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THE EFFECT OF HYDROPHILIC POLYMERS ON THE ELECTROPHORETIC MOBILITY OF SUSPENDED PARTICLES

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SUMMARY

The effects of various grades of polyvinylpyrrolidone (PVP), sodium carboxymethylcellulose (SCMC), acid and alkaline gelatins and hydroxypropylmethylcellulose (HPMC) on the electrophoretic mobility of polystyrene latex, and particles of the drugs, nystatin and sulphadimidine, have been examined. In all cases, particle mobility was influenced by the adsorbed polymer molecules with the observed effect being dependent on polymer type, grade and concentration. The non-ionic polymer, PVP, resulted in an appreciable decrease in particle mobility, the effect being greater for the higher molecular weight fractions. However, with the anionic polymer, SCMC, the mobility of particles was controlled by the ionization of the polymer carboxylic groups. The effect of adsorbed gelatin on particle mobility was dependent upon the ionization of the amino acid groups and thus enabled the isoelectric point of the gelatins to be determined from pH–particle mobility plots. HPMC adsorption resulted in a low negative mobility which was independent of pH.

INTRODUCTION

The microelectrophoretic examination of suspended drug particles has been used extensively to study the influence of surface-adsorbed adjuvants on the zeta potential and the subsequent effect on suspension stability. The relationship between the zeta potential and the flocculation behaviour of suspended drug particles forms the basis of the controlled flocculation approach to suspension formulation first developed by Haines and Martin (1961a, b and c) and later by Matthews and Rhodes (1968a and b, 1970), Jones et al. (1970) and Short and Rhodes (1973). In this work the effect of various molecular weight fractions of polyvinylpyrrolidone (PVP), sodium carboxymethylcellulose (SCMC), hydroxypropylmethylcellulose (HPMC) and acid- and alkaline-processed gelatins on the electrophoretic mobility of polystyrene latex, sulphadimidine and nystatin particles has been examined. The adsorption of these polymers onto polystyrene latex has previously been reported (Kellaway and Najib, 1980).

MATERIALS AND METHODS

The samples of polystyrene latex, PVP and SCMC were as described previously (Kellaway and Najib, 1980). The sulphadimidine was obtained from ICI, Macclesfield, U.K. and nystatin from Squibb, Moreton, U.K. The HPMC 450 was obtained from British Cellanese Chemicals, Derby, U.K.

All solutions and dispersions were, unless otherwise stated, made in 1 mM NaCl as a supporting electrolyte and to keep the ionic strength as constant as possible. The pH was adjusted by the addition of 1 mM NaOH or HCl. Electrophoretic mobilities at 25°C were measured at the upper stationary level in a cylindrical cell of a Rank Mark II microelectrophoresis apparatus (Rank, Bottisham, U.K.). The particles were timed successively in opposite directions to minimize polarization effects. At least 20 particles were timed in each direction and the mean velocity from 40 observations was calculated.

RESULTS AND DISCUSSION

The effect of pH on the electrophoretic mobility was determined for polystyrene latex (Fig. 1), sulphadimidine (Fig. 2) and nystatin (Fig. 2). The mobility plot for polystyrene latex exhibits 3 distinct regions when examined in 1 and 100 mM NaCl. The mobility at the low pH is due to the ionization of the sulphate groups adsorbed at the latex surface from the potassium persulphate used in the polymerization process. These groups are only ionized in strong acid conditions. It has been noted (Kayes, 1972) that if the sulphate groups were not present, the mobility would fall sharply below pH 5 and become zero at pH < 2. Ottewill and Shaw (1967) found that the mobility decreased very slowly and would not be zero if the sulphate groups were present on the surface. The observed

