

Electrokinetics and Stability of a Cellulose Acetate Phthalate Latex

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ABSTRACT: An experimental investigation is described on the surface electric characterization of a commercially available latex, Aquateric, composed of cellulose acetate phthalate polymer particles, and used in enteric-controlled drug release. Since the surface charge of dispersed systems is an essential parameter governing most of their behavior, it is of fundamental importance to characterize how that quantity changes in the different environments in which the colloids could be used. The experimental method used in this work is electrophoresis; we report measurements of electrophoretic mobility of the latex as a function of pH and ionic concentration in the dispersion medium. It is shown that the zeta potential of the polymer particles is negative for the whole pH range studied and increases with pH as the dissociation of surface acetic acid groups proceeds. A plateau value is found for $\text{pH} > 5$, corresponding to complete dissociation of available ionizable sites. The values of the electrophoretic mobility (μ_e) and the zeta potential (ζ) of Aquateric are also analyzed as a function of the concentration of 1-1 (NaCl) and 2-1 (CaCl_2) concentration. The anomalous surface conductance (associated to the mobility of counterions adsorbed in the inner part of the electric double layer of the particles) manifests in a maximum in the $|\mu_e|$ -NaCl concentration plot for $10^{-3}M$ concentration. No such behavior is observed in the presence of CaCl_2 solutions, where only a decrease of the mobility with ionic strength is observed. The effect of AlCl_3 concentration on the mobility is also considered; it is found that at pH 2 aluminum ions adsorb on the particles and render them positively charged. When the pH of the suspensions is not maintained constant, the hydrolysis of aluminum gives rise to a less efficient control of the charge of the particles and no positive mobilities are observed. Electrophoretic mobility measurements as a function of pH at constant AlCl_3 concentration show an abrupt change of μ_e from negative to positive, interpreted as due to surface precipitation of $\text{Al}(\text{OH})_3$. When the pH is further increased, a second charge reversal is found, corresponding to the isoelectric point (pH of zero zeta potential) of $\text{Al}(\text{OH})_3$. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **65**: 2721–2726, 1997

Key words: cellulose acetate phthalate latex; electrophoretic mobility; zeta potential; charge reversal; polymer chemical stability

INTRODUCTION

There exists a large variety of technological and industrial processes in which polymers play a fun-

damental role. Thus, in the past years, many works have been devoted in pharmaceutical research to the design of formulations containing polymers with the aim of delivering different drugs in a prolonged and controlled fashion.^{1,2} The active principle can be incorporated into the polymer particles in a number of ways; most often it is solubilized in the polymerization medium and enclosed in the particles. An alternative procedure is possible when the adsorbent has a high

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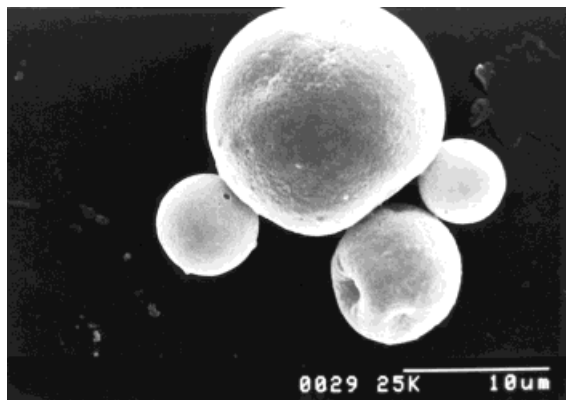


Figure 1 Scanning electron micrographs of Aquateric particles, after latex cleaning.

specific surface area: The therapeutically useful compound can be adsorbed on the dispersed solid and eventually desorbed when and where required.³

The latter is the case of interest in this work. When this is the method chosen, the surface characteristics of the dispersed colloid play an essential role in both the adsorption and desorption steps. In particular, the electric nature of the surface in the dispersion medium containing the drug will essentially affect the interactions between the particles and the active component. Hence, the interest in carrying out a characterization of the electric properties of the interface. Electrokinetic methods^{4,5} are very useful in this respect, since they allow one to have a quantitative measure of the strength of electric contributions to the overall behavior of the suspension.

