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Inorganic suspensions–interaction with salts and ionic surfactants

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Summary

The interaction of dispersions with pharmaceutical excipients (salts, detergents, preservatives) dissolved in the dispersion medium can have a major influence on the physical and microbiological stability of the system. Inorganic suspensions were investigated to assess the effects of the concentration and nature of the excipients and dispersed material. Charge (zeta potential) and size measurements were employed to quantify the interactions. The presence of salts led to either an increase or decrease in the physical stability of the dispersion. The effect was dependent on both the concentration and nature of the electrolytes. Detergents led to a general enhancement of stability with increasing concentration. The degree of adsorption of preservatives, such as cetylpyridinium chloride (CPC), could be followed by monitoring increases in particle charge. The high affinity of CPC to the particle surface led to a reduction of free, active CPC in the dispersion medium, resulting in an enhanced physical but a diminished microbiological stability.

Introduction

The interaction of components of the dispersion medium with the particle surface influences the stability of disperse systems. This may result in either an increase or decrease in the degree of particle aggregation.

A major factor in dispersion stability is the electrostatic repulsion between similarly charged particles (Ottewill, 1977). The surface charge of particles can be due to the presence of charged groups on their surface (e.g., on minerals (Ney, 1973a)) or the adsorption of ions from the dispersion medium leading to the formation of the Stern plane and the diffuse layer (Sennet and Olivier, 1965). The net charge of dispersed particles therefore depends on the nature, valency and concentrations of the ions present in the dispersion medium. In general, with increasing salt concentrations above 10^{-6} M, the particle charge will increase to a maximum and then diminish at higher ionic strengths (approx. 0.01–1 M) (Lagaly, 1984). This behaviour is of importance for many pharmaceutical suspensions. The addition of ionic drugs to suspensions or emulsions can cause changes in the particle or emulsion droplet charge leading to instability. Stable dispersions can be obtained by adjusting the ionic strength to a level at or close to the charge maximum. Electrophoretic mobility (μ) in an electrical field can be determined as a measure of the particle charge:

Electrophoretic mobility

$$= \frac{\text{particle velocity}}{\text{field strength}} \frac{(\text{m/s})}{(\text{V/cm})}$$

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The zeta potential (ZP) of the particles can be calculated from the electrophoretic mobility by using the Helmholtz-Smoluchowski equation (Hunter, 1981):

$$ZP = \frac{4\pi\eta\mu}{\epsilon_0\epsilon_r}$$

where μ denotes electrophoretic mobility, η represents dynamic viscosity, ϵ_0 and ϵ_r being the dielectric constants of vacuum and water, respectively.

For some applications, higher salt concentrations, which lead to a strong reduction in zeta potential, are required. Such dispersions are not electrostatically stable and tend to aggregate. Stabilization of such systems can be achieved by addition of nonionic, sterically stabilizing surfactants (Napper, 1983) such as Poloxamer. Poloxamer surfactants are block co-polymers of poly(ethylene oxide) (EO) and poly(propylene oxide) (PO) with the general structure $(EO)_n$-$(PO)_m$-$(EO)_n$, where n and m are the number of ethylene oxide and propylene oxide units, respectively (n and $m \gg 1$). The polymers adsorb onto the particle surface creating a sterically stabilizing coating layer.

Alternatively, ionic surfactants can be used to increase the particle charge at high ionic strengths. The surfactants adsorb to the particle surface resulting in a greater total charge on the particle.

Ionic surfactants such as cetylpyridinium chloride (CPC) are employed as preservatives in suspensions. The interaction of such compounds with a dispersion is important for its microbiological stability. Adsorption of the surfactant onto the particle surface might enhance the physical stability of the dispersion, but the adsorbed ionic surfactant is no longer active as a preservative.

Measurement of the interaction of ionic surfactants with pharmaceutical dispersions is therefore important.

Short-chained, ionic organic acids such as citric and sorbic acids are used as preservatives in inorganic dispersions (e.g., antacid suspensions of aluminium hydroxide). Due to the large surface area of the suspended material which can adsorb a major proportion of the added preservative, the interaction between ionic compound and suspended particle is of great importance.

