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Electrophoretic Study of Nitrofurantoin in Aqueous Suspensions. Effect of the Addition of a Polymeric Thickener

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Abstract—The electrophoretic mobility of nitrofurantoin (based on the microelectrophoresis method) has been studied in dilute dispersions of the drug. Specifically, the effect of NaCl, $CaCl_2$ and $AlCl_3$, pH, and a thickener, Carbopol 934, was determined. The electrophoretic mobility (μ) increases in absolute terms when the pH is raised between 3 and 9, although μ remains negative in this pH range. The variation of absolute mobility ($|\mu|$) with NaCl concentration shows a pronounced maximum for a concentration of about 10^{-4} M. However, when the concentration of $CaCl_2$ in the medium is increased, $|\mu|$ decreases steadily. The effect of $AlCl_3$ concentration on the mobility is markedly influenced by the pH of the dispersing medium although a general trend is observed for μ to become more positive with increasing concentration of the salt. Finally, Carbopol 934 appears to impart an extra negative charge to the nitrofurantoin surface, since higher negative mobilities were measured in the presence of the polymer.

The electrophoretic study of suspensions is the most widely employed electrokinetic method (Overbeek 1952a, b; Dukhin & Derjaguin 1974) for obtaining detailed qualitative and quantitative information on the electrical characteristics of the solid-liquid or liquid-liquid interface, especially in industrial or pharmaceutical laboratories (Haines & Martin 1961; Gerdes 1966; Dipak & Bhogi 1978).

Calculating zeta potential or surface charge from an experimentally available quantity such as electrophoretic mobility entails the use of theoretical models. Although these are numerous, and vary in terms of complexity and predictive accuracy (Overbeek 1950; Dukhin & Derjaguin 1974; O'Brien & White 1978), it is often sufficient (and nearly always within the bounds of acceptable precision) to consider the mobility itself as a reliable indicator of the electrical properties we wish to study. This is particularly true when, as here, qualitative data are compiled for the purpose of establishing the stability of systems such as pharmaceutical suspensions.

Nitrofurantoin is commonly administered by mouth as an aqueous suspension but the electrokinetic properties of such a system have been little studied. We now report the changes in electrophoretic mobility in response to various concentrations of inorganic electrolytes (NaCl, $CaCl_2$ and $AlCl_3$) and the effect of pH on this quantity. As thickeners are used to enhance the physical stability of disperse systems, the present study was also designed to determine whether Carbopol 934 improves stability by influencing the electrical properties of the double layer.

Materials and Methods

Materials

Nitrofurantoin was obtained from Merck and Carbopol 934 from BF Goodrich. Water was double distilled and deionized and filtered through a Milli-Q Reagent Water System (Millipore).

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Methods

Preparation of suspensions. The nitrofurantoin sample was pulverized in a mechanical mortar to reduce the average particle size to values appropriate for microelectrophoresis. The powder was dispersed in water and allowed to settle for 8 h. The solid phase remaining in the supernatant thus consisted of particles with equivalent spherical diameter approximately equal to 2 μm. This supernatant was used as the stock suspension from which all study systems were prepared. In all suspensions assayed the solid volume fraction was $(3{\cdot}81 \pm 0{\cdot}01) \times 10^{-4}$ (v/v) based on gravimetric determinations.

Electrophoretic mobility determinations

Electrophoretic mobilities (μ) were determined at $25{\cdot}0 \pm 0{\cdot}5$ °C with a commercial microelectrophoresis apparatus (Zeta-Meter). In all runs a 1000 Vm^{-1} electric field was applied, and the data points illustrated in the Figures represent the average mobility of 20 separate particles in each direction of the applied field. Each 20 particle run was duplicated for all systems tested, using fresh, previously unused samples for all assays. Typical values of 95% confidence intervals for mobility yield an estimation of $\pm 5\%$ relative error for μ.