Furthermore, the stability of the latter, i.e., the tendency of the particles to remain individually in suspension, as opposed to the thermodynamic requirement of aggregation, is strongly related to the charge distribution on and around the particle. The control of the stability is an essential factor in the design and applications of pharmaceutical suspensions. The stability cannot only be measured, but also predicted with a high degree of accuracy if previous data on the charge or potential on the particle surface are available.

We focused our attention on a kind of commercially available colloidal dispersion, potentially useful as part of a controlled-release system. Both acrylic and cellulosic acids polymers have been proposed with that aim; in this work, the electrokinetic properties of a cellulose acetate phthalate polymer (Aquateric)^{6,7} was analyzed as a function of the composition of the aqueous dispersion medium. This latex has actual applications for en-

teric-controlled drug release; even at high volume fractions,⁶ the latex has a moderate viscosity, and it is suitable for film forming by addition of very different plasticizers. The disintegration of the polymer and the subsequent drug release occurs at pH above ≈ 6.5 , at a rate little affected by other environmental conditions.

EXPERIMENTAL

Aquateric (FMC Corp., U.S.A.) was kindly supplied by Foret S.A., Spain. As received, it contains 10% Myvacet-940, 20% Pluronic acid-F8, and 0.3% Tween 60. To get rid of the highest possible amount of these surfactants, the original latex was repeatedly centrifuged and redispersed in water (Milli-Q reagent water systems, Millipore), until the supernatant conductivity fell below $3 \mu\text{S cm}^{-1}$. This “clean” material had a 10% volume fraction of solids, and it was used to prepare the suspensions to be studied.

Dilute samples were dried and studied by both transmission and scanning electron microscopy. Figure 1 is an example: As observed, Aquateric is composed of approximately spherical particles of two different sizes—one population has an aver-

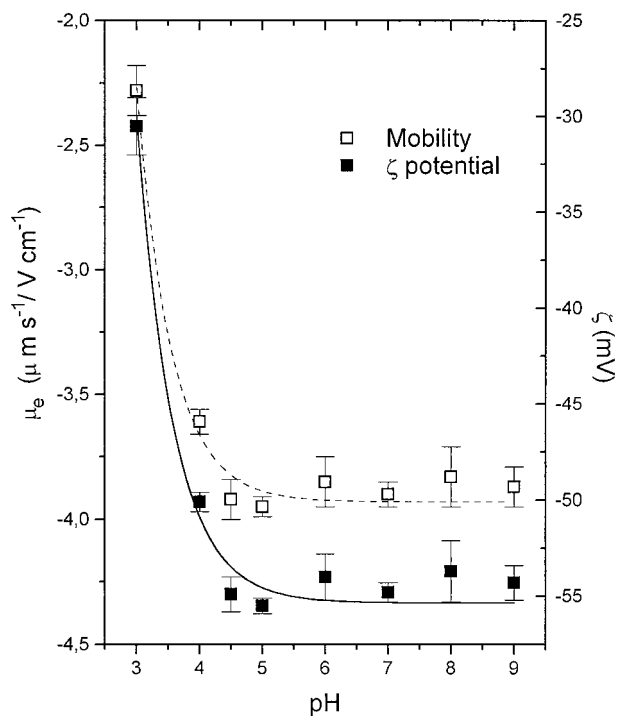


Figure 2 Electrophoretic mobility and zeta potential of Aquateric as a function of pH in the presence of 10^{-3}M NaCl .

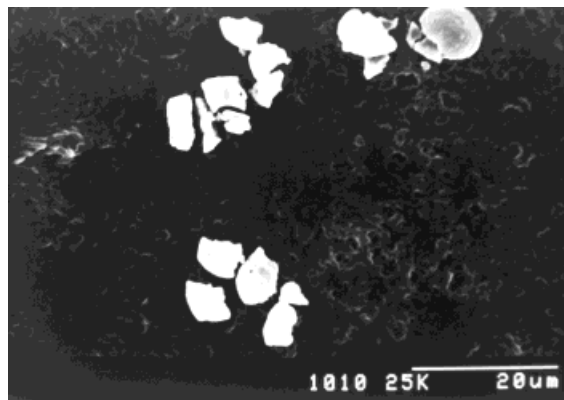


Figure 3 Scanning electron micrographs of Aquateric particles dispersed in basic solutions.

age particle diameter of $\approx 16 \mu\text{m}$, and the other, of $\approx 6 \mu\text{m}$. All chemicals used in the preparation of the suspensions were of analytical quality from Merck (Germany) and were employed as received, without further purification.

