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STERIC STABILIZATION OF SUSPENSIONS

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INTRODUCTION

The vast majority of work on pharmaceutical suspensions is concerned with the electrical stabilization of such systems, incorporating the DLVO theory of colloid science to account for the suspensions characteristics observed(1). Stabilization of particles, produced by the adsorption of polymers at the solid-liquid interface, has not been extensively investigated in the area of pharmaceutical suspensions. It is only recently that theories describing this 'steric stabilization' have been introduced(2) and these may be used only with certain restrictions

Steric stabilization has one major advantage over electrostatic stabilization in that it is relatively insensitive to the presence of added electrolytes. The addition of ionic excipients such as colourings, flavourings, buffers and preservatives must be taken into account when formulating a dispersion where stabilization is by electrostatic means alone. Possible leaching of ionic species from glass containers may also cause unwanted changes in suspension appearance and redispersibility. Stabilization of particles through the adsorption of polymers avoids this problem as the steric effect is independent of added electrolyte and high ionic strengths are usually required before the solution properties of nonionic polymers are affected.

It should be recognized that polymers or surfactants added as thickening or wetting agents will tend to adsorb at the drug-solution interface and that as a result a steric stabilizing effect will operate.

MATERIALS AND METHODS

Nonionic Pluronic surfactants L61, L62, L64 and F68 were used as received from the suppliers. Each molecule possesses two statistically equal ethylene oxide chains comprising 10, 20, 40 and 80% by weight of the total molecule respectively. Sample purity was checked by an extraction procedure and NMR spectroscopy analysis, as reported previously(3), and indicated substantial quantitites of free polyoxyethylene compounds - particularly in Pluronic F68. The second group of nonionic surfactants used were the nonylphenylethoxylates (NPE) which are stated to possess 8, 13, 20, 30 and 35 ethylene oxide units per molecule. NMR analysis of the surfactants together with their critical micelle concentrations is given in Table 1.

TABLE 1

Properties of Nonylphenylethoxylates

Surfactant	Manufacturer	Ethylene Oxide Content	cmc µmoles l^{-1}
NPE 8	I.C.I.	8.4	51
NPE 13	I.C.I.	12.8	71
NPE 20	I.C.I.	20.1	68
NPE 30	I.C.I.	31.7	100
NPE 35	Lankro	35.8	114

Adsorption isotherms were determined by shaking drug powder with the required amount of a known concentration of surfactant solution for 24 hours at 25°C. This was found to be ample time for equilibrium to be established. The initial dispersions were prepared by placing glass vials containing the dispersions in a sonic bath (Kerry Ltd.) for two minutes. Hand shaking for a further minute followed by the equilibration period gave suspensions which were completely dispersed when viewed under a microscope. Filtration through well soaked 0.45 µm membrane filters allowed the equilibrium concentration to be determined using an iodine solubilization technique(4). Dissolved drug did not interfere with the assay procedure and adsorption onto the glass vials and filtration assembly could not be detected.

The electrophoretic mobilities of drug suspensions were determined on a Rank Mk II microelectrophoresis apparatus (Rank Bros., Bottisham, Cambridge, UK). Particles were viewed in a flat cell via a television monitor. Mobilities were measured at constant ionic strength in 10^{-3} M sodium chloride solution except where mentioned in the text. As the particles are large ($\kappa a > 100$) (κ the Debye-Huckel reciprocal length parameter, a the particle diameter) the Smoluchowski equation ($\mu = \varepsilon\zeta/\eta$) ($\varepsilon$ the permittivity and η the viscosity of the aqueous medium), may be used to convert observed mobilities, u, to zeta potentials ζ. Where necessary the pH was adjusted using sodium hydroxide or hydrochloric acid solutions and in subsequent experiments where surfactants were adsorbed on the particles, mobility measurements were made at pH 8.0 ± 0.5 corresponding to the plateau region of the mobility-pH curves, Fig. 1.

Suspensions for stability evaluation were prepared as for the adsorption isotherms. In all cases 1 g of drug was used and 25 ml of surfactant solution made up in 10^{-2} M NaCl added. At this ionic strength the maximum zeta potential is -7 mV which is insufficient to provide a significant stabilizing force. Different suspension types therefore reflect the effect that surfactant adsorption has on suspension stability. After three days of standing at 25°C the appearance and sedimentation volume of the samples were recorded.