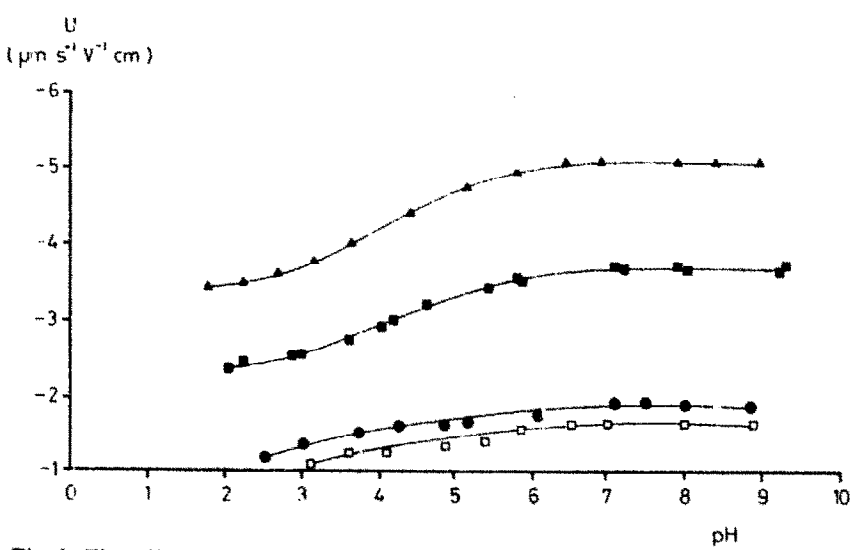

Fig. 1. The effect of pH on the electrophoretic mobility (U) of polystyrene latex at 25°C. Key: 100 mM NaCl (■); 1 mM NaCl (▲); 1 mM NaCl + 0.1% (w/v) PVP 10,000 (□); 1 mM NaCl + 0.1% (w/v) PVP 24,500 (●).

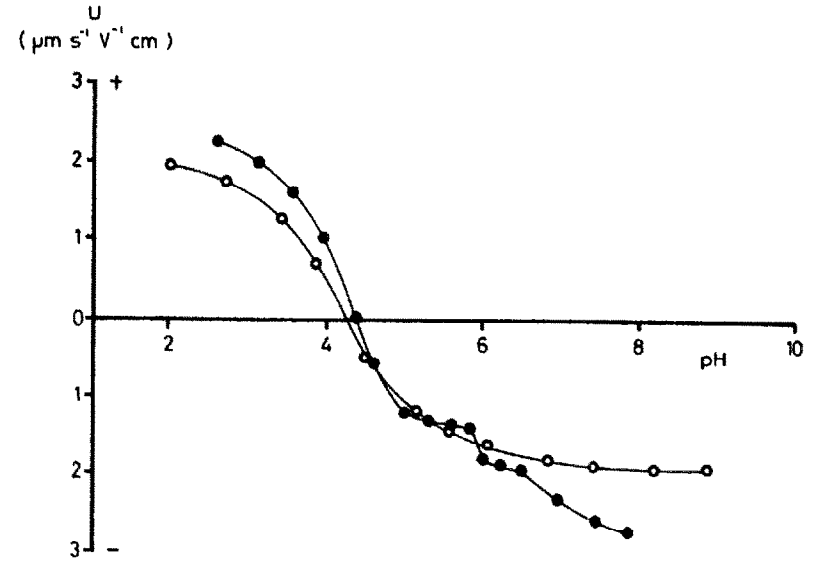

Fig. 2. The pH–electrophoretic mobility (U) plots for sulphadimidine (•) and nystatin (○) particles at 25°C in 1 mM NaCl.

increase in mobility as the pH increases to 5.5 is due to the partial ionization of the carboxylic acid groups. For pH > 6.0, the mobility remains constant indicating complete ionization of the carboxylic acid groups. Sulphadimidine in contrast (Fig. 2) exhibited a positive mobility at low pH, zero mobility at pH 4.4 and negative mobility at higher pHs. The positive mobility at the low pH is due to the ionization of the basic amino and imino groups which are only ionized in strong acid conditions. The negative mobility at higher pHs is due to the ionization of the sulphonic acid groups and is probably due in part to the adsorption of hydroxyl ions. The two reproducible steps obtained at pH 5–5.5 and 6–6.25 may be attributed to pH-dependent ion adsorption. Nystatin (Fig. 2) showed similar behaviour to sulphadimidine with positive mobility at low pH (amino group ionization), zero mobility at pH 4.5 and negative mobility at higher pHs (carboxylic acid group ionization).

The mobility of the latex in 0.1% solutions of PVP was examined and the results for PVP 10,000 and 24,500 shown in Fig. 1. Latex mobility was reduced and zero mobility obtained for PVP of molecular weight >44,000 over the pH range examined, This reduced or zero mobility is due to the masking of the charge on the latex surface by the adsorbed, non-charged PVP molecules. The thickness of this adsorbed film (Δ) has previously been determined (Kellaway and Najib, 1980) and shown to be a function of PVP molecular weight. Δ increased rapidly up to a molecular weight of 44,000, thereafter only a relatively small increase was observed over an extended molecular weight range.

