

## Pharmaceutical suspension studies III. The redispersibility of suspensions

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### Summary

The redispersibility of a series of drug suspensions coated with adsorbed surface-active agents or polyvinylalcohol fractions has been investigated. A maximum in the redispersibility–surfactant concentration plot has been interpreted in terms of partial steric stabilization. A polystyrene latex model was used to substantiate this theory. Long-term stability of the suspensions was also studied.

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### Introduction

The use of polymers as a means of controlling the balance of repulsive and attractive forces between particles is particularly well documented in the field of colloid chemistry where particles generally less than 1  $\mu\text{m}$  in any dimension are studied (Napper, 1977). Although polymers are frequently used in suspension formulation as a means of retarding sedimentation, little attention has been focussed on the capacity of such polymers to provide a stabilizing effect when adsorbed at the particle interface. The use of polymers at low concentrations to promote flocculation in pharmaceutical suspensions by means of a bridging mechanism has been studied by Felmeister et al. (1973). Farley and Lund (1976) have investigated the effect of several polymeric materials on the stability of suspensions while Otsuka et al. (1973) and Bondi et al. (1973) studied suspension stability in the presence of adsorbed non-ionic surface active agents.

Information on the redispersibility of sedimented particles is particularly scant

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although it is recognized that systems which are flocculated in nature are more readily dispersed than deflocculated suspensions having comparatively low sedimentation volumes.

The assessment of suspension redispersibility varies considerably between authors. The method most usually encountered is inversion by hand (e.g. Farley and Lund, 1976) but rotation of the containers at a constant rate is also used (Matthews and Rhodes, 1968). The present work investigates the concentration-dependent effects of non-ionic polymers and surface-active agents on the ease of suspension redispersibility.

## Materials and methods

The non-ionic surface-active agents of the nonylphenylethoxylate (NPE) group have previously been described (Rawlins and Kayes, 1980) as have the polyvinyl-alcohol (PVA) fractions used in this work (Rawlins and Kayes, 1982). The methods of analysis for these materials are also found in the above references.

The drug used in this study, diloxanide furoate B.P. was of a different batch from that previously used and had a mean diameter of  $12.5 \mu\text{m}$  determined by Coulter Counter analysis. The specific surface area found by mercury intrusion porosimetry was  $1.206 \text{ m}^2 \cdot \text{g}^{-1}$ . Suspensions of diloxanide furoate were prepared in 30 ml glass vials having polyethylene stoppers. The total volume of polymer solution added to the drug was 25 ml. As in previous experiments the suspensions were made to a final concentration of  $10^{-2} \text{ M}$  sodium chloride solution to suppress any electrostatic contribution to interparticulate repulsion. After shaking in a water bath for 24 h the tubes were placed vertically in the water bath for 3 days before the suspension characteristics were noted. All suspensions were kept after testing and left at room temperature ( $22 \pm 3^\circ\text{C}$ ) for one year before retesting.

The sedimentation volume of each suspension was recorded as the ratio of the settled height to the original height.

The redispersibility of the suspensions was evaluated by rotating the tubes containing the dispersions in a vertical plane about the midpoint of the tube. A variable speed rotor was used for this purpose (Palmer) to which a shortened apparatus clamp was attached. Lateral movement of the tube centre from the axis of rotation amounted to 10 mm on revolving the tube. The number of revolutions necessary to resuspend the drug was noted and this value was termed the redispersibility value (RV). The optimum rate of rotation to cause maximum impact of liquid upon the sediment was 60 rpm.

