# The Distribution of Oleic Acid Between Salbutamol Base Drug and Different Propellant Blends

**Patrik M. Eriksson,[1,2] Kenneth B. Sandström,[1] and Jarl B. Rosenholm[1]**

*Received August 8, 1994; accepted December 6, 1994*

The distribution of oleic acid between Salbutamol base drug and the solvent in metered-dose inhalers (MDI's) has been investigated. The equilibrium surfactant concentration in the drug dispersions has been determined using a colorimetric method. The samples examined contained Salbutamol base drug particles and oleic acid dispersed in different propellant blends of freon 11 and 12. The maximum equilibrium concentration observed depended on the propellant blend used. The propellant blend and the distribution of the surfactant affected the dispersion stability. The effect of the surfactant is illustrated by the adsorption isotherm for oleic acid onto the Salbutamol particles. The results are correlated with zeta-potentials and particle size measurements made on similar systems in order to characterize the properties of surfactant stabilized MDI's.

**KEY WORDS:** salbutamol base drug; oleic acid; propellant; metered-dose inhaler; stability; adsorption.

## INTRODUCTION

Inhalation aerosol devices such as metered-dose inhalers (MDI's), used in the treatment of asthma, consist of a pressurized chamber containing usually a liquid propellant mixture of freon 11 and freon 12, in which the active drug is dispersed. The pressurized container is most often equipped with a metered valve delivering a preselected dose of the drug in the inhaled airstream. The inhalation aerosol formulations require some surface active substances in order to aid the formation and to enhance the stability of the dispersion. The drug particles in the dispersion, being of precolloidal size, have a tendency to sink or to float in the pressurized container. It is thus important to identify the factors that are predetermined for the dispersion stability and to find the optimum type of the surfactant and its concentrations. Because of disadvantages resulting from too high surfactant concentrations, it is desirable to control the critical stability properties by keeping the concentration as low as possible. High surfactant content may result in enhanced dissolution of the drug and a subsequent recrystallization, resulting in particle growth.

Unsaturated fatty acids have successfully been used to stabilize nonaqueous dispersions (1–4). In order to optimize the dispersion stability it is important to characterize the adsorption mechanism in detail. With oleic acid a reorientation of the molecules at the particle surface has been found to occur followed by a multilayer adsorption at higher concentrations (1,4,5).

The pharmaceutical dispersions for MDI's can be considered as nonaqueous, nonpolar, dispersions for which the dielectrical constant is very low. Therefore the influence of the surfactants on the stability of the dispersion is different from that of aqueous dispersions. One consequence of this is that only a very small amount of charged species can be formed and stabilized in the pure anhydrous solvent and the DLVO-theory is as such not applicable.

The propellants 11 and 12 contain various amounts of fluorine and chlorine, which introduces differences in the acid-base properties. We have chosen to relate the acid-base properties by estimating the ratio of the values of the polarizability ($\alpha$) and the dipole moment ($\mu$) of the molecules. Drago and co-workers have used this ratio to define the softness and the hardness of the molecules (6,7). These aspects of the aprotic propellants 11 and 12 have been discussed in detail in an earlier communication (8).

The aim of this investigation is to characterize the distribution of oleic acid between the Salbutamol base drug and different propellant blends. In order to evaluate the influence of the adsorbed layer on the macroscopic stability the results are further related to measured zeta-potential and particle size, which has been reported in detail elsewhere (8). This report focuses on the adsorption of oleic acid onto the drug particles providing a more elaborated insight to the factors that control the stability of MDI's.

## EXPERIMENTAL

The concentration of free fatty acid in solution was measured using a colorimetric method, reported by Lowry and Tinsley in 1976 (9). The method is based on the formation of a free fatty acid complex with cupric acetate and the surfactant. The formed complex absorbs UV-light at 715 nm, which can be monitored by UV-spectroscopy.

The samples for the determination of free oleic acid were prepared to comply with the samples for the zeta-potential and particle size measurements (8). Each sample contained 0.16 w-% of micronized Salbutamol base and different concentrations of oleic acid. The dispersion was left to stabilize after preparation, and shaken by hand at regular intervals for two days, before further treatment. A cream of Salbutamol particles was formed at the liquid surface during storage and the almost clear continuous phase was filtered through a 0.2 μm Millipore Millex-FGS single use filter. In order to keep the sample pressurized throughout the filtration procedure a filtration system was constructed, according to the setup in Figure 1. Using the liquid densities the corresponding volume could be obtained by weighing the glass containers before and after treatment. The filtrated phase was then allowed to evaporate through the continuous working valve leaving only the surfactant unadsorbed and eventually some dissolved Salbutamol in the container. The remainder was then dissolved in benzene from which the surfactant concentration was analyzed. The absorbance of the cupric acetate complex was measured with a Schimazdu UV-240 UV-VIS spectrometer at 715 nm and at 25°C.