The electrokinetic properties of the suspensions were determined by electrophoresis.⁴ A Malvern Zetasizer 2c (Malvern Instruments, England) was used to measure the electrophoretic mobility of dilute Aquateric suspensions (volume fraction of solids $\approx 10^{-4}$). At least 10 determinations of mobility were performed on each sample; the standard error of the average values are shown as error bars in the figures below. All experiments were carried out at $25.0 \pm 0.5^\circ\text{C}$. Zeta potentials were computed from electrophoretic mobilities using the O'Brien and White's theory.^{8,9}

RESULTS AND DISCUSSION

Effect of pH on the Electrophoretic Mobility and Zeta Potential of Aquateric

Prior to any further characterization of the latex suspensions, it is of fundamental importance to analyze the electrokinetic behavior of the particles as a function of pH, since it is to be expected that the concentrations of H^+ and OH^- will control the charge generation mechanisms of the particles. Figure 2 shows the electrophoretic mobility (μ_e) and the zeta potential (ζ) of Aquateric, as a function of pH at constant ionic strength (10^{-3}M NaCl).

The data in Figure 2 show that the surface charge of this polymer remains negative for the whole pH range studied; hence, no isoelectric point (or pH of zero zeta potential) is observed. Furthermore, both μ_e and ζ increase in absolute

value upon increasing the pH of the medium from pH 3 to pH 5. If the pH is further increased, no change is observed in μ_e and a plateau value of $\approx -3.9 \mu\text{m s}^{-1}/\text{V cm}^{-1}$ is reached. These results can be explained by assuming that the surface charge is generated by acetate surface groups: Their dissociation will leave negative charges on the particles, responsible for the negative ζ values observed. As the pH is increased, a larger fraction of those surface groups will be dissociated, thus increasing the negative charge density and, hence, the values of either μ_e or ζ .

According to this argument, the plateau value must be originated by the fact that all groups available will be dissociated when $\text{pH} \approx 5$ is reached. This is compatible with the $\text{p}K_a$ value of acetic acid groups ($\text{p}K_a = 4.75$, ref. 10).

No mobility measurements were performed above pH 9, since the disintegration of the particles brought about a larger imprecision in the determinations. In fact, electron micrographs of Aquateric particles at basic pH values (Fig. 3) clearly demonstrated the decomposition of the colloid in alkaline environment.

Effect of Mono- and Divalent Electrolytes on μ_e and ζ

The effect of the NaCl molar concentration on the electrophoretic mobility and zeta potential of

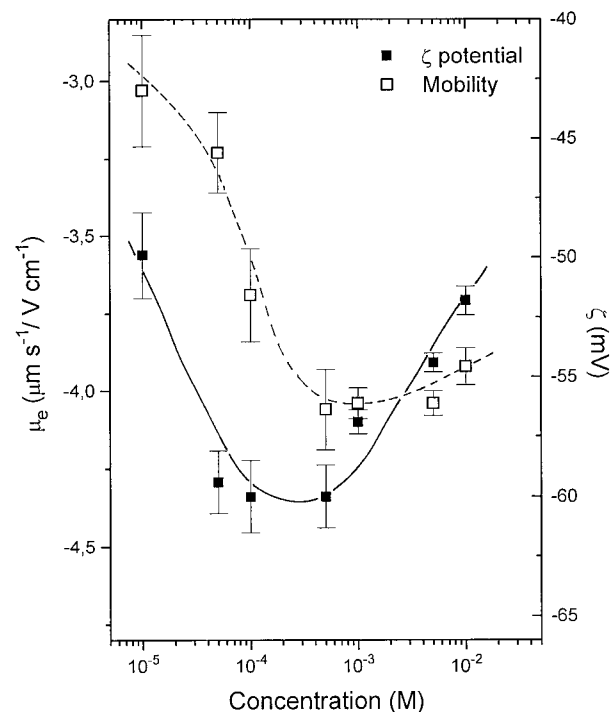


Figure 4 Electrophoretic mobility and zeta potential of Aquateric as a function of NaCl concentration.