Results and Discussion

Effect of pH

Fig. 1 shows the effect of pH on the electrophoretic mobility (μ) of nitrofurantoin, in the absence of electrolytes other than the acid or base necessary for adjusting pH. Absolute values for mobility rise as pH increases. In addition, mobility, and hence the surface charge density of nitrofurantoin, remain negative throughout the range of pH values examined. Given

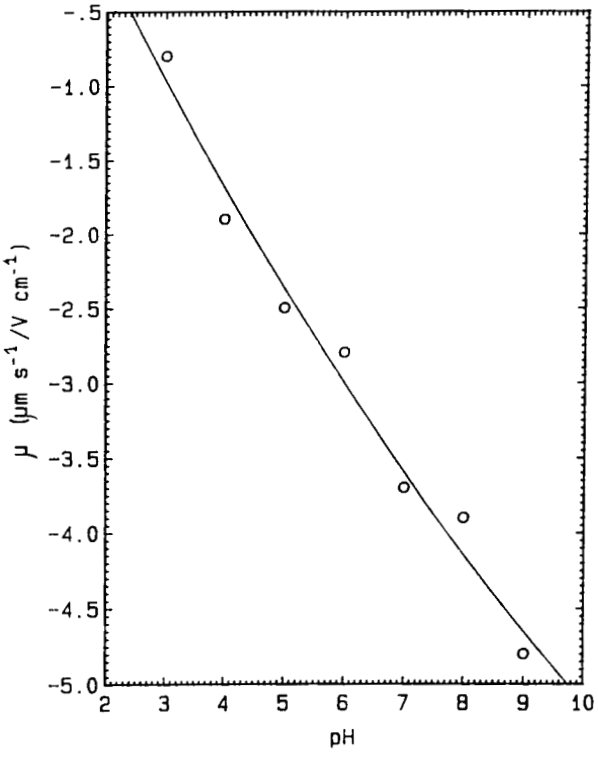

FIG 1. Electrophoretic mobility of nitrofurantoin as a function of pH.

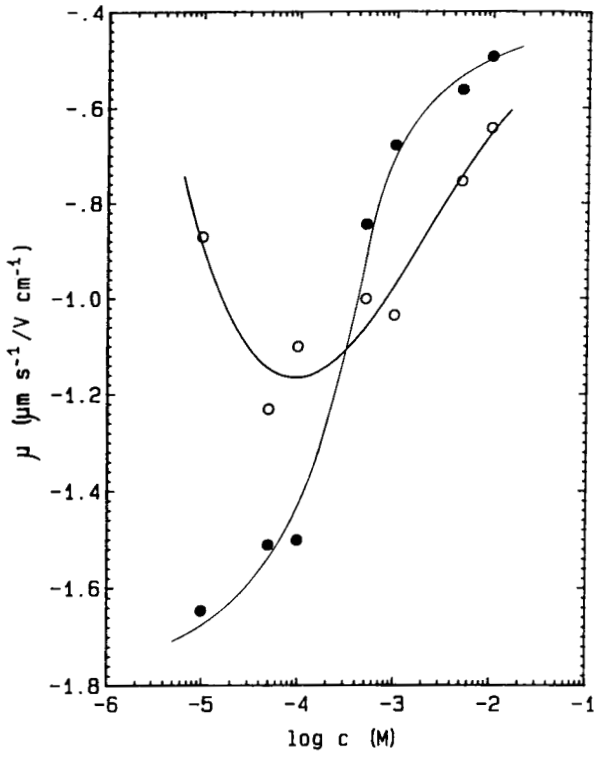

FIG. 2. Electrophoretic mobility of nitrofurantoin as a function of NaCl (○) and $CaCl_2$ (●) concentration at pH 4.

the acidic character of the hydrogen atom in the imide group of nitrofurantoin, deprotonation may be responsible for the resulting net negative charge. The more markedly negative values of μ may reflect the influence of increasing concentration of OH^- ions in solution. In contrast, the progressive neutralization of these negatively charged zones via the chemical adsorption of a growing number of H^+ ions as pH falls is the most likely explanation for the lower mobility recorded in the acid pH range. Thus, the maximum physical stability of nitrofurantoin suspensions would be expected at high pH, where the electrostatic repulsion between the drug particles is most significant. However, those conditions also imply a very thin electric double layer and hence short distances of interparticle approach. Also for larger particles a low volume sediment can form which is difficult to redisperse. Some intermediate pH value, close to neutrality, should be optimum for the preparation of nitrofurantoin dispersions.

