the concentration error, microemulsions with low concentrated dispersed phases (3–6%) were measured. Microemulsion formation could already be found at a surfactant–cosurfactant concentration of 5–10% (w/w). Thus, the sample remains in a measurable concentration range for the PCS, which is also characterized by a 5–10% particle concentration in other reports (8, 19). Shinoda (21) describes microemulsions with such low surfactant–cosurfactant fractions, but he defines them as “solubilized solutions.”

The tested systems consisted of a constant water fraction of 3.6%, a potassium oleate component of 0.5–3.0%, alcohol as cosurfactant, and liquid paraffin oil, added to obtain 100% volume. To determine the microemulsion region, component diagrams for each alcohol were established. They show the dependence of the microemulsion formation on the surfactant structure. The homogeneous alcohol series butanol, pentanol, hexanol, heptanol, octanol, and decanol was used. A distinct microemulsion region could only be observed for pentanol, hexanol, and heptanol at these concentrations (Figs. 2–4). Other ranges of concentration also show a distinct microemulsion formation using the remaining alcohols. Baviere *et al.* (22) describe that—in addition to the surfactant structure—factors such as salt concentration have an influence, but they are not considered here.

Figure 3 shows that hexanol is a particularly good cosurfactant. A minimum surfactant quantity (~1%) must exist before water-in-oil microemulsions are formed. Higher surfactant concentrations (2%) result in a lower particle diameter due to an optimization of the surfactant–cosurfactant ratio. The optimal surfactant–cosurfactant ratio is ~1:3 for hexanol. If the surfactant content is below the optimum, it can be compensated to a certain degree by a higher quantity of cosurfactant. With pentanol, microemulsion formation requires higher quantities of surfactant and cosurfactant. The microemulsion region is smaller than that of hexanol and shifts to higher pentanol and potassium oleate concentrations. The more hydrophilic pentanol has a larger region of solubilization than hexanol. The microemulsion region of heptanol is smaller than the other alcohols. Heptanol is more lipophilic; therefore,

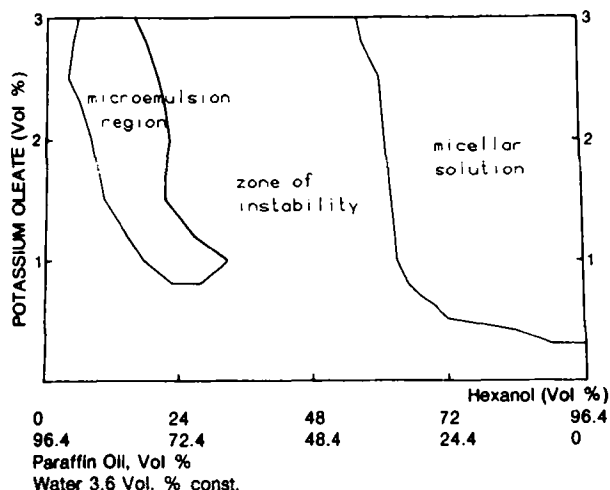


Figure 3—Component diagram with hexanol.

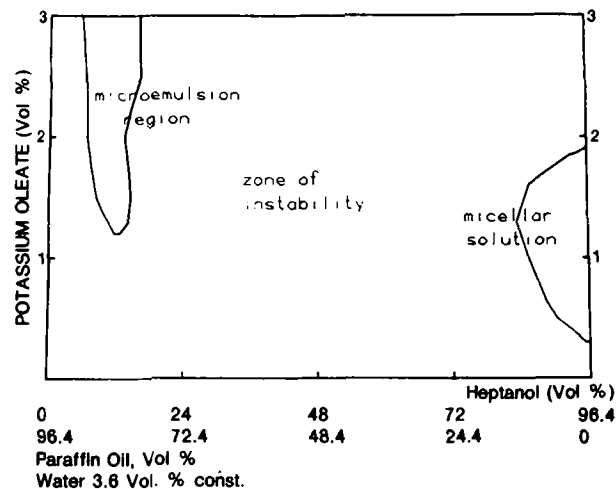


Figure 4—Component diagram with heptanol.

microemulsions are formed at a lower cosurfactant concentration. However, the solubilization region is narrower.

If microemulsions are considered as swollen micelles, an abrupt diminution in particle size from the macroemulsion to the microemulsion region, and after that a continuous transition to a micellar solution, should be expected. According to the emulsion theory, there should be a distinct separation between the solubilization and the microemulsion regions due to the transition of a single-phase liquid into a system with at least two phases characterized by micelles with different diameters. Between the two regions an instability zone is assumed, with big particles (in the dimension of macroemulsions) caused by coalescence. Such a zone was discovered in the component diagrams of the above systems. The storage tests showed that the microemulsions are unstable and that the dispersed phase undergoes coalescence toward the macroemulsion and also toward the solubilization regions. This fact was unexpected.