### *Polystyrene latex stability*

Preliminary studies on the stability of polymer-coated latices by determining the optical density of the supernatant after coagulation had occurred gave non-reproducible results. Small flocs of latex were observed to adhere to the glass container walls in preference to sedimenting under gravity and these flocs interfered with turbidimetric techniques. For this reason the method used by Long et al. (1973) was

adopted. For spherical, non-absorbing particles the relationship between the turbidity  $\tau$ , of the dispersion and the wavelength at which this was measured  $\lambda$  is given by

$$(\tau/c)_{c \rightarrow 0} = k\lambda^{-n} \quad (1)$$

where  $c$  is the particle concentration and  $k$  a constant. The value of  $n$  decreases on increasing the particle size. This may be used as an assessment of the degree of aggregation, for as coagulation proceeds the average particle size increases causing  $n$  to decrease. The above equation may be rewritten as

$$n = - \left( \frac{d \ln \tau}{d \ln \lambda} \right)_c + \left( \frac{d \ln k}{d \ln \lambda} \right) \quad (2)$$

For polystyrene latices  $k$  is virtually constant over the wavelength region considered and hence  $n$  is given by the slope of the log turbidity-log wavelength plot.

A latex of 0.716  $\mu\text{m}$  diameter was used in these experiments. This dispersion was prepared by an aqueous phase polymerization technique using potassium persulphate as the initiator (Kayes, 1972) and obviates the use of surfactants in its preparation.

To assess the effectiveness of a surface active agent in preventing coagulation, a series of latex dispersions were made in 10 ml glass vials with screw-on bakelite tops. Various quantities of a stock solution of surface active agents were added to the dispersion in order that a range of surface coverages of the latex could be obtained. The volume fraction of particles in the final dispersion was low enough for changes in the surfactant concentration due to adsorption onto the latex to be considered negligible. After equilibration for 24 h aggregation was induced by the addition of a volume of a barium nitrate solution sufficient to give a final electrolyte concentration of  $3 \times 10^{-2}$  M. This concentration is of sufficient strength to coagulate the bare latex but is too low to cause salting out of the hydrophilic ethylene oxide chains (Boucher and Hines, 1976). To prevent sedimentation of any aggregates the dispersions were subjected to a gentle rocking action at a frequency of  $2 \text{ min}^{-1}$ . The dispersions were then slowly transferred to 1, 2, 5 or 10 mm absorbance cells and the turbidities were determined as a function of wavelength over the range 400–600 nm using a Pye Unicam SP600 Series 2 spectrophotometer. The slope of the log turbidity-log wavelength plots were determined to give values of  $n$ .

## Results and discussion

The redispersibility values are plotted as a function of the initial concentration for the nonylphenylethoxylates in Fig. 1 and for the polyvinylalcohols in Fig. 2. Different types of plot are obtained for the two polymer groups. Increasing the surfactant concentration rapidly increases redispersibility over a small concentration range to a maximum value after which a plateau is obtained at higher concentrations. For PVA this maximum does not occur and the redispersibility increases to a constant value.