Effect of inorganic electrolytes

As pH can affect the way in which different ions influence the electrical characteristics of the nitrofurantoin/solution interface, changes in mobility in response to electrolyte concentration were studied over a wide range of pH values. Figs 2–4 show the effects of NaCl and $CaCl_2$ at pH 4, 7 and 9. A common feature in these cases is that μ is consistently negative, while absolute mobility ($|\mu|$) tends to decrease as salt concentration rises. This overall trend demonstrates the non-specific character of these electrolytes. Compression of the double layer leads to a fall in mobility as the counterions approach the surface of the particles more closely, thus

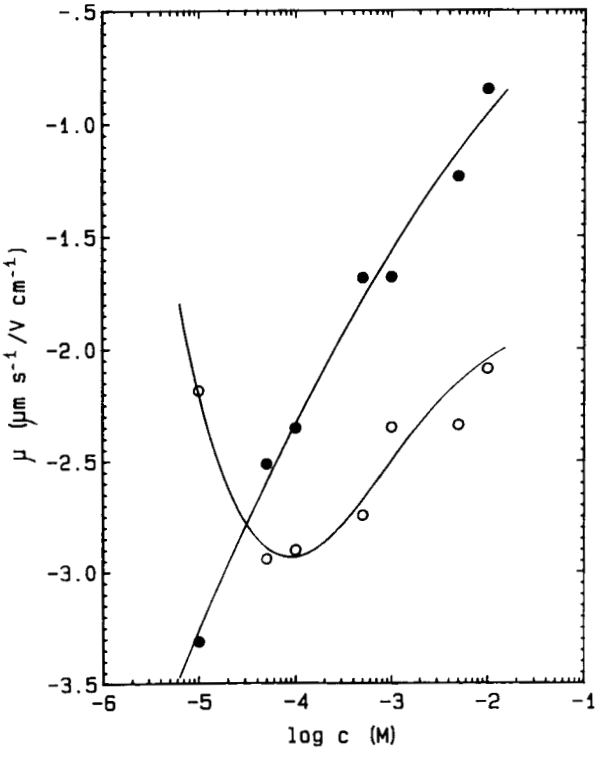

FIG. 3. Electrophoretic mobility of nitrofurantoin as a function of NaCl (○) and $CaCl_2$ (●) concentration at pH 7.

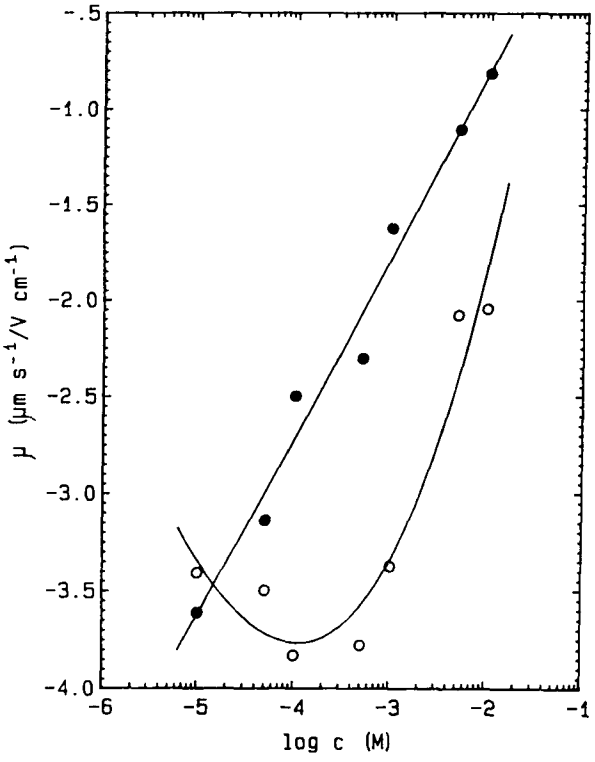

FIG. 4. Electrophoretic mobility of nitrofurantoin as a function of NaCl (○) and $CaCl_2$ (●) concentration of pH 9.