The Hamaker constants of the pure surfactants were measured using the dispersion technique of Gregory(5). The refractive index, n of the compounds was determined using an Abbe 60 refractometer from which the compensating Amici prism had been

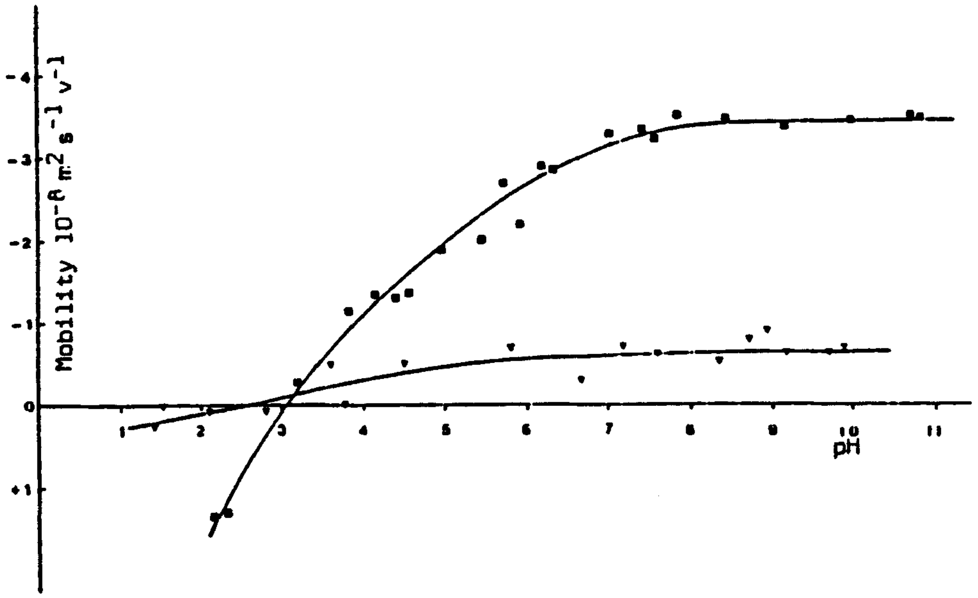

FIGURE 1

The pH mobility plot of Diloxanide Furoate B.P. in 10^{-2} M (▼) and 10^{-3} M (■) sodium chloride solution

removed to allow measurement at several wavelengths. Where the samples were solid or semi-solid at room temperature measurement was made at 60°C. Measurements were made at five wavelengths: 589, 546, 436, 644 and 480 nm, isolated from light emitted by sodium, mercury and cadmium discharge lamps. Linear plots were obtained by plotting $(n^2+2)/(n^2-1)$ against $(\text{frequency})^2$ and from these the Hamaker constant A_{33} was obtained.

To obtain the Hamaker constant for diloxanide furoate the powder was first recrystallized from chloroform to produce larger crystals and the refractive index of these crystals determined using the Beckeline method(6). This procedure involves immersing the crystals in a fluid and altering the refractive index of the fluid until it matches that of the crystals. At this point no differences are found in the optical behaviour between the two materials. No evidence of anisotropy could be found with the drug within the range of refractive index studied.

Programmes were written to evaluate the potential energy of interaction between particles using the ICL 1904S computer at th University of Aston in Birmingham. For the drug the attraction between semi-infinite flat plates covered with an adsorbed layer of polymer were used. These equations take into account the effect of electromagnetic retardation upon V_A(7).

RESULTS AND DISCUSSION

Adsorption isotherms of both the Pluronics and the nonylphenylethoxylates were similar in shape to those observed for the adsorption onto polystyrene latex(3,8) and could be fitted to the Langmuir equation for monolayer surface coverage. The maximum amount of surfactant adsorbed was however approximately half of that found on the latex. It has been shown that the hydrophobicity of a silica surface has a great effect on the amount of polyvinylalcohol adsorbed(9) and a similar variability is found for the adsorption of PVA onto the two surfaces used in the current work(8). The same is therefore probably applicable to the surfactants used here.