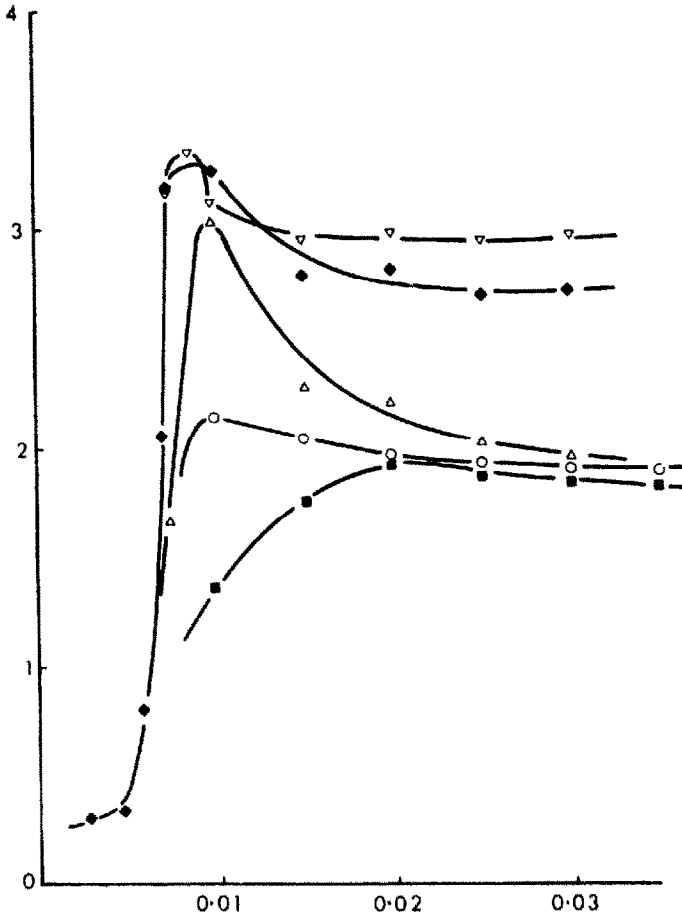


Fig. 1. The effect of surfactant concentration on suspension redispersibility. Ordinate: log redispersibility value. Abscissa: initial surfactant concentration (%w/v). NPE 35,  $\nabla$ ; NPE 30,  $\blacklozenge$ ; NPE 20,  $\Delta$ ; NPE 13,  $\circ$ ; NPE 8,  $\blacksquare$ .

For the two high molecular weight polymer fractions high RVs were found at very low concentrations.

A more detailed investigation of the redispersibility behaviour of the suspensions was carried out using a non-ionic surfactant containing 20 ethylene oxide units (NPE20) and a polyvinylalcohol fraction of molecular weight 36,700. Results are shown in Figs. 3 and 4 where sedimentation volumes, and redispersibility values are presented in conjunction with the adsorption isotherms. For NPE20 the sedimentation volume rapidly decreases over a small increase in the equilibrium concentration and the lowest sedimentation volume obtained first occurs before the plateau region of the adsorption isotherm. The maximum in R.V. occurs at approximately two-thirds of maximum surface coverage and results with the other nonylphenylethoxylates show that this maximum exists between 1/3 and 2/3 maximum coverage.

Anomalous suspension behaviour at half-maximum surface coverage has previously been reported (Ohno et al., 1974; Rupprecht and Hofer, 1979). However, in

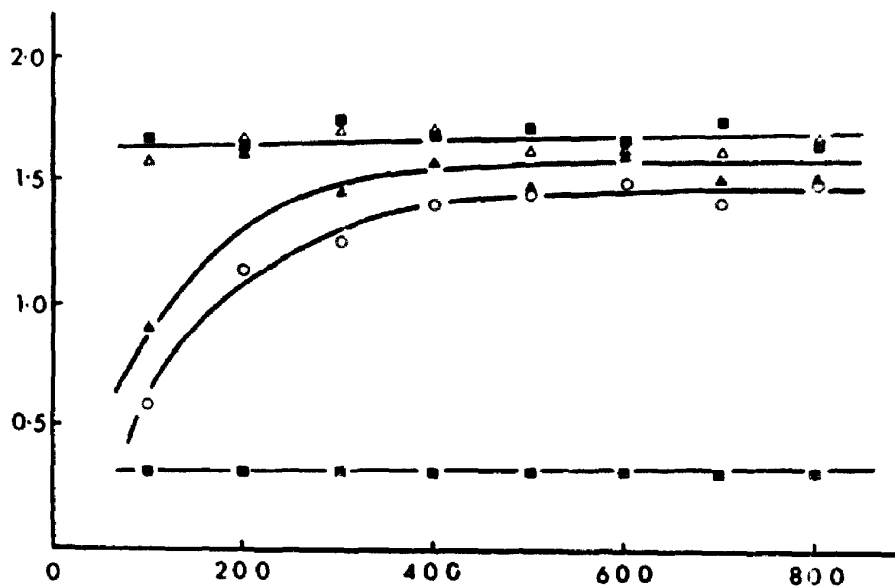


Fig. 2. The effect of PVA concentration on suspension redispersibility. Ordinate: log redispersibility value. Abscissa: initial PVA concentration (ppm).  $M = 95,900$ ,  $\blacksquare$ ;  $M = 76,200$ ,  $\triangle$ ;  $M = 36,700$ ,  $\blacktriangle$ ;  $M = 22,400$ ,  $\circ$ ;  $M = 13,700$ ,  $\square$ ;  $M = 5,100$ ,  $\blacktriangledown$ .