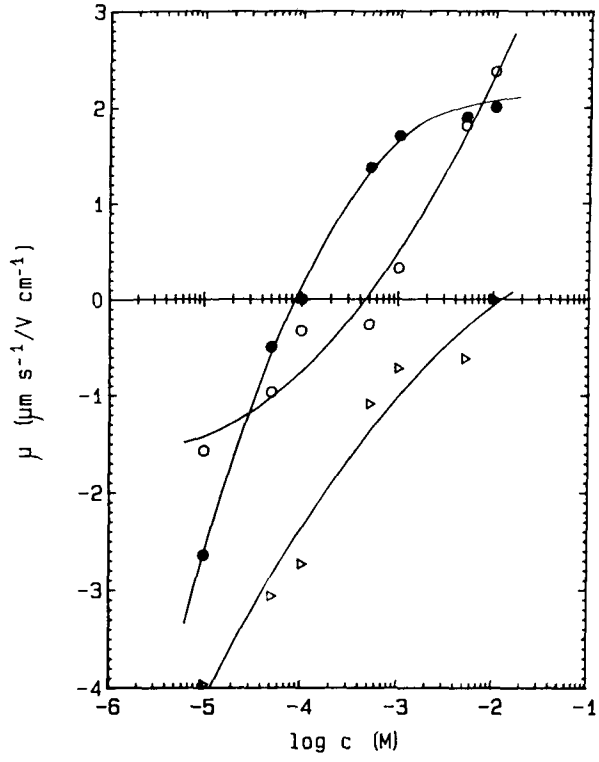

FIG. 5. Electrophoretic mobility of nitrofurantoin as a function of $AlCl_3$ concentration. ○ pH 4; ● pH 7; ▷ pH 9.

shrinking the double layer and giving rise to reduced zeta potentials.

The differential effects of the Na^+ and Ca^{2+} counterions on μ are also evident (cf, Figs 3, 4). Ca^{2+} is markedly more influential than Na^+ as has been found by other authors with a variety of colloidal systems (Swartzen-Allen & Matijevic 1975; Delgado et al 1986). This behaviour is in accordance with the Schulze-Hardy rule (Overbeek 1952a, 1980): the greater the valency of the counterion, the greater the flocculating effect of the salt involved, hence the greater the reduction in zeta potential. However, at low concentrations the mobility of nitrofurantoin is less in the presence of NaCl than with the same concentration of $CaCl_2$, an unexpected finding in the light of the Schulze-Hardy rule. Moreover, between 10^{-5} and 10^{-4} M NaCl $|\mu|$ actually increases and reaches a value larger than that attained in the presence of $CaCl_2$. This apparently anomalous variation may be explained on the basis of the interaction between Cl^- ions and the nitrofurantoin surface, i.e. in terms of specific or chemical adsorption of Cl^- onto the drug particles. At low NaCl or $CaCl_2$ concentrations the counterions may be unable to coat the entire surface, thereby allowing Cl^- ions to be adsorbed. This event would raise the net negative charge, and hence the mobility. As the calcium salt provides double the concentration of chloride ions as does sodium chloride (for the same concentration of electrolyte), the effect would be more marked with the $CaCl_2$, leading to greater (i.e. more negative) mobility, as is indeed the case (Figs 2–4).

The results suggest that changes in the concentration of NaCl in the dispersing medium will have little effect on the stability of nitrofurantoin suspensions, whereas $CaCl_2$ added in small amounts, may favour the stability of the drug preparations.

Fig. 5 illustrates the change in mobility with rising $AlCl_3$ concentration at all pH values tested. Mobility goes from positive to negative at $AlCl_3$ concentrations of approximately 5×10^{-4} (pH 4), 5×10^{-5} (pH 7) and 10^{-2} (pH 9) M. The marked rise denoted by this last figure may be explainable by the findings in Fig. 1: as rising pH tends to shift mobility toward increasingly negative values, higher concentrations of Al^{3+} ions become necessary to neutralize the surface charge and make it positive. The results demonstrate that interaction between the aluminium cation and the particle surface is strong; even when surface charge is positive, the addition of further $AlCl_3$ makes it more positive.

Fig. 6 shows the change in mobility with pH for the lowest and highest $AlCl_3$ concentrations tested. Although both curves are similar in shape, the higher salt concentration displaced mobility to more positive values. As H^+ and Al^{3+} ions compete to occupy negative sites on the nitrofurantoin surface, the trivalent cations are adsorbed more efficiently when the pH is approximately 5. Taking into account that hydrolysis of aluminium becomes significant above pH 4, it can be assumed to reach relatively influential levels by pH 5. This implies that hydrolysis favours the chemical adsorption of Al^{3+} cations, a finding which has been previously reported for other hydrophobic colloids (Swartzen-Allen & Matijevic 1975). At pH values above 5, the rising concentration of OH^- ions would govern the entire process, thus making mobility increasingly negative.