[1] Department of Physical Chemistry, Åbo Akademi University, Porthansgatan 3-5, FIN-20500 Turku, Finland.
[2] To whom correspondence should be addressed.



0724-8741/95/0500-0715$07.50/0 

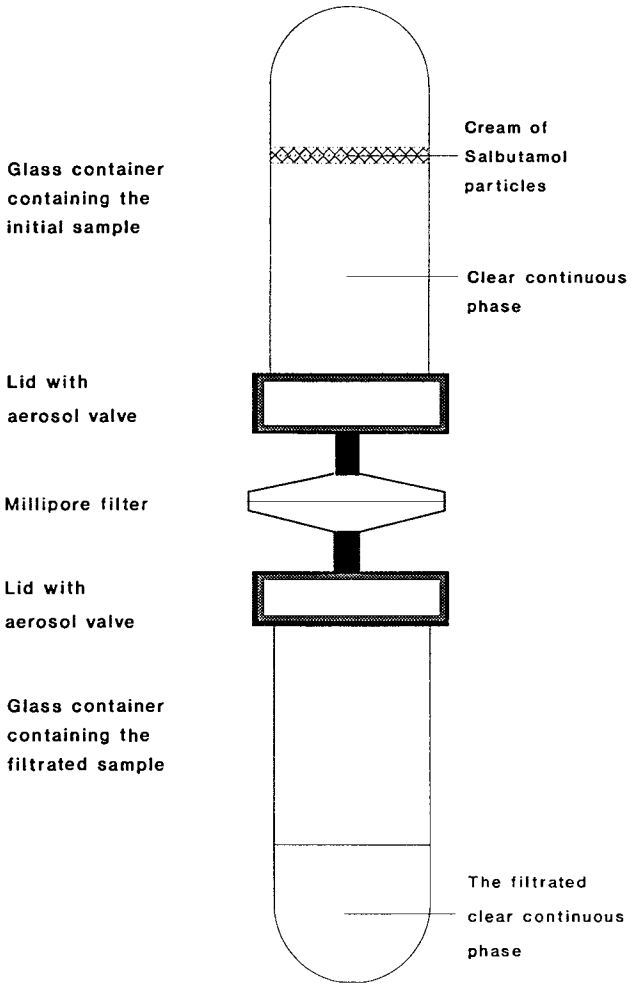


Fig. 1. The filtration system.

## MATERIALS

The micronized drug used was a Salbutamol base powder, 2-(tert-butylamino)-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol (Huhtamaki OY Leiras, Finland. lot 914098) with a specific surface area of 8.8 $m^2/g$ (B.E.T., nitrogen adsorption). The surfactant used was oleic acid, cis-9-Octadecenoic acid, (MERCK 471, extra pure). The propellants were trichloromonofluormethane (P11) and dichlorodifluoromethane (P12). The reagents used for the colorimetric method were benzene, pro analysis from MERCK, Cupric acetate, monohydrate from Sigma and Pyridin, 99% purity from Sigma.

## RESULTS AND DISCUSSION

At first we investigated if possible dissolved Salbutamol drug could affect the concentration measurements. Two calibration curves were constructed, one containing some amount of dissolved Salbutamol and one with only the surfactant in pure benzene. Using the same concentrations of oleic acid as used in the MDI-samples (0–6 mM) no differences could be observed between the two calibration curves. Hence the dissolved salbutamol drug did not affect the measurements.

No formation of dimers or polymerized fatty acids at high concentration (4,10) was observed as deducted from the linear intensity concentration relationship for each calibration curve. A reduction in the peak height at 715 nm of the cupric acetate complex occurred only after equilibrating with salbutamol base in MDI's. This indicates that the reduced amount of oleic acid in the dispersion medium is due to the adsorption of the surfactant onto the Salbutamol particles.