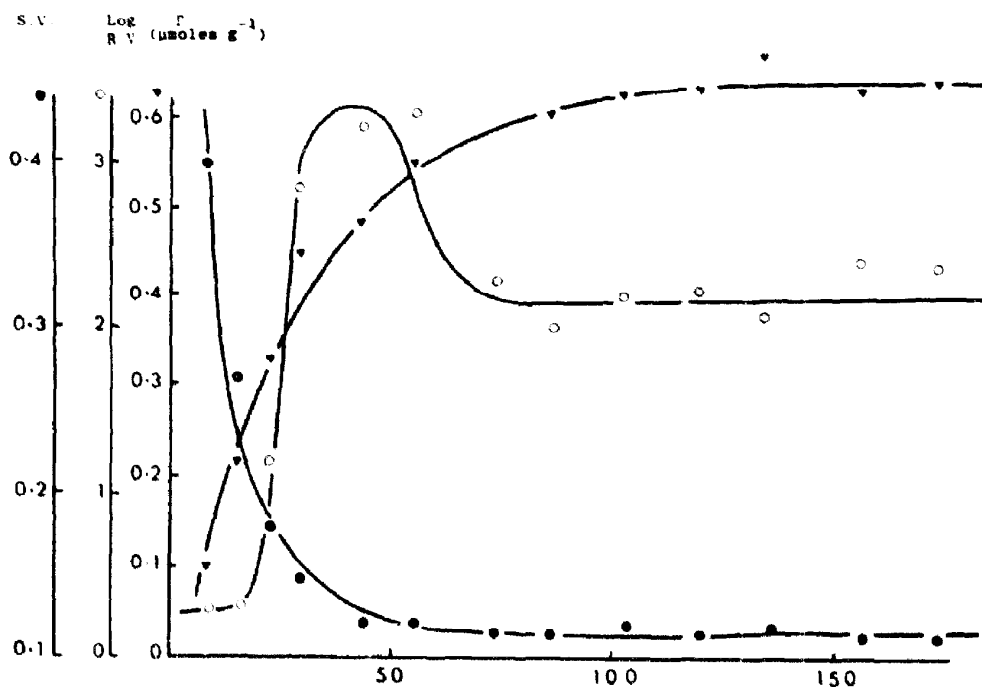


Fig. 3. Suspension characteristics in the presence of NPE 20 after 3 days storage. Abscissa: equilibrium concentration ( $\mu\text{mol}\cdot\text{l}^{-1}$ ).