The effect of PVP on the mobility of sulphadimidine particles was not as great (Fig. 3). The adsorption of PVP from 0.1% (w/v) solutions resulted in a reduction in the mobility of the dispersions and caused a shift of approximately one unit in the pH of zero charge. There was no clear difference in the profiles of the PVP 10,000, 24,500, 40,000 and

44,000 and hence the results are represented as a hatched area (Fig. 3). PVP 360,000 and 700,000, in contrast, completely abolished the positive mobility at low pHs and resulted in low negative mobility for pH > 5.0. This further demonstrates the differences in adsorbed film properties obtained with the longer chain, i.e. higher molecular weight, PVPs. The latter were more effective in masking the surface charge on the sulphadimidine particles, a result similar to that found with PVP adsorption on latex.

The effect of PVP on the electrophoretic mobility of nystatin (Fig. 4) was to reduce particle surface charge. For pH > 6, the reduction in mobility increased with increasing PVP molecular weight. No such relationship was found for pH < 6.0, although the shape of the curves were similar and all PVP fractions produced a lowering of the mobility compared with untreated nystatin particles for pH < 4.

The effect of acid and alkaline gelatins on the electrophoretic mobility of polystyrene latex and sulphadimidine particles is shown in Fig. 5. The alkaline gelatin showed a greater negative mobility than the acid for both latex and drug particles suggesting a greater net molecular charge. The point of zero mobility was that of the isoelectric point of the gelatins showing that the mobility of the latex and the drug with adsorbed gelatin was determined by the ionization of the constituent amino acids and therefore estimates of the isoelectric points can be made from the mobility–pH curves. As previously noted by Robinson et al. (1975), this was at pH 4.5 for the alkaline gelatin and 6.25 for the acid gelatin. The agreement between data for both latex and sulphadimidine particles containing adsorbed gelation was good for particles with negative mobilities, i.e. pH > isoelectric point, although deviations were noted for pH < isoelectric point.

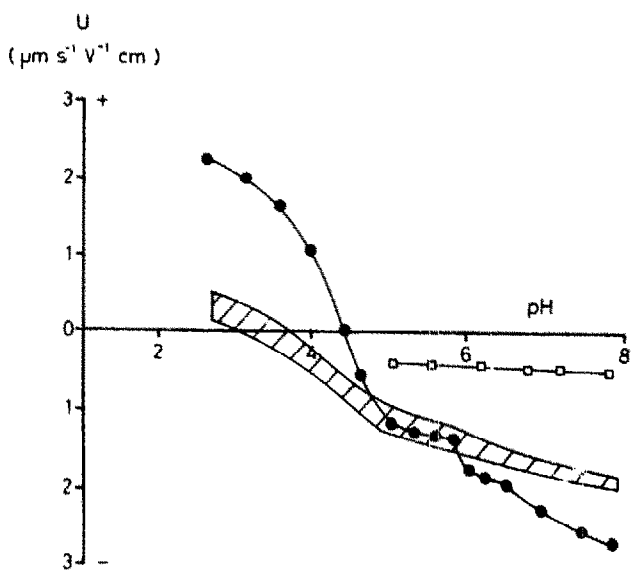

Fig. 3. The effect of PVP on the electrophoretic mobility (U) of sulphadimidine particles in 1 mM NaCl at 25°C. Key: sulphadimidine (●); sulphadimidine + 0.1% (w/v) PVP 360,000 (□); sulphadimidine + 0.1% (w/v) PVP 700,000 (□). Hatched area: sulphadimidine in 0.1% (w/v) solution of PVP 10,000, 24,500, 40,000 and 44,000.

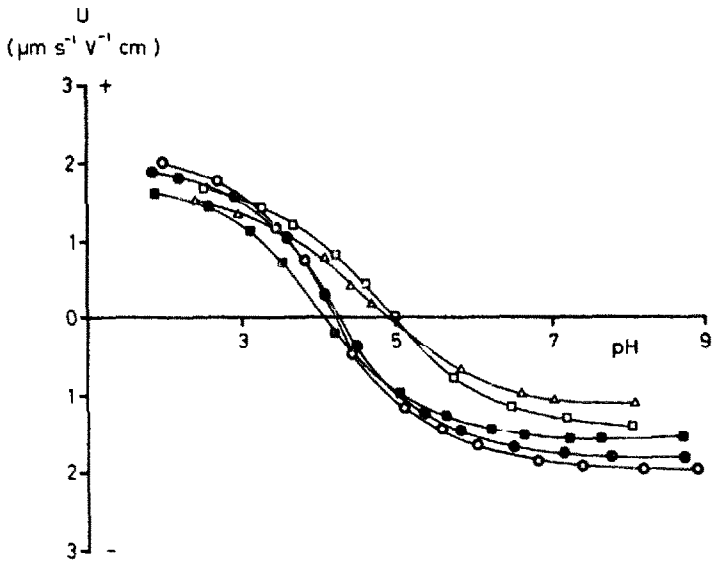

Fig. 4. The effect of 0.1% (w/v) PVP on the electrophoretic mobility (U) of nystatin particles at 25°C in 1 mM NaCl. Key: nystatin (○); nystatin + PVP 10,000 (●); nystatin + PVP 24,500 (■); nystatin + PVP 44,000 (□); nystatin + PVP 360,000 (△); nystatin + PVP 700,000 (▲).