To verify that the oleic acid really had adsorbed onto salbutamol we collected the particles left in the Millipore-filters, during the filtration process, and analyzed these by in situ measurements, using Diffuse reflectance Infrared spectroscopy (Kubelka Munck). A Bruker IFS 66, FRA 106 Fourier transform infrared spectrometer was used. We could from these measurements qualitatively observe a change in the peak area for the $CH_3$- and the $CH_2$-groups (at 3005–2850 $cm^{-1}$), with the different amounts of oleic acid correlating with the colorimetric method used.

The distribution of oleic acid between Salbutamol base and different propellant blends was then determined, for different blends of freon 11 and 12, using the colorimetric method. The initial surfactant concentration in these samples were 0–6 mmol/l. The amount of oleic acid adsorbed onto salbutamol from pure freon 11 and from a 50:50 or 30:70 blend of propellant 11 and propellant 12 is shown in Figure 2. It is clear that the type of dispersion medium plays an important role for the distribution of oleic acid between the liquid phase and the Salbutamol particles. Equilibrium concentrations up to 6 mmol/l (or more) can be achieved in propellant 11 but introducing the low boiling propellant, freon 12, a limited equilibrium concentration is observed. The maximum equilibrium concentration is further lowered with the increase of freon 12, being about 2.9 mmol/l for the 50:50 blend and about 1.7 mmol/l for the 30:70 blend. The results suggest that the limit of oleic acid dissolution in the drug suspension depends on the propellant blend.

The influence of freon 12 on solubility is due to its inferior solvent property compared with freon 11 (11). The different acid-base properties of freon 11 and 12 also play a

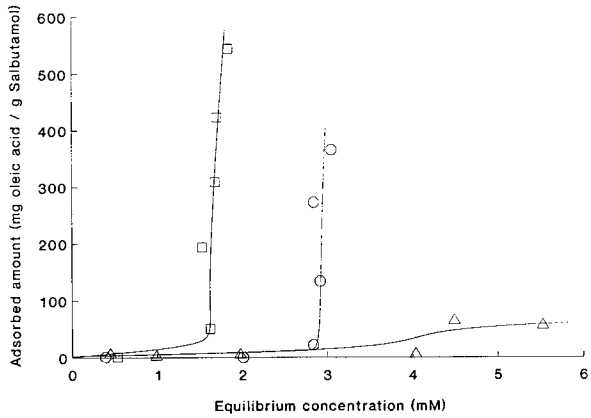


Fig. 2. The adsorption isotherm for sample series containing 0.16 w% Salbutamol base. Adsorbed amount (mg oleic acid/g Salbutamol) as a function of the equilibrium concentration oleic acid (mM). The dispersion medium is P11 △, (50:50) ○ or a (30:70) □ blend of P11:P12.

significant role. Freon 12, with the $\alpha/\mu$-ratio of 4.6 $m^2C^{-1}$, is a harder molecule than freon 11, with the $\alpha/\mu$-ratio of 6.3 (8). The $\alpha/\mu$-ratio affects the interactions between the particles and the surfactant on the one hand and between the particles and the solvent on the other hand. The more freon 12 the dispersions contains the stronger the oleic acid is assumed to adsorb onto the drug particles. We thus can say that both the dispersion medium and the surfactant are competing for the surface sites on the particles. Adsorption may involve the formation of a monolayer, which would correspond to a concentration difference of approximately 0.004 mmol/l, between the equilibrium and the initial oleic acid concentration, if we assume horizontal adsorption. A monolayer of a so-called two-point attachment would correspond to a reduction of approximately 0.07 mmol/l and a reduction of approximately 0.13 mmol/l for vertical adsorption. These concentrations relate to 0.16 w-% Salbutamol base particles with the specific area of 8.8 $m^2/g$ (8) calculated from the area per molecules given in the literature (2,4,5,12). In order to characterize the adsorption to a monomolecular layer a sample series containing an excess amount of Salbutamol, 1.0 w-% instead of 0.16 w-% was prepared. The freon 11 and 12 ratio was 30:70, and the initial concentration range of oleic acid 0–2 mmol/l. Instead of drawing the adsorbed amount against the equilibrium concentration we applied a modified Langmuir isotherm equation to fit these results according to equation 1 (13):

$$\frac{c}{n_2^s/w} = mc + b \tag{1}$$

where $(n_2^s/w)$ is the number of moles of solute (component 2) adsorbed per unit weight of adsorbent, c is the surfactant concentration at equilibrium and m and b are constants. By plotting $c/(n_2^s/w)$ versus c we received a straight line with the slope m, as shown in Figure 3. We obtained the value 55.86 * $10^3$ g/mole for the slope and 4.80 g/l for the intercept by linear regression. The occupied area per molecule for oleic acid could then be calculated for the saturation adsorption using equation 2 (13):