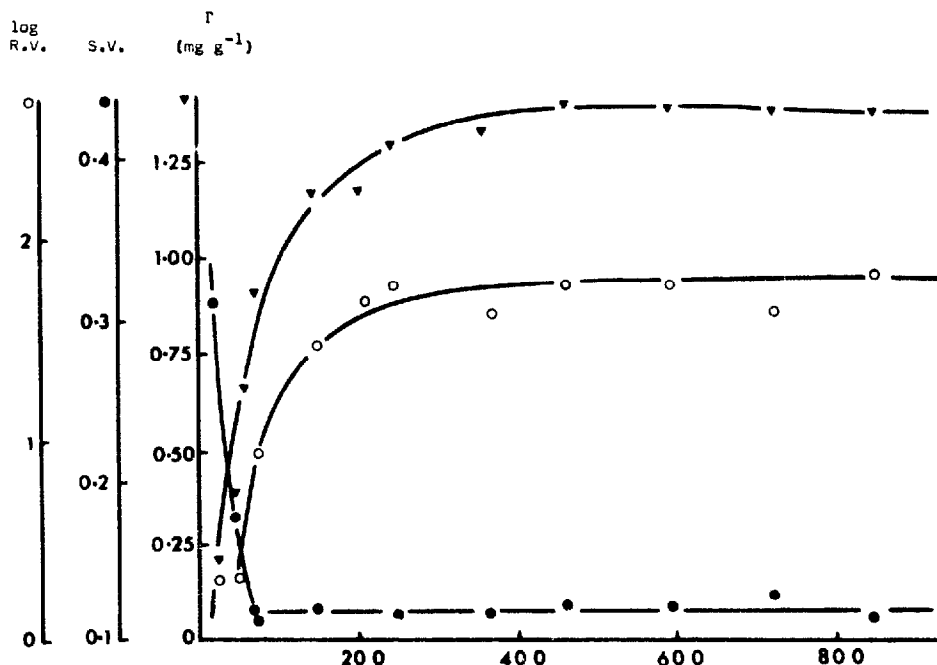


Fig. 4. Suspension characteristics in the presence of PVA 36,700 after 3 days storage. Abscissa: equilibrium concentration (ppm).

these reports suspensions were flocculated and the mechanisms proposed cannot be applied to the results reported here as deflocculated systems are under consideration.

To interpret the redispersibility data observed in Fig. 1 a model is invoked which relates suspension characteristics to the stabilization of the particles produced by adsorbed polymer layers. The adsorption isotherm is divided into sections corresponding to the different regions of redispersibility behaviour, i.e. region A-zone of low R.V., region B-zone of maximum R.V., region C-zone of plateau R.V.

In region A very low surface coverage of the drug particles takes place and in this state the surfactant molecules lie in a flattened form upon the surface. This has previously been proposed by Mathai and Ottewill (1966) as the method of adsorption of non-ionic surfactants at low concentrations upon silver iodide sol and microelectrophoretic studies confirm this adsorption pattern. There is no effective repulsion provided by these adsorbed molecules and large patches of drug surface are exposed to the aqueous medium. Approach of a second similarly coated particle creates strong van der Waals attractive forces and primary minimum coagulation occurs. Randomly packed, open textured sediments result, which readily disperse as the open network of particles permits the passage of the aqueous medium throughout the sediment assisting in the break up of the sediment structure.

In region C saturation coverage of the particle surface occurs and in this form the nonylphenylethoxylates extend from the interface into the surrounding medium (Rawlins and Kayes, 1980). The ethylene oxide chains of the surfactant molecule provide a strong steric repulsion between particles which outweighs the attractive

van der Waals forces. Particles sediment individually and on reaching the container base roll over each other with smaller particles filling the voids created between larger particles. A small dense sediment is formed in this instance. Fluid movement within the sediment is restricted and the major force separating the particles is the striking motion of the supernatant upon the drug.

At region B a situation intermediate to regions A and C occurs. There is sufficient surface-active agent adsorbed for the molecules to project some way into the aqueous phase and additionally patches of drug surface will be exposed between these molecules. Due to adequate steric stabilization the particles settle individually and a small sedimentation volume is formed in the manner described for region C. The intimate contact of particles within the sediment promotes van der Waals attraction or crystal bridging between the bare surface patches. This effect coupled with the high viscosity of the dense sediment gives rise to very large redispersibility values. This effect of steric stabilization at sub-maximum coverages or partial steric stabilization serves to interpret the maximum in the redispersibility curves.