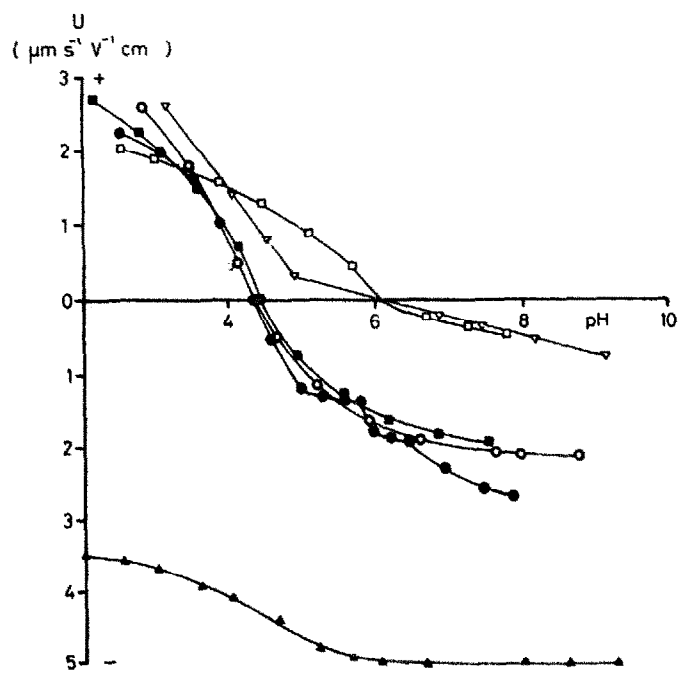

Fig. 5. The electrophoretic mobility (U) of latex and sulphadimidine particles in 0.1% (w/v) gelatin solutions at 25°C. Key: Latex (▲); latex + alkaline gelatin (○); latex + acid gelatin (△); sulphamidine (●); sulphadimidine + alkaline gelatin (■); sulphadimidine + acid gelatin (□).

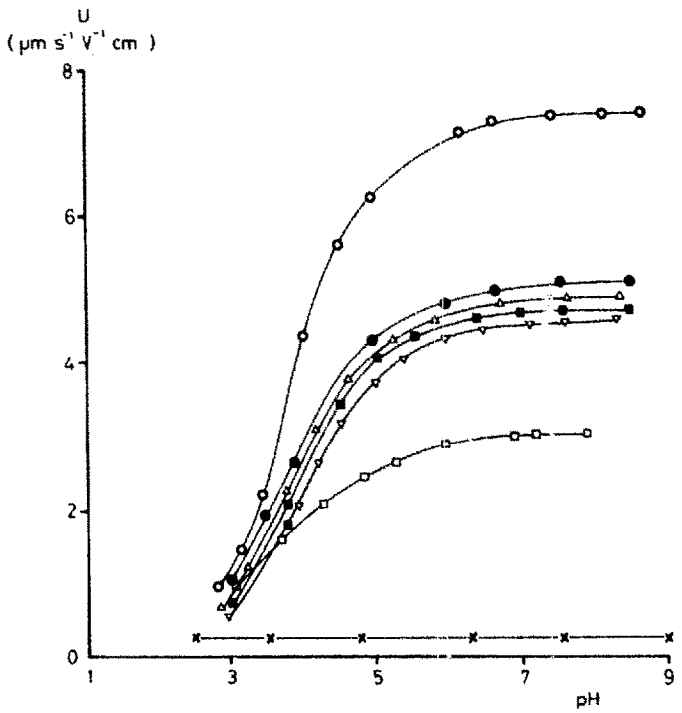

Fig. 6. The effect of 0.1% w/v SCMC and HPMC solutions on the electrophoretic mobilities (U) of various particles at 25°C. Key: sulphadimidine in SCMC P20 (▽); sulphadimidine in SCMC P40 (■); sulphadimidine in SCMC P75 (△); sulphadimidine in SCMC P1000 (●); polystyrene latex in SCMC P20 (○); nystatin in SCMC P20 (□); polystyrene latex in HPMC 450 (×).