Materials and Methods

Inorganic materials (titanium dioxide, barium sulphate, calcium carbonate, zinc oxide and kaolin) were suspended in triple-distilled water. Salts (NaH_2PO_4, Na_2HPO_4, sodium citrate, sodium pyrophosphate) and ionic surfactants (SDS and CPC) were added in increasing concentrations from 10^{-6} to 10^{-1} M. All materials were either Analar or German and European pharmacopeia grade and were purchased from Sigma (F.R.G.).

Prior to suspension, the inorganic materials were ground in a Fritsch Pulverisette type 601 (Fritsch, F.R.G.), a centrifugal ball mill, to obtain smaller particle sizes with a lower sedimentation velocity.

Electrophoretic measurements using laser Doppler anemometry were performed to determine the electrophoretic mobility [μ] of the suspended particles. The laser Doppler anemometer used was a Zetasizer II (Malvern Instruments, Malvern, U.K.). The electrical field strength applied in the measurements was 20 V/cm. A wide-bore capillary with an inner diameter of 4 mm (PC 4) was employed as the measuring cell. The electrophoretic mobility was converted into a zeta potential by application of the Helmholtz-Smoluchowski equation.

Particle size determinations were performed with a laser diffractometer (model 2600D particle sizer, Malvern Instruments). The apparatus is based on Frauenhofer diffraction and allows size determinations in aqueous salt solutions.

Results and Discussion

Suspensions of zinc oxide were used to investigate the influence of (i) the concentration of electrolyte on the increase in particle charge; (ii) the electrolyte concentration required to obtain a charge maximum; and (iii) the influence of the nature of the salt.

Three salts (NaH_2PO_4, sodium citrate and sodium pyrophosphate) were added in increasing

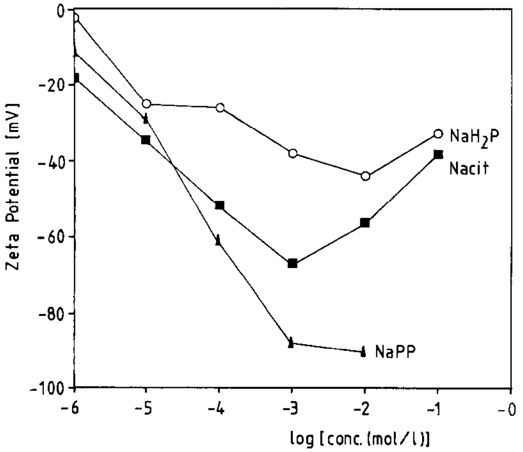

Fig. 1. Zeta potential of ZnO, plotted as a function of concentration for different salts, namely sodium citrate (Nacit), NaH_2PO_4 (NaH_2P) and sodium pyrophosphate (NaPP).

concentrations to the zinc oxide suspensions and the resulting zeta potentials determined (Fig. 1).

The addition of salts at 10^{-6} M had little or no effect on the zeta potential compared to the ZP value of zinc oxide in triple-distilled water (−6.8 mV). However, addition of salts at 10^{-5} M led to a distinct increase in the zeta potential due to adsorption of the negative ions onto the particle surface. Salt concentrations above 10^{-5} M led to an increase in zeta potential which was dependent on the affinity of the salt anions to the particle surface. The increase in zeta potential was moderate for NaH_2PO_4, indicating a low affinity, whereas those for sodium citrate and sodium pyrophosphate were more pronounced, indicating a higher affinity for the particle surface.

Charge maxima were obtained at ionic concentrations of 10^{-3}–10^{-2} M. The concentration required for the maximum charge depended on the nature of the added salt and its affinity to the surface of the particle. Salts with high surface affinities (sodium citrate and sodium pyrophosphate) reached a charge maximum at the lower concentration of 10^{-3} M. In addition, the absolute value of the charge maximum was much greater for high-affinity salts as compared to those with low affinity, such as NaH_2PO_4.