$$(n_2^s/w)_{sat} = A_{sp}/N_A\sigma^0 \tag{2}$$

where $A_{sp}$ is the specific area of the adsorbent (8,8 $m^2/g$), $N_A$ is the Avogadro's number and $\sigma^0$ is the occupied area per molecule. The calculated value for $\sigma^0$ was 81.6 $Å^2$/molecule, which corresponds to a horizontal adsorption of oleic acid (2,4,5,12). The equilibrium constant, K′, for the adsorption reaction is defined as $K * a_1^b$. K is a constant which can be calculated from the Langmuir curve according to equation 3 (13):

$$K = \frac{m}{b} \tag{3}$$

and $a_1^b$ is the activity of the solvent (component 1) in the solution. We can assume that the activity of the solvent is constant in the system during the adsorption reaction and therefore $a_1^b \sim 1$ and $K \sim K'$. We received the value 11.6 * $10^3$ l/mole for K. The value for K could then be used in equation 4 (13):

$$\theta_2 = \frac{Ka_2^b}{Ka_2^b + 1} \tag{4}$$

where $a_2^b$ is the activity for the surfactant (component 2) in the solution. By replacing the activity with the concentration we were able to plot the fraction of the surface occupied by the surfactant, $\theta_2$, as a function of the surfactant concentration for this system (Figure 4). We can see that the curve levels out at about 0.7–0.8 mM, which means that the monolayer is almost completed at this concentration.

The zeta-potential has been shown to be a reliable indicator of the stability and of the acid-base property of nonaqueous dispersions (1,3,14–22). We had previously modified a cell that made it possible to measure the zeta-potential directly from a pressurized MDI. Here we measured the zeta-potential of micronized Salbutamol base suspended in different propellant blends of freon 11 and 12 using Malvern Zetasizer IIc particle electrophoresis analyzer and a modified Malvern ps26 nonaqueous cell. The samples measured

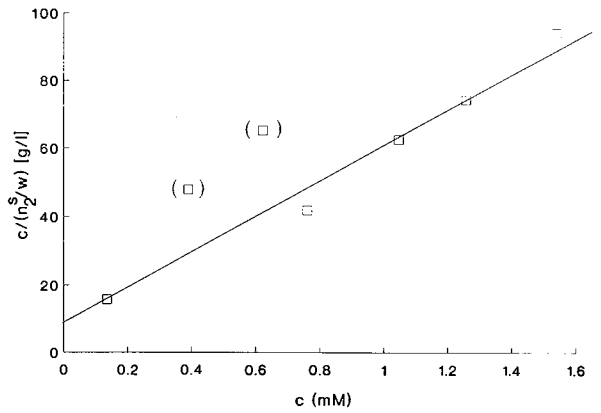


Fig. 3. The Langmuir isotherm for a sample series containing 1.0 w-% Salbutamol base. The equilibrium concentration oleic acid divided by the number of moles of oleic acid adsorbed per unit weight of Salbutamol base, $\{c/(n_2^s/w)\}$ [g/l], as a function of the equilibrium concentration oleic acid, c (mM).

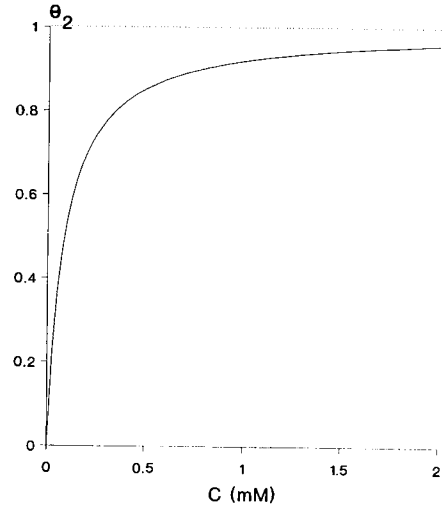


Fig. 4. Schematic plot of the Langmuir equation showing the fraction of the surface occupied by the surfactant, $\theta_2$, as a function of the concentration, c (mM).

had the same composition as those in Figure 2. The zeta-potential initially increased to a maximum with increasing oleic acid concentration at low surfactant concentrations. By increasing the surfactant concentration well beyond this maximum the dispersions became unstable, as a result of increased particle size, measured by laser diffraction Malvern 2600c particle sizer (8). The maximum zeta-potentials obtained are shown in Table I. It can be seen that the maximum zeta-potential for the 30:70 blend is reached at about 0.7 mM, i.e., at the same concentration range where the monolayer was completed.