Results obtained with a large diameter (3–4  $\mu\text{m}$ ) polystyrene latex covered with an adsorbed layer of non-ionic surfactants support the concept of partial steric

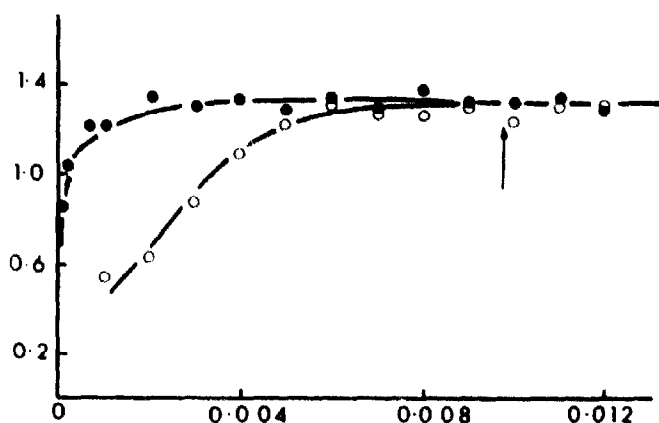
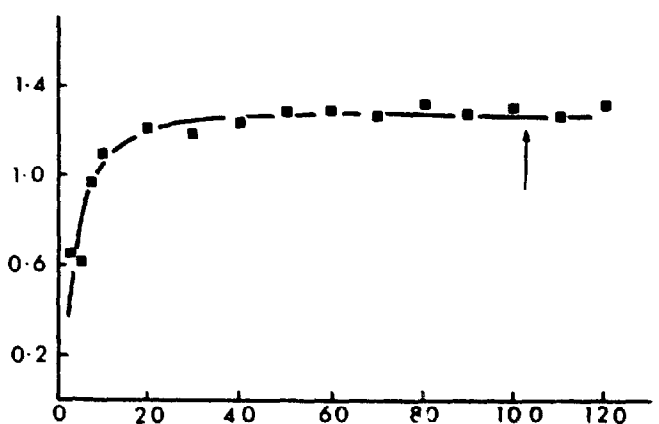


Fig. 5. The effect of surfactant concentration on latex stability. Ordinate:  $n$ . Abscissa: (top graph) surfactant conc. ( $\mu\text{mol}\cdot\text{l}^{-1}$ ); (bottom graph) surfactant conc. (%w/v). NPE 20, ■; F68, ●; L64, ○.

stabilization (Law, 1981) although in this case the observed maxima in the R.V.-concentration plot are not as marked as with the drug used above. The results with the latex also indicate that it is the attraction between exposed surface patches rather than crystal bridging which is responsible for the maximum in the redispersibility curve as polystyrene is totally water-insoluble.

Mechanisms for primary minimum coagulation (region A) and steric stabilization (region C) are well documented (e.g. Kruyt, 1952; Napper, 1977). The existence of partial steric stabilization requires that an effective steric repulsion occurs at sub-maximum surface coverages. To confirm this, a model polystyrene latex was employed as weak aggregation between particles may be observed with this system. The technique described above gave linear relationships between  $\log \tau$  and  $\log \lambda$  indicating the applicability of Eqn. 2. The effect of increasing the initial concentration of surfactant on the stability of the latex is shown in Fig. 5. Differences between the initial and equilibrium concentrations are insignificant due to the low surface area of latex available for adsorption and direct comparison can be made with the adsorption isotherms. Three stability curves are shown for NPE20 and Pluronic L64 and F68, the latter being members of the polyoxyethylene-polyoxypropylene group of non-ionic surface-active agents used in earlier suspension studies (Rawlins and Kayes, 1980). In every case maximum stability is demonstrated at concentrations corresponding to the onset of the plateau regions of the adsorption isotherms as