The electrophoretic mobility of the drug shown in Fig. 1 shows a slight net positive charge below pH 3 due to protonation of the substituted amide groups within the molecule. Above pH 3 a rapid reversal of charge occurs until a constant negative mobility is attained above pH 7.5. Hydroxyl ion adsorption onto the surface can give rise to this effect or alternatively it may be due to the fact that the centres of the smaller anions may approach closer to the surface than the hydrated cations in the manner proposed by Haydon(10).

The effect on the electrophoretic mobility of adsorbing the nonionic surfactants onto the drug surface is shown in Fig. 2 and demonstrates that the mobility falls until a plateau region is reached.

These results parallel the adsorption isotherms. At low surface coverage the adsorbed molecules lie in an extended configuration upon the surface and displacement of the shear plane away from the surface is not very great. Further adsorption crowds the molecules together and pushes them out from the surface until at maximum coverage there is maximum displacement from the surface and little change in mobility is apparent. The decrease observed at high concentrations is due to viscosity effects rather than multilayer formation.

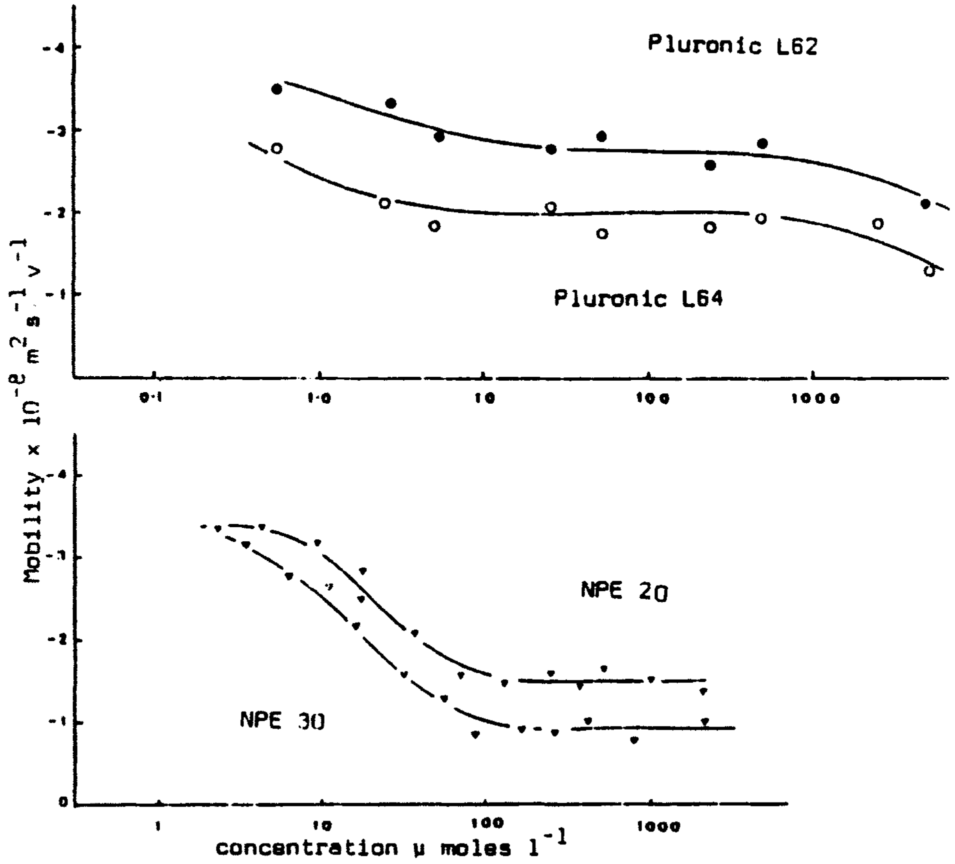

FIGURE 2

The effect of surfactant concentration on drug mobility

Attempts to obtain the thickness of the adsorbed layer from the results in Fig. 2 using a previously described method(11) were unsuccessful. Adsorbed layer thicknesses determined on polystyrene latex were therefore employed.