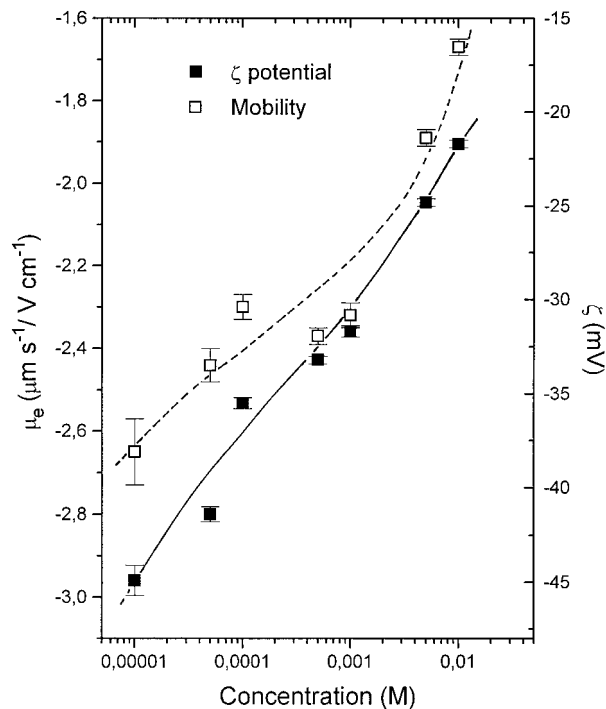


Figure 5 Same as Figure 4 for CaCl_2 solutions.

Aquateric particles is depicted in Figure 4. Both quantities increase in absolute value when the concentration of sodium chloride is increased between 10^{-5} and 10^{-3} M , whereas higher concentrations give rise to a decrease in $|\mu_e|$ or $|\zeta|$. However, it is well known from classical electrokinetic theory^{4,8,9} that, if no adsorption of ions takes place in the inner part of the electric double layer, the electrokinetic potential (and, hence, μ_e) should decrease in absolute value when the ionic strength is increased. This phenomenon, known as double-layer compression, is a consequence of surface charge screening by ions in the medium.

Since such behavior is not observed, it could be argued that chloride ions adsorb specifically on the particles and increase their surface charge density. However, similar experiments carried out with other monovalent electrolytes (NaNO_3 , KBr) showed that the electrokinetic behavior was approximately identical to that shown in Figure 4. Previous work from this and other laboratories on a wide variety of polymers^{11–14} reached similar conclusions.

Other arguments have been given to explain this anomalous increase in the zeta potential. Thus, it has been suggested that polymer chains extend into the dispersion medium, thus rendering the particle surface "hairy": Changes in ionic strength would provoke conformational modifications in the protruding chains. This will, in turn,

shift the position of the shear plane (where the electric potential equals ζ) and bring about changes in ζ .^{15,16}

Although some experiments performed on latexes heated above the glass transition temperature appear to confirm this hypothesis,^{17,18} the facts that the phenomenon has been found in suspensions of inorganic particles,¹⁹ and that other anomalies have been demonstrated in the analysis of such phenomena as dielectric dispersion^{20,21} or viscosity of the suspensions,²² suggest that the inconsistencies can be solved in a different way. A large body of work has elaborated on the modification of classical electrokinetic theories to account for the possibility of ionic transport in the inner part of the double layer (that part has classically been considered to be rigidly bound to the solid surface). This phenomenon has been called anomalous surface conductance (or simply surface conductance, since it could be a universal feature of electrokinetics) and has been successful in explaining some of the anomalies found experimentally.^{13,20,23,24}

Any of the physical processes above mentioned must be masked by a sufficient increase in ionic