The mobility of the latex in HPMC solution is shown in Fig. 6. The adsorption resulted in a low negative mobility which was independent of pH. In contrast, the adsorption of SCMC imparted a greater negative mobility to the latex compared with a sample without added polymer. This increased negative mobility is due to the ionization of the carboxylic acid groups on the SCMC molecules. In the case of sulphadimidine and nystatin there was a complete elimination of the positive mobility indicating good surface coverage of the particles by the polymer. In all cases the mobility rises with a decrease in acidity to pH 6 above which little change in mobility was noted. This behaviour is characteristic of ionization of the carboxylic acid groups as shown by the mobility–pH curve for polystyrene. This increased mobility of the latex and drugs as a result of SCMC adsorption may be due to the fact that SCMC is an anionic polymer, the adsorption of which onto a negatively charged surface such as polystyrene latex must be hydrophobic in nature. The negative charges will therefore be directed away from the surface into the diffuse layer which will result in an increase in potential at the shear plane and hence an increase in mobility.

The negative mobility resulting from SCMC adsorption onto the latex and drug particles was found to show a dependence on SCMC molecular weight, with greater mobility resulting from higher molecular weight fractions (see results for sulphadimidine in Fig. 6). This probably arises due to larger quantities of higher molecular weight fractions being adsorbed per unit area of surface. The following relationship (Perkell and Ullman, 1961)

describes the amount of polymer required to saturate a surface (A_s) as a function of molecular weight (M)

$$A_s = K \cdot M^{\alpha}$$

where K and α are constants. This relationship had previously been found to hold for both the PVP and SCMC fractions adsorbed onto latex (Kellaway and Najib, 1980). The influence of surface characteristics in determining polymer adsorption is also demonstrated in Fig. 6, where it can be seen that widely differing mobilities were found for SCMC P20 adsorbed onto latex, sulphadimidine and nystatin, although the shape of the pH–mobility plots were similar.

Although all data have been presented as the experimentally determined value of the electrophoretic mobility (U), it is a simple matter to convert these values into the corresponding zeta potentials (ζ) using the Smoluchowski equation

$$U = \frac{\epsilon\zeta}{4\pi\eta}$$

and substituting appropriate values for the dielectric constant (ϵ) and the viscosity (η). This equation does not, however, allow for retardation effects arising as a consequence of the ion-atmosphere around the particle. To correct for the retardation effect, the particle radius (a) and the Huckel double-layer thickness (1/K) is required. It was therefore considered that in the present context, nothing would be gained by using estimates of K_a in order to convert the data to zeta potentials.

In conclusion, this study has shown that the adsorption of hydrophilic polymers onto drug particles greatly modifies the zeta potential, which controls the flocculation state and hence stability of suspensions. The presence of the adsorbed polymer may well be a pharmaceutical factor influencing drug-particle dissolution rates and hence bioavailability.

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REFERENCES

Haines, B.A. and Martin, A.N., Interfacial properties of powdered material; caking in liquid dispersions. I, II and III. J. Pharm. Sci., 50 (1961a, b and c) 228–232; 753–756 and 756–759.

Jones,, R.D.C., Matthews, B.A. and Rhodes, C.T., Physical stability of sulphaguanidine suspensions. J. Pharm. Sci., 59 (1970) 518–520.

Kayes, J.B., Microelectrophoretic studies on polystyrene latices in the presence of polyoxyethylene glycol ethers of *n*-alkanols. Kolloid-Z.u.Z. Polymere, 250 (1972) 939–944.

Kellaway, I.W. and Najib, M.J., The adsorption of hydrophilic polymers at the polystyrene water interface. Int. J. Pharm., 6 (1980) 285–294.

Matthews, B.A. and Rhodes, C.T., Coagulation and flocculation in suspensions of griseofulvin and polystyrene latex. J. Pharm. Pharmacol., 20 Suppl. (1968a) 204S–212S.

Matthews, B.A. and Rhodes, C.T., Some studies of flocculation phenomena in pharmaceutical suspensions. J. Pharm. Sci., 57 (1968b) 569–573.

Matthews, B.A. and Rhodes, C.T., Use of the Derjaguin, Landau, Verwey and Overbeek theory to interpret pharmaceutical suspension stability. J. Pharm. Sci., 59 (1970) 521–525.

Ottewill, R.H. and Shaw, J.N., Studies on the preparation and characterization of monidisperse polystyrene latices. Kolloid-Z.u.Z. Polymere, 218 (1967) 34–40.

Robinson, J.A.J., Kellaway, I.W. and Marriott, C., The effect of ageing on the rheological properties of gelatin gels. J. Pharm. Pharmacol., 27 (1975) 653–658.

Short, M.P. and Rhodes, C.T., Formulation of steroidal suspensions. Can. J. Pharm. Sci., 8 (1973) 46–48.