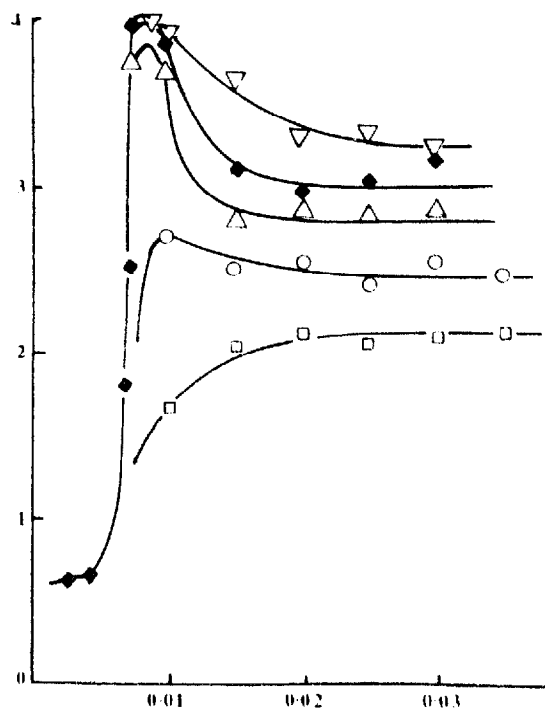


Fig. 6. The effect of surfactant concentration on suspension redispersibility after 1 year's storage. Ordinate: log redispersibility value. Abscissa: initial surfactant concentration (%w/v). NPE 35,  $\nabla$ ; NPE 30,  $\blacklozenge$ ; NPE 20,  $\Delta$ ; NPE 13,  $\circ$ ; NPE 8,  $\square$ .



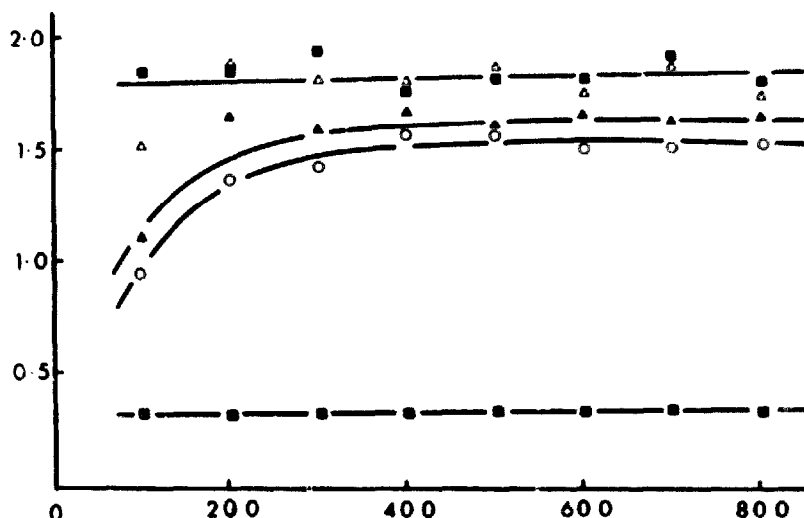


Fig. 7. The effect of PVA concentration on suspension redispersibility after 1 year's storage. Ordinate: log redispersibility value. Abseissa: initial PVA concentration (ppm).  $M = 95,900$ , ■  $M = 76,200$ ,  $\Delta$ ;  $M = 36,700$ ,  $\blacktriangle$ ;  $M = 22,400$ ,  $\circ$ ;  $M = 13,700$ ,  $\square$ ;  $M = 5100$ ,  $\nabla$ .

indicated by the arrows. In addition, the same degree of stability is found at concentrations well below maximum adsorption, e.g. NPE20 and Pluronic F68 show maximum stability at approximately one order of magnitude below the surface saturation concentration. The concept of partial steric stabilization is supported by the results with the model latex system.

From Figs. 2 and 4 it is apparent that no maximum in the redispersibility curves occurs with the adsorbed polyvinylalcohol fractions. The two lower fractions gave aggregated systems throughout the concentration range studied and consequently showed low redispersibility values. The probable explanation for the lack of R.V. maxima with these polymers lies in the dimensions of the molecules at the interface. The work of Fleer et al. (1972) demonstrated monolayer coverage of a silver iodide sol by polyvinylalcohol. At half-maximum surface coverage the number of available surface sites occupied by the polymer, as deduced by potentiometric titration, approached 100%. Due to the large size of the molecules they are able to effectively cover the surface of the particles at sub-maximal coverage but in addition are able to project into the aqueous environment. Steric stabilization will occur but no attraction between particle surfaces in the sediment takes place due to complete occupancy of the surface. The transition from low