From all cases, when calculating the forces of attraction between drug particles, equations for semi-infinite flat plates have been used. Due to the non-sphericity of the particles and the large surface irregularities, equations for spherical particles were considered inappropriate. Use of spherical particle equations would also lead to very large energy minimum values which cannot be reconciled with the experimental evidence that in some cases deflocculated suspensions are formed.

In studying the mechanisms of particle aggregation, Evans and Napper(12) concluded that aggregation is probably induced as a result of the attraction between the stabilizing adsorbed layer sheaths rather than the attraction between the core particles. This applies where the core and sheath attractions are of the same magnitude. This procedure is adopted in the present work and calculations of the attractive potential V_A are performed which take into account the presence of adsorbed layers.

The presence of these layers presents certain difficulties in calculating the depth of the energy minimum as these equations for V_A predict that upon contact of the adsorbed layers V_A tends to $-\infty$. In this event all sterically stabilized dispersions would aggregate. To overcome this problem a few layers of solvent molecules are envisaged bound to the ethylene oxide chains and this provides a cut-off point at which Vs, the steric term increases rapidly. This cut-off point is taken to be 0.6 nm which corresponds to 4 molecules of water sandwiched between the interacting polymer layers.(13) This method of obtaining the energy minima obviates the need to calculate Vs exactly from the equations of Ottewill and Walker.(2) For polyoxyethylene chains in water the polymer-solvent interaction is strong.(14) Under such circumstances the steric term Vs, will be very strong and hence it is justifiable to represent Vs by a straight line rising nearly vertically from the V_A curve at a polymer layer separation of 0.6 nm.

Values of the Hamaker constants of the pure materials used are listed in Table 2 with the type of suspension that each adsorbed polymer produced and the depth of the potential energy minima.

TABLE 2

Material	Hamaker Constant $\times 10^{-20}$J	Suspension Type	Depth of Potential Energy curve $kT.nm^{-2}$
Water	3.78	-	
Diloxanide Furoate	5.88	-	
Pluronic L61	6.69	Aggregated	-12.48×10^{-3}
Pluronic L62	6.74	"	-13.15×10^{-3}
Pluronic L64	6.81	"	$- 5.94 \times 10^{-3}$
Pluronic F68	6.97	Deflocculated	$- 4.80 \times 10^{-3}$
NPE 8	7.00	"	$- 4.80 \times 10^{-3}$
NPE 13	6.91	"	$- 4.23 \times 10^{-3}$
NPE 20	6.85	"	$- 3.51 \times 10^{-3}$
NPE 30	6.79	"	$- 2.65 \times 10^{-3}$
NPE 35	6.78	"	$- 2.07 \times 10^{-3}$

Calculations of V_A at a polymer surface separation of 0.6 nm are shown in Figure 3 for data corresponding to:

a) Hamaker constant of adsorbed layer -4.5×10^{-20} J, Hamaker constant of core variable.

b) Hamaker constant of core -5.88×10^{-20} J, Hamaker constant of adsorbed layer variable.

At any one adsorbed layer thickness the depth of the minimum in the potential energy curve is more strongly affected by the Hamaker constant of the adsorbed layer than by that of the core. These calculations substantiate the view of Evans and