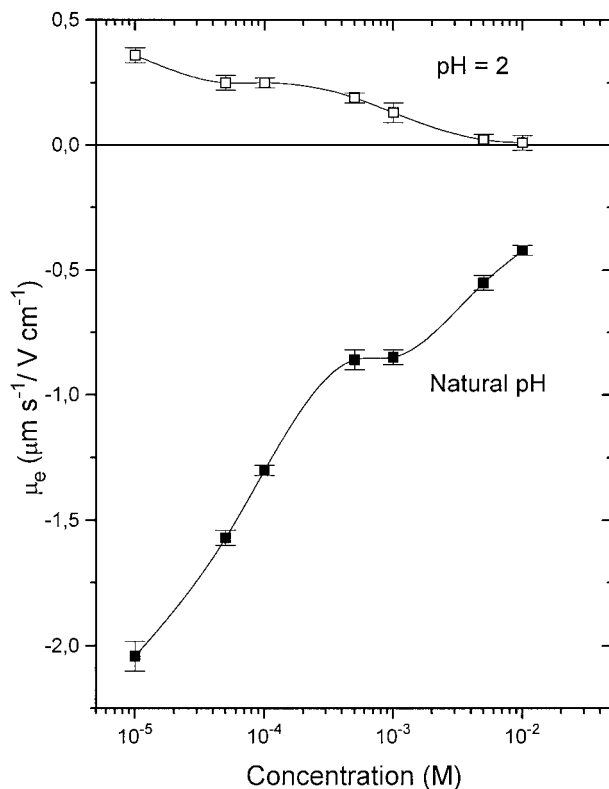


Figure 6 Electrophoretic mobility of Aquateric particles as a function of AlCl_3 concentration at pH 2 and at natural pH.

strength, since, as observed in Figure 4, when the concentration of NaCl is above $\approx 10^{-3}M$, the "normal" behavior ($|\mu_e|$ decreases with [NaCl]) recovered. This is confirmed by data in Figure 5, including μ_e and ζ as a function of CaCl_2 concentration. Both the mobility and the zeta potential of the particles decrease in a roughly monotonous fashion when $[\text{CaCl}_2]$ is changed between 10^{-5} and $10^{-2}M$.

Effect of AlCl_3 in the Dispersion Medium

Given the important effect of highly charged counterions on the magnitude (and sign) of the surface charge of colloids, we also performed electrophoretic mobility determinations of Aquateric when the dispersion medium contained AlCl_3 . Since aluminum is a highly hydrolyzable cation, the pH of the suspensions will be the determinant for the relative concentrations of the different species in solution. Thus, we determined μ_e as a function of $[\text{AlCl}_3]$ both at pH 2 and without control of the pH. The results are plotted in Figure 6. When the pH is maintained at a value of 2, the mobility of Aquateric is positive for the whole concentration range studied. Since at this pH almost 100% of the aluminum species in solution are Al^{3+} ,¹⁰ the results indicate that aluminum cations at low concentration adsorb on the particles and render them positively charged. When the concentration of AlCl_3 in the medium is increased, both μ_e and ζ tend to diminish: As a consequence of electrostatic repulsion, the phenomenon of double-layer compression prevails and gives rise to a decrease in the zeta potential and, hence, in the mobility.

When the pH of the suspensions is not maintained constant, a significantly different behavior is observed (Fig. 6). The pH was measured and found to range between 4.8 and 4.0 for concentrations 10^{-5} and $10^{-2}M$, respectively. Hydrolysis of the acid ion Al^{3+} must occur to some extent, and the solution must contain appreciable amounts of $\text{Al}(\text{OH})_3$, $\text{Al}(\text{OH})_2^+$, and $\text{Al}(\text{OH})_2^+$. The decrease in $|\mu_e|$ shown in Figure 6 could be due to both adsorption of the charged species and double-layer compression, since it is expected that the two phenomena will be present. In this case, however, no sign reversal of μ_e is observed, even for the highest AlCl_3 concentration: Hydrolysis makes aluminum less efficient, on the average, for positively charging Aquateric particles.