The results in Fig. 6 are particularly significant in the consideration of the stability of nitrofurantoin suspensions;

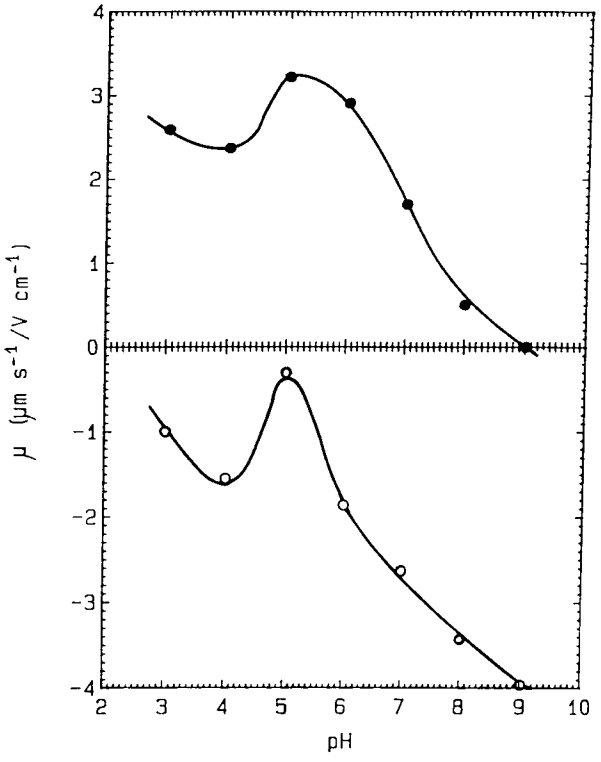

FIG. 6. Electrophoretic mobility of nitrofurantoin as a function of pH for two different $AlCl_3$ concentrations. ○ 10^{-5} M; ● 10^{-2} M.

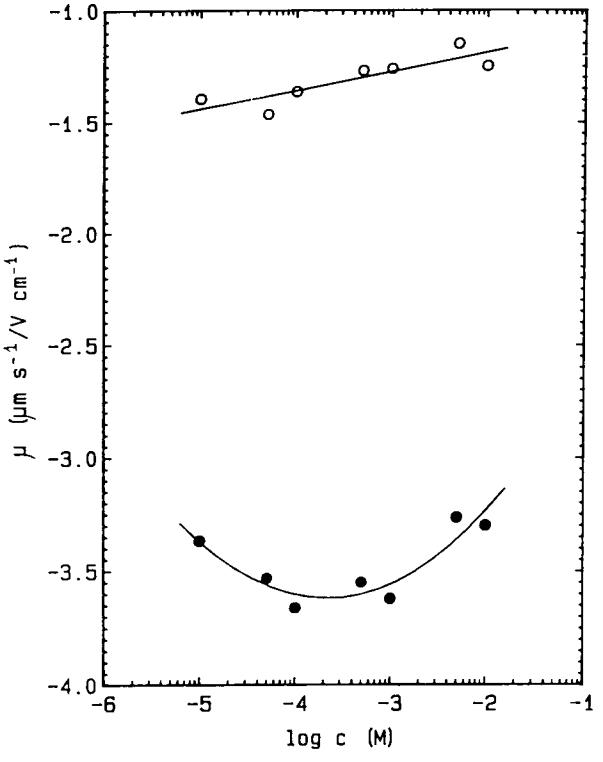

FIG. 7. Electrophoretic mobility of nitrofurantoin with 0·1% Carbopol 934 as a function of NaCl concentration. ○ pH 4; ● pH 7.

at intermediate pH values (6–8) and low $AlCl_3$ concentration, the double layers will be relatively thick and the surface charges moderate. The tendency of the particles will be to remain stable in suspension, but should aggregation and sedimentation occur, redispersion and recovery of a homogeneous dispersion may be easy. At high salt concentrations, the double layer will be compressed, and a lower pH ($\approx$3–6) will be needed to ensure stability and easy redispersion of the system. $AlCl_3$ appears to be a suitable electrolyte for the control of stability of nitrofurantoin suspensions.

Influence of thickener

Thickening agents are added to pharmaceutical suspensions to increase the viscosity of the medium and hence reduce the sedimentation velocity. However, such agents may also affect the electrical properties at the solid-liquid interface. The addition of 0·1% Carbopol 934 was sufficient to cause notable changes in the viscosity of the test suspension without significantly influencing its Newtonian characteristics. Its effects on electrical properties which illustrate the electrophoretic mobility of nitrofurantoin at various concentrations of NaCl and $AlCl_3$ are shown in Figs 7 and 8. Two pH values were analysed: pH 4, which is near that of the suspension itself and pH 7, which according to data published earlier for Carbopol 934 (Perotti 1970), is the value at which the effects of this polymer on viscosity are greatest.