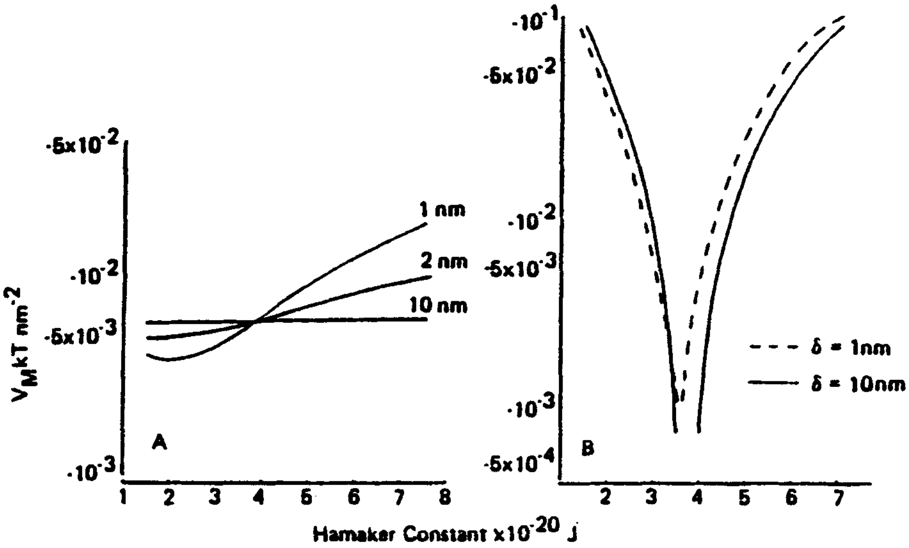

FIGURE 3

The effect of a) particle and b) adsorbed layer Hamaker Constant on the depth of the primary minimum.

Napper that it is the attraction between adsorbed layer sheaths which is primarily responsible for the promotion of particle aggregation.

The depth of the potential energy minima given in Table 2 is seen to depend on the surfactant used. The values of the adsorbed layer Hamaker constant is dependent upon the proportion of solvent within that layer(7) and mean surface concentrations are evaluated from the maximum amount of surfactant adsorbed and from the adsorbed layer thickness. The agreement between suspension type and the corresponding energy minimum is reasonable if a value of -5×10^{-3} kT.nm^{-2} is taken as the critical depth above which aggregation will not occur. The attraction between particles is therefore dependent upon the concentration of polymer in the adsorbed phase and these values are given in Table 3.

TABLE 3

Surfactant	Mean Conc$^{\underline{n}}$ of surfactant in Adsorbed Phase %^{w}/v	Ethylene Oxide Conc$^{\underline{n}}$ in Adsorbed Phase %w/v
Pluronic L61	34	3
Pluronic L62	36	7
Pluronic L64	15	6
Pluronic F68	4	3
NPE 8	22	13
NPE 13	21	15
NPE 20	18	14
NPE 30	16	13
NPE 35	16	14

The concentrations at the interface of the Pluronics which promote particle aggergation are higher than those where deflocculated systems are observed (except Pluronic L64). In addition, the concentration of the stabilizing ethylene oxide chains are far less in the Pluronic series and hence repulsive forces due to steric interactions will not be as great as those of the nonylphenylethoxylates. Aggregation of particles coated with adsorbed layer of Pluronics L61, L62 and L64 may therefore be due to a combination of two mechanisms: i) high interparticulate attraction due to high interfacial surfactant concentration, (ii) insufficient steric stabilization to prevent aggregation due to low adsorbed layer ethylene oxide concentrations.

REFERENCES

1. B. A. Mathews and C. T. Rhodes, J. Pharm. Sci., 57, 569 (1968).
2. R. H. Ottewill and T. Walker, Kolloid -Z.u.Z. Polymere 227, 108 (1968).
3. D. A. Rawlins and J. B. Kayes, J. Pharm. Pharmacol. 30 Suppl, 50P (1979).
4. M. B. Baleaux, C.R. Acad. Sci. Paris 274, 1617 (1972).
5. J. Gregory, Adv. Colloid Interface Sci., 2, 400 (1968/70).
6. E. E. El-Hinnawi, 'Methods in Chemical and Mineral Microscopy' Elsevier (1966).

7. B. Vincent, J. Colloid Interface Sci., 42, 270 (1973).

8. D. A. Rawlins and J. B. Kayes, Proc. Int. Conf. on Powder Technology, Basle, June (1979).

9. Th. F. Tadros, J. Colloid Interface Sci., 64, 36 (1978).

10. D. A. Haydon, Recent Progress in Membrane Science, 1, 147 (1964).

11. J. B. Kayes and D. A. Rawlins, Colloid and Polymer Science, 257, 622 (1979).

12. E. Evans and D. E. Napper, Kolloid-Z.u.Z. Polymere, 251, 329 (1973).

13. H. Van Olphen, 'Introduction to Clay Colloid Science' Interscience, New York (1963).

14. A. T. Florence and J. A. Rogers, J. Pharm. Pharmacol., 23, 153 (1971).