To clarify the effects we have plotted the zeta-potentials alongside the equilibrium concentration of oleic acid in Figure 5. The propellant ratio 30:70 is chosen as an example because this propellant blend is the one usually used in conventional MDI's.

Three regions have been identified in the figure and marked by A, B and C. In the region A both the surfactant and the solvent are competing for the surface sites at the particle surface. The adsorption is weak as was shown by the isotherm and the surfactant is predominantly dissolved in the propellant. The surface charge is increasing with the increasing concentration of oleic acid due to the adsorption, and also due to a subsequent proton exchange between reactive sites at the solid surface (8,20).

At the early stages within region B the surface charge is still increasing with the increase of oleic acid. At about 0.7 mM the surface charge have reached its maximum value and the adsorbed oleic acid has formed a monolayer on the particle surface. For another propellant blend the maximum zeta-potential would have been at another concentration due to the solubility and acid-base properties of the propellants (Table I). After this maximum the surface charge is decreasing due to formation of a multilayer at the particle surface. The first larger changes between the initial and the equilibrium concentration can be observed at the end of region B indicating a multilayer formation.

In the region C the particle surface is entirely covered by a surfactant phase resulting in an unchanged surface charge value, even when more surfactant is added. The dispersion will become unstable in this region and the surfactant covered particles are starting to form aggregates through coalescence of the surfactant phase. This was observed as an increase in the particle size (8) when the equilibrium concentration reaches it's maximum value, 1.6 mM. It follows that all added surfactant exceeding equilibrium concentration is adsorbed onto the particle surface or forms a separate liquid crystal phase on the particles.

**Table I.** The Maximum zeta-potentials and the Concentration of Oleic Acid at the Maximum for Different Propellant Blend

| Solvent (P11:P12) | Oleic acid (mmol/l) | Zeta-Potential (mV) |
|---|---|---|
| 100:0 | 1.5 | 50 |
| 50:50 | 1.3 | 75 |
| 40:60 | 1.1 | 80 |
| 30:70 | 0.7 | 100 |

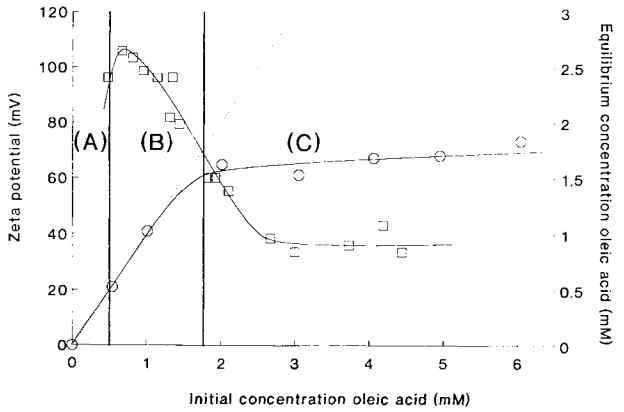


Fig. 5. The zeta-potential (mV) □ and the equilibrium concentration oleic acid (mM) ○ as a function of the initial concentration oleic acid (mM). The dispersion medium is a 30:70 blend of P11:P12 and the amount Salbutamol base is 0.16 w-%.

## CONCLUSION

We have characterized three important parameters of aerosol dispersions (MDI's), namely the zeta-potential of the drug particles, the particle size and the distribution of the surfactant between the particles and the liquid phase. This gives us a better understanding of the properties of pressurized aerosol dispersions.

Making an aerosol dispersion with a certain propellant blend there is a limit of how much surfactant can be dissolved in the propellants in the presence of a solid phase depending on the acid-base properties. If this amount is exceeded it will result in an unstable dispersion. We have shown that the drug particles are covered by a monomolecular layer of the surfactant at the same initial concentration where the surface charge reaches its maximum value and that the dispersions are stable in a concentration range near this.

## ACKNOWLEDGMENTS

We thank M. Sc. Micaela Berglund for the IR-measurements. The work was financed by Leiras OY, Orion Pharmaceutical and the Technology Development Center, TEKES, Finland.