To investigate the influence of the interaction of a single salt with the dispersed material, dispersions of $CaCO_3$, TiO_2 and ZnO were incubated with increasing concentrations of Na_2HPO_4. Only small increases in zeta potential were measured in $CaCO_3$ suspensions after salt addition, indicating a low affinity of the salt for the particle surface (Fig. 2). The adsorption behaviour of Na_2HPO_4 was strongly influenced, however, by the nature of the dispersed material. Incubation with TiO_2 suspensions led to a more distinct and steeper rise in zeta potential. An increase in potential of −36.9 mV was obtained between 10^{-6} M and the charge maximum at 10^{-2} M. Na_2HPO_4 was found to have an even higher affinity for the surface of ZnO producing a charge increase of −67.9 mV between the same salt concentrations. This indicates that the effect of salt addition is dependent on the nature of the dispersed material. Therefore, a single salt cannot be used as a stabilizer for a range of dispersions for which it has different adsorption affinities, without prior investigation of the interaction within each system.

At high salt concentrations of 0.1 M, a reduction in zeta potential was found. This is due to compression of the diffuse layer at higher ionic strengths (Wnek and Davies, 1977). The higher concentration of counterions leads to a steeper decay in potential, resulting in a thinner diffuse layer (Fig. 3, modified according to Lagaly (1984)). The reduction in zeta potential due to compres-

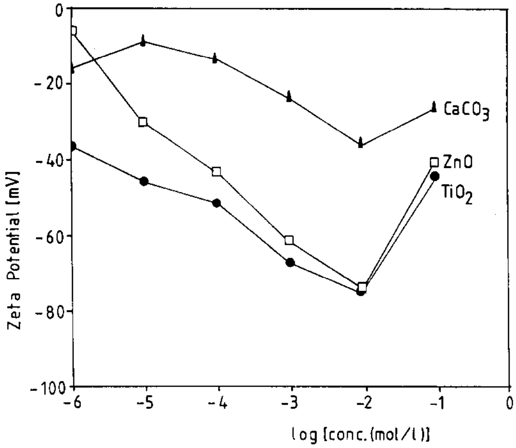

Fig. 2. Zeta potential of different suspensions ($CaCO_3$, TiO_2 and ZnO) plotted vs. concentration of Na_2HPO_4.

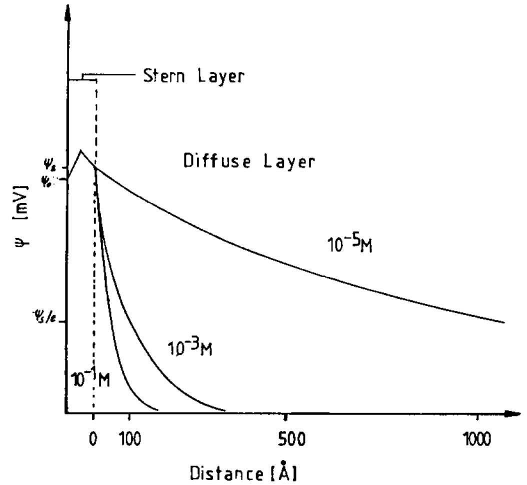

Fig. 3. Decay of the potential in the diffuse layer as a function of the electrolyte (1 : 1) concentration. The thickness of the diffuse layer decreases with increasing salt concentration.

sion of the diffuse layer compensates a possible increase in zeta potential due to enhanced adsorption of anions.

To study the effect of negatively charged ionic surfactants on dispersions, $BaSO_4$ and ZnO suspensions were prepared in the presence of increasing concentrations of SDS. SDS exhibits a high affinity for the surface of both suspended particles, as shown by the steep and large increase in zeta potential with increasing ionic concentrations (Fig. 4). At the charge maximum (10^{-2} M), increases of −73.1 mV for $BaSO_4$ and −64.7 mV for ZnO (vs. the zeta potentials in distilled water) were measured. The similarity between the zeta potential vs. concentration profiles indicates that SDS has a similar affinity for the surface of both dispersions.

Preparation of $BaSO_4$ and ZnO suspensions with increasing CPC content led to charge reversal of the suspensions. The positively charged CPC strongly adsorbed with high affinity, leading to a steep potential enhancement (Fig. 5). The absolute zeta potential change was less than that obtained with SDS (around 40–50 mV). The high affinity of CPC for particle surfaces illustrates the problems concerned with the microbiological stability of dispersions due to the adsorption of preservatives. The increase in charge of the particles and consequent enhancement of electrostatic repulsion are correlated with reduced antimicrobial activity due to adsorbed CPC.