The change in particle diameter can be investigated by PCS with great accuracy and little difficulty using the specimen tubes as storage containers for the emulsions. The measured particle diameters of the microemulsions were 9–30 nm; those of the micellar solutions were 4–6 nm and smaller (Figs. 5–7). The most apparent increase in particle size before the zone of instability toward the solubilization region was observed in microemulsions prepared with hexanol. Curve B in Fig. 6 (1.5% potassium oleate) reveals a relatively big particle diameter of 225 Å at the border of the microemulsion region toward the macroemulsions. With increasing alcohol concentration, the particle diameter decreases to 160 Å. This is the smallest possible particle size at this surfactant–cosurfactant ratio, and it is constant over a wide range. Before the zone of instability, a distinct increase in particle diameter of up to 225 Å can be seen. This effect is even more obvious in the case of microemulsions with 1.0% potassium oleate (Fig. 6, curve A). After having reached 280 Å, the smallest possible particle size, a considerable increase (up to 400 Å) was found. The particle sizes measured in microemulsions with pentanol

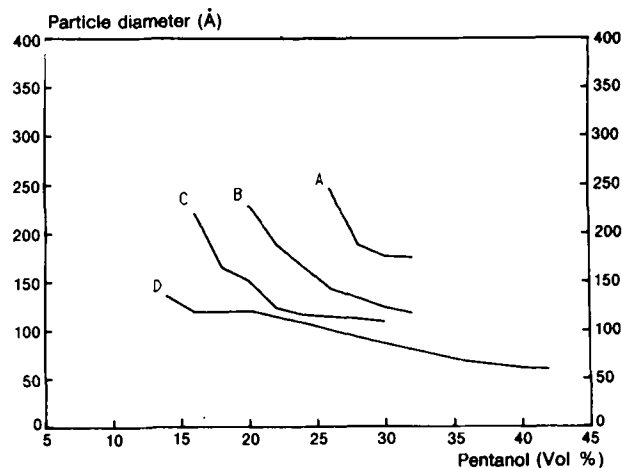


Figure 5—Particle sizes of microemulsions with pentanol (cf. Fig. 2), measured shortly after production. Composition: 3.6% water, potassium oleate, and pentanol, q.s. to 100% with paraffin oil. Potassium oleate content: (A) 1.5%; (B) 2.0%; (C) 2.5%; (D) 3.0%.

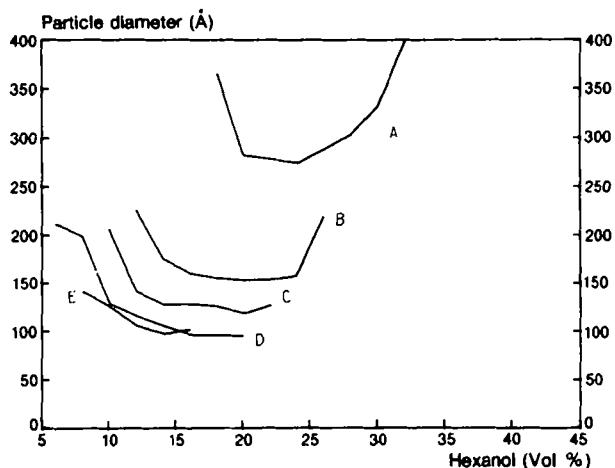


Figure 6—Particle sizes of microemulsions with hexanol (cf. Fig. 3), measured shortly after production. Composition: 3.6% water, potassium oleate, and hexanol, q.s. to 100% with paraffin oil. Potassium oleate content: (A) 1.0%; (B) 1.5%; (C) 2.0%; (D) 2.5%; (E) 3.0%.

(Fig. 5) show a comparable alteration. However, the increase in droplet diameter before the zone of instability appears only during the aging process and is less distinct. Constant surfactant concentration together with low cosurfactant concentrations result in big particles. If the cosurfactant concentration increases, the particle sizes decrease toward a minimal limiting value. It is remarkable that in microemulsions with hexanol, a minimal particle size of 95 Å appears (Fig. 6, curve D), which cannot be lowered by a further increase of the surfactant and cosurfactant concentrations (Fig. 6, curve E). The same limiting value can be found in microemulsions with pentanol.

The particle sizes of the emulsions formed by a minimum fraction of cosurfactant (e.g., pentanol) decreased from 246 to 135 Å relative to increasing surfactant concentration (1.5 to 3.0%), due to the optimization of the sur-

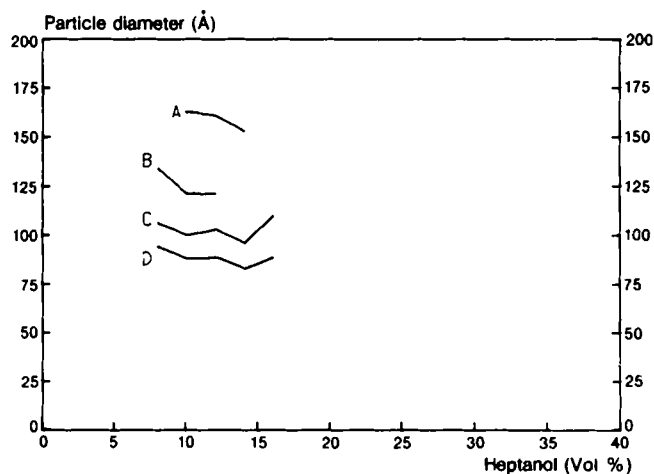


Figure 7—Particle sizes of microemulsions with heptanol (cf. Fig. 4), measured shortly after production. Composition: 3.6% water, potassium oleate, and heptanol, q.s. to 100% with paraffin oil. Potassium oleate content: (A) 1.5%; (B) 2.0%; (C) 2.5%; (D) 3.0%.

factant-cosurfactant ratio. Figure 5 shows a continuous transition from the microemulsion to the solubilization region if the microemulsion contains ~3% potassium oleate. This seems to contradict the results described before. However, it has to be considered that the emulsions in this region break after a short storage time (23). Thus, a separation in the microemulsion and solubilization regions was obtained, and the continuous transition disappeared. With regard to the particle sizes and their alteration during the storage, the cosurfactant heptanol is comparable with pentanol. On the other hand, the formation of microemulsions is reduced to a smaller region. What is important is that the particle sizes decrease with the increasing chain length of the alcohol. Table V compares the particle sizes of microemulsions prepared with the same molar concentrations of differing alcohols.

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