Fig. 7 shows mobility (μ) as a function of NaCl concentration. The curves are flatter and more negative than those in Figs 2 and 3 (results with NaCl but without Carbopol). At pH 7, μ is around $-2{\cdot}5$ $\mu m\ s^{-1}/Vcm^{-1}$ in Fig. 3, and about $-3{\cdot}5$ $\mu m\ s^{-1}/Vcm^{-1}$ in Fig. 7. At pH 4, the difference

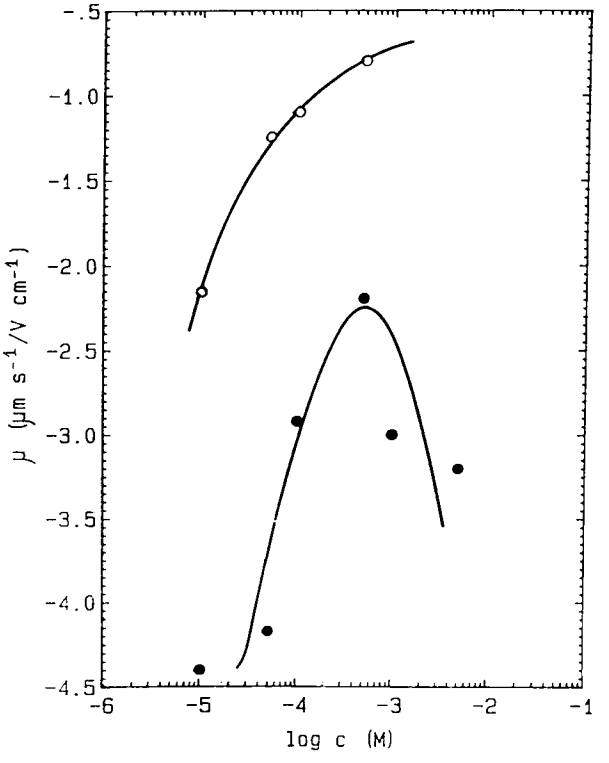

FIG. 8. Electrophoretic mobility of nitrofurantoin with 0·1% Carbopol 934 as a function of $AlCl_3$ concentration. ○ pH 4; ● pH 7.

between the curves is similar, but in absolute terms smaller; μ is around $-0{\cdot}9$ μm s^{-1}/Vcm^{-1} in Fig. 2, and about $-1{\cdot}3$ μm s^{-1}/Vcm^{-1} in Fig 7. These data suggest that Carbopol is able to increase the net negative charge on nitrofurantoin. To appreciate the full implication of this finding, the increase in viscosity needs to be considered in comparison with the same suspension without thickener. Based on Smoluchowski's simple theory, the rise in viscosity should involve a corresponding fall in the absolute value of μ if charge remains constant. The present results, however, show that just the opposite occurs in our system.

Figs 8 and 5 portray the effect of aluminium chloride on mobility in the presence and absence of Carbopol, respectively. At pH 4 μ becomes less negative in both cases as the salt concentration is increased. Nevertheless, when no thickener is added the mobility corresponding to the lowest $AlCl_3$ concentration is $-1{\cdot}5$ μm s^{-1}/Vcm^{-1}, and a zero mobility is attained when the concentration is 5×10^{-4} M, whereas in the presence of Carbopol the corresponding mobility is -2 μm s^{-1}/Vcm^{-1} and μ fails to reach positive values within the range of concentrations tested. These observations indicate an increase in the net negative charge on the particles. Figs 8 and 5 show that Carbopol apparently prevents μ taking positive values. Moreover, μ does not even approach zero at pH 7 in Fig. 8. A minimum absolute mobility occurred at a concentration of approximately 5×10^{-4} M in the presence of Carbopol, due most likely to the combination of salt and thickener raising ionic strength and thus leading to a decline in zeta potential in response to compression of the double layer. More significantly, Figs 7 and 8 both show that Carbopol raises the net negative charge on the drug. As others have pointed out (Perotti 1970), the addition of a base to a suspension containing Carbopol leads to ionization of the latter's -COOH groups, resulting in negative charges throughout the polymer chain. It is these negative charges which are responsible for the unwinding mechanism, and hence the thickening action of the compound. In light of our results however, these charges also mean that part of the stabilizing effect of Carbopol is traceable to an electrical phenomenon. The interaction with the nitrofurantoin surface (and possibly with other pharmaceutical systems), especially at pH 7, imparts an extra negative charge to the particles, which enhances their mutual repulsion and thus avoids flocculation.

Acknowledgements

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