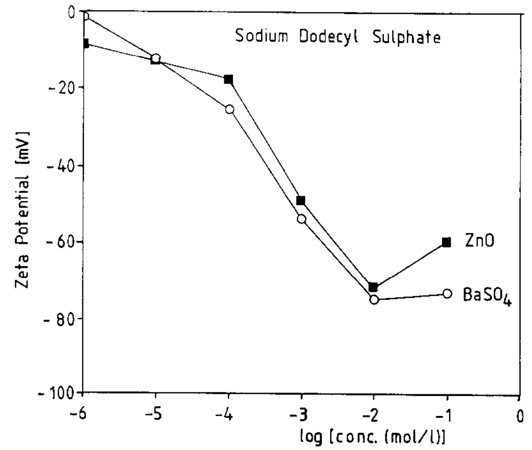

Fig. 4. Zeta potential of $BaSO_4$ and ZnO plotted as a function of SDS concentration.

The reduction in zeta potential due to compression of the diffuse layer at concentrations of 10^{-1} M is less extensive or non-existent for the ionic surfactants. The surfactants adsorb perpendicularly to the particle surface, similarly to the structure of surfactants in a neat phase or the arrangement of phospholipids in membranes. Assuming a 'palisade'-like structure, a coating layer on the particle of approx. 20 Å for SDS (length of the

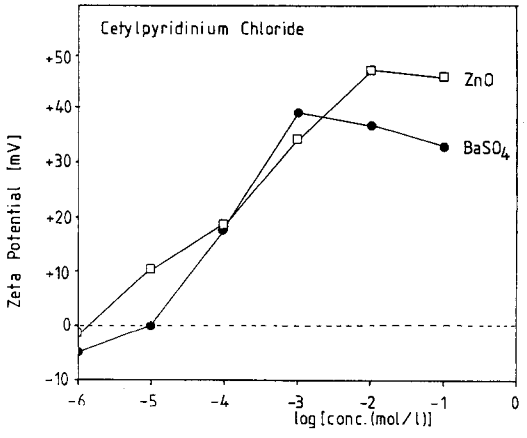

Fig. 5. Zeta potential of $BaSO_4$ and ZnO plotted with respect to the concentration of CPC.

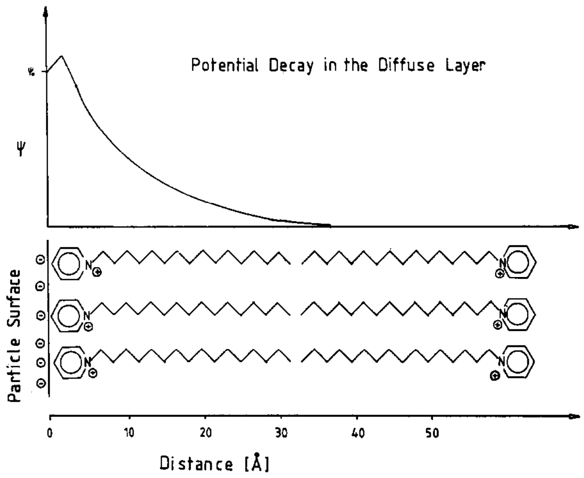

Fig. 6. Decay of the potential in the diffuse layer at 0.1 M electrolyte (1 : 1) concentration plotted as a function of the distance to the particle surface (upper) and with respect to the formation of the adsorbed double layer of CPC which covers the diffuse layer (lower).

SDS molecule 20 Å) and approx. 60 Å for CPC (length of CPC molecule 30 Å) will result.

The CPC molecule most likely adsorbs in a double layer (Fig. 6) as described for similar detergents used in mining processes (Ney, 1973b). The positively charged end of the molecule adsorbs onto the negatively charged surface of the particle, forming a monolayer with hydrocarbon chains protruding into the dispersion medium. A second layer of CPC adsorbs onto this monolayer with the charged groups directed towards the dispersion medium. At 10^{-1} M, the diffuse layer is around 15 Å in thickness and therefore is covered by the adsorbed layers of SDS and CPC. For adsorption of non-ionic polymers such as Poloxamer, this results in uncharged particles (Müller et al., 1988). However, SDS and CPC possess charged groups which are located outside the diffuse layer leading to the observed high zeta potential at 10^{-1} M (Fig. 6). This model presumes that the adsorbed SDS and CPC do not give rise to a new surface on which the formation of a Stern and diffuse layer takes place as suggested by Rupprecht (1975). As judged from the high zeta potentials measured, this seems to be unlikely in the investigated dispersions. If a diffuse layer were present on the SDS or CPC layers, a reduction in charge at high ionic concentrations, similar to that observed in salt solutions (Fig. 3), would be expected.