A different way of analyzing the effect of AlCl_3 , stressing the influence of hydrolysis, is measuring μ_e as a function of pH at constant aluminum chloride concentration. The results of such determina-

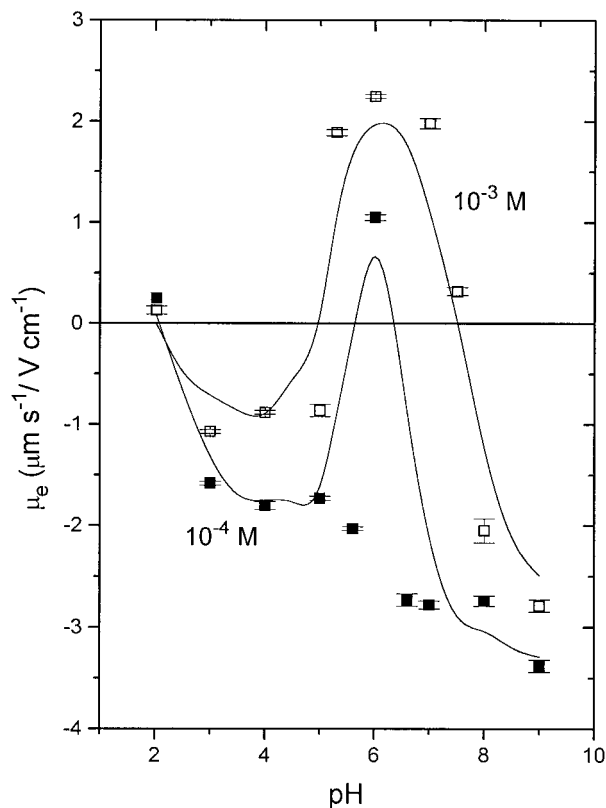


Figure 7 Electrophoretic mobility versus pH for Aquateric particles in the presence of 10^{-4} and $10^{-3}M$ AlCl_3 .

tions are shown in Figure 7, for two AlCl_3 concentrations, 10^{-4} and $10^{-3}M$. For both values, the behavior of μ_e (no attempt was made to compute ζ , since due to hydrolysis, the exact ionic concentrations are difficult to estimate) is similar: μ_e is positive at pH 2 (indicating the affinity between the Al^{3+} cation for the Aquateric surface), but changes to negative after a small pH increment. The mobility remains negative and approximately constant between pH 3 and 4 (for $10^{-3}M$ AlCl_3) or 5 ($10^{-4}M$) and then shows an abrupt change to positive. For higher pH values, a third charge reversal is found and, finally, the negative mobility increases in absolute value as the pH is further increased. Similar results were reported in Ref. 25 for an ethylcellulose latex and conform to the general features of the behavior described by James and Healy²⁶ for inorganic colloids. According to the conclusions of these authors, the second charge reversal (pH 5 or 6) corresponds to a precipitation of $\text{Al}(\text{OH})_3$ on the colloidal particles (the effect will be more important the higher the initial concentration of AlCl_3 , as, in fact, observed). Beyond this charge reversal pH, the electrokinetic behavior of the particles tends to ap-

proach that of $\text{Al}(\text{OH})_3$, the more so the more extensive their aluminum hydroxide coverage. Thus, the second charge reversal pH found for $10^{-3}M$ AlCl_3 (pH ≈ 7.5) is close to that of pure Al_2O_3 (pH 9, see ref. 4). When the concentration is $10^{-4}M$, the charge reversal takes place at a lower pH, this indicating that the coverage of the particles is limited and the behavior of Aquateric at high pH values (see Fig. 2) tends to be approached.

CONCLUSIONS

The study carried out of the electrophoretic behavior of cellulose acetophthalate latex (Aquateric) shows that the surface charge of the polymer particles is strongly affected by the ionic composition of the environment. The effect of pH on the zeta potential demonstrates that the charge is fully generated at pH 5, corresponding to the situation in which all surface acetate groups are dissociated. Calcium chloride has proved to be a suitable electrolyte to control the electrokinetic charge of Aquateric. Experiments with aluminum chloride show that a large variety of situations (charge sign and magnitude) can be reached if both pH and salt concentration are controlled.

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