## REFERENCES

1. H. Koelmans and J. T. Overbeek. Stability and electrophoretic deposition of suspensions in non-aqueous media. *Discussion of the Faraday Society* 18:52–63 (1954).
2. A. Doroszkowski and R. Lambourne. Effect of molecular architecture of long chain fatty acids on the dispersion properties of Titanium Dioxide in non-aqueous liquids. *Discussion of the Faraday Society* 65:252–263 (1978).
3. D. A. Wyatt and B. Vincent. Electrical effects in non-aqueous systems. *Journal of Biopharmaceutical Science* 3 (1/2):27–31 (1992).
4. R. H. Ottewill and J. M. Tiffany. The adsorption of long chain acids onto rutile from n-heptane. *Journal of Oil Colour Chemical Association* 50:844–864 (1967).
5. D. H. Wheeler, D. Potente, and H. Wittcoff. Adsorption of dimer, trimer, stearic, oleic, linoleic, nonanoic and azelaic acids on ferric oxide. *Journal of the American Oil Chemist's Society* 48:125–128 (1971).
6. R. S. Drago and B. B. Wayland. A double-scale equation for

correlating enthalpies of Lewis acid-base interactions. *Journal of the American Chemical Society* **20**:3571–3577 (1965).
7. R. S. Drago, G. C. Vogel, and T. E. Needham. A four-parameter equation for predicting enthalpies of adduct formation. *Journal of the American Chemical Society* **17**:6014–6060 (1971).
8. K. B. Sandström, P. M. Eriksson, and J. B. Rosenholm. Electrophoretic Mobility of Salbutamol Drug Powder in Mixed Propellant blend. *Journal of Pharmaceutical Science* **83(10)**:1380–1385 (1994).
9. R. R. Lowry and I. J. Tinsley. Rapid colorimetric determination of free fatty acids. *Journal of the American Oil Chemists' Society* **53**:470–472 (1976).
10. M. A. Taylor and L. H. Princen. Fatty acids in solutions. In E. H. Pryde (editor) *Fatty Acids*. The American Oil Chemists' Society–Champaign, Illinois, 1979, pp. 195–198.
11. P. A. Sanders. *Handbook of Aerosol Technology*. Robert E. Krieger publishing company, Malabar Florida, 1987, pp. 165–187.
12. J. J. Kipling and E. H. M. Wright. Adsorption from binary of limited concentration range: Application of some fundamental concepts. *Journal of the Chemical Society* 855–860 (1962).
13. P. C. Hiementz. *Principles of Colloid and Surface Chemistry*. Marcel Dekker, INC., New York and Basel, 1986, pp. 353–425.
14. B. K. Sidhu, C. Washington, S. S. Davis, and T. S. Pureval. Electrophoretic properties of lactose and Salbutamol sulfate suspensions in halogenated solvents. *Langmuir* **9**:839–843 (1993).
15. P. E. Kornebekke, I. D. Morrison, and T. Oja. Electrophoretic mobility measurements in low conductivity media. *Langmuir* **8**:1211–1217 (1992).
16. I. D. Morrison. Criterion for electrostatic stability of dispersions at low ionic strength. *Langmuir* **7**:1920–1922 (1991).
17. M. Kosmulsky and E. Matejevíc. Microelectrophoresis of silica in mixed solvents of low dielectric constant. *Langmuir* **7**:2066–2071 (1991).
18. R. J. Pugh, T. Matsunga, and F. M. Fowkes. The dispersibility and stability of carbon black in media of low dielectric constant. 1. Electrostatic and steric contributions to colloidal stability. *Colloids and Surfaces* **7**:183–207 (1983).
19. F. M. Fowkes, H. Jinnai, M. A. Mostafa, F. W. Andersen, and R. J. Moore. Mechanism of electrical charging of particles in nonaqueous liquids. *American Chemical Society Symposium*, Series 240, Washington DC, 1982, pp. 307–324.
20. A. Kitahara, M. Amano, S. Kawasaki, and K. Kon-no. The concentration effect of surfactants on zeta-potential in non-aqueous dispersion. *Colloid and Polymer Science* **255**:1118–1121 (1977).
21. K. E. Lewis and G. D. Parfitt. Stability of non-aqueous dispersions. *Transaction of the Faraday Society* **62**:1652–1661 (1966).
22. D. N. L. McGown, G. D. Parfitt, and E. Willis. Stability of non-aqueous dispersion. I. The relationship between surface potential and stability in hydrocarbon media. *Journal of Colloidal Science* **20**:650–664 (1965).