To investigate the effect of charge-enhancing additives such as salts and ionic surfactants on the dispersion process of inorganic materials, suspensions of $BaSO_4$, kaolin and TiO_2 were prepared in the presence of varying concentrations of sodium citrate. On consideration of the zeta potential vs. concentration profiles, the maximum deaggregating effect was expected to occur at the concentration which results in the highest zeta potential (i.e. 10^{-3} M).

The size decrease during the dispersion process was continuously monitored by laser diffractometry. The apparatus allowed non-invasive measurements to be made during aqueous dispersion of the materials. The dispersion of choice was placed in the diffractometer measuring cell and stirred continuously by using an intrinsic magnetic follower.

To characterize the removal of aggregates the diameter, *D*90%, measured at different times was plotted vs. stirring time. The diameter 90% (*D*90%) represents the size at which 90% of the volume of particles is smaller. The variation in values of *D*90% demonstrated that greater changes took place during the de-aggregation (dispersion) pro-

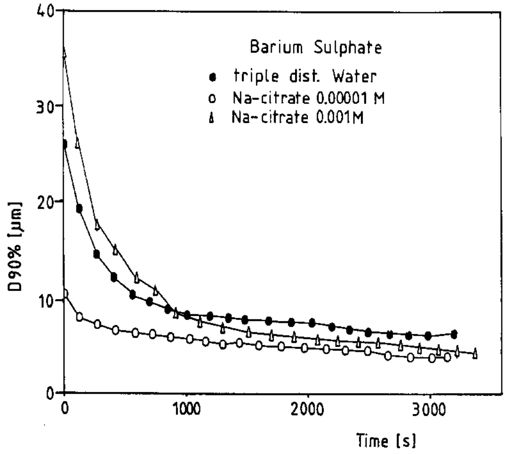

Fig. 7. Diameter (*D*90%) of $BaSO_4$ dispersions plotted with respect to stirring time in triple distilled water and after addition of the particle charge-enhancing salt sodium citrate (concentration: 0.001 and 0.00001 M).

cess than in the case of *D*50% and was therefore considered to be more suitable for assessing the effect of added salts.

$BaSO_4$ was dispersed in distilled water, in the presence of 10^{-5} and 10^{-3} M sodium citrate. The latter concentration corresponds to the point at which the maximum zeta potential was attained.

No major difference in particle size was found after stirring for 1 h (Fig. 7). This is believed to be due to weak binding forces within the aggregates which can readily be overcome by stirring. However, de-aggregation took place more rapidly in 10^{-3} M sodium citrate as indicated by the steep decay in *D*90% within the first 3 min.

Larger differences were observed for the dispersion of kaolin in the presence of 10^{-5} and 10^{-3} M sodium citrate. The particle size after 1 h stirring was smaller in the presence of the optimum additive concentration (maximum zeta potential at 10^{-3} M) (Fig. 8). In water or at low additive concentrations (i.e. 10^{-5} M), the binding forces within the aggregates are too strong to be overcome by simple stirring. Only the additional increased electrostatic repulsion at 10^{-3} M leads to the removal of aggregates.

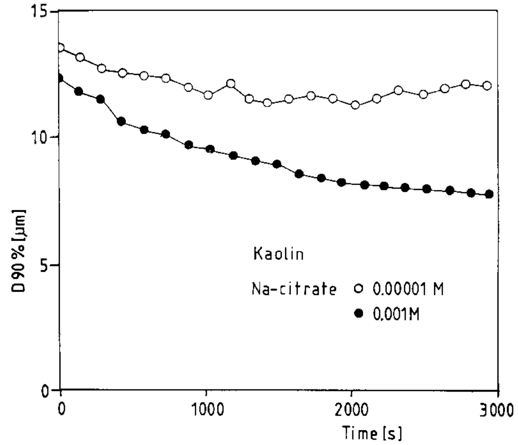

Fig. 8. Diameter (*D*90%) of kaolin dispersions plotted with respect to stirring time after addition of the particle charge-enhancing salt sodium citrate (concentration: 0.00001 and 0.001 M).

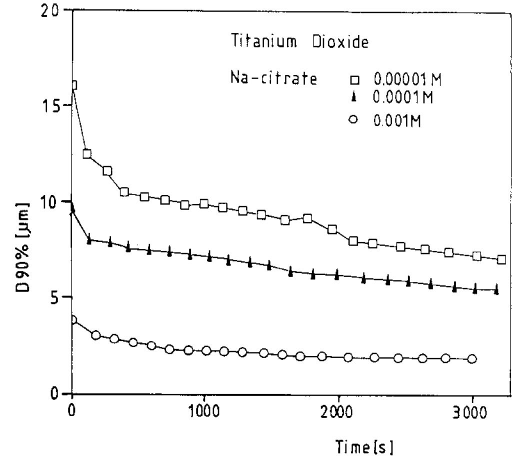

Fig. 9. Diameter (*D*90%) of TiO_2 dispersions plotted with respect to stirring time after addition of the particle charge-enhancing salt sodium citrate (concentration: 0.00001, 0.0001 and 0.001 M).

The addition of sodium citrate proved to be very effective in the dispersion of TiO_2 over the concentration range employed (10^{-3}–10^{-5} M). Marked differences in the velocity of de-aggregation and final particle size were noted after 1 h of stirring. The addition of 10^{-3} M sodium citrate created a zeta potential maximum and a sharp decrease in *D*90% within the first 2 min of stirring (Fig. 9).

A plateau in the values of *D*90% was reached after stirring in the presence of sodium citrate for 40 min. A further decrease cannot be achieved, since the forces of interaction within the aggregates could not be overcome by the electrostatic repulsion created by the additive concentration used. Increased additive concentration resulted in greater repulsion and consequently in a lower D90% plateau level due to the compensation of the cohesive forces within the aggregates.

From the dispersion studies, it can be concluded that the efficiency of additives in stabilizing dispersions depends on the strength of the cohesive forces present in the aggregates. When the cohesive forces are weak, salt addition can only accelerate the dispersion process. Conversely, in the presence of strong cohesive forces which cannot be overcome by simple stirring, increasing the additive concentration leads proportionally to the compensation of stronger cohesive forces resulting in a lower *D*90% plateau level.

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References

Hunter R.J., *Zeta Potential in Colloid Science: Principles and Application*, Academic Press, London, 1981.

Lagaly, G., Energetische Wechselwirkungen in Dispersionen und Emulsionen. In Asche, H., Essig, D. and Schmidt, P.C. (Eds.), *Technologie von Salben, Suspensionen und Emulsionen*, APV Paperback Vol. 10, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1984.

Müller, R.H., Blunk, T and Koosha, F., Determination of the thickness of adsorbed polymer layers on colloidal drug carriers by charge measurements. *Arch. Pharm.*, 321 (1988) 678.

Napper, D.H., *Polymer Stabilization of Colloidal Dispersions*, Academic Press, London, 1983.

Ney, P., Zetapotentiale und Flotierbarkeit von Mineralien (Applied Mineralogy Vol. VI), Springer, Vienna, 1973a.

Ney, P., Zetapotentiale und Flotierbarkeit von Mineralien (Applied Mineralogy Vol. VI), Springer, Vienna, 1973b, p.63.

Ottewill, R.H., Stability and instability in disperse systems. In Kerker, M., Zettlemoyer, A.C. and Rowell, R.L., *Colloid Interface Sci.* Vol. I, Academic Press, New York, 1977, pp. 379–395.

Rupprecht, H., Gesichtspunkte zur Optimierung arzneilicher Suspensionen. *Pharm. Ztg.*, 120 (1975) 1265–1274.

Sennet, P. and Olivier, J.P., Colloidal dispersions, electrokinetic effects and the concept of zeta potential. *Ind. Eng. Chem.*, 57 (1965) 32–50.

Wnek, W.J. and Davies, R., An analysis of the dependence of the zeta potential and surface charge on surfactant concentration, ionic strength, and pH. *J. Colloid Interface Sci.*, 60 (1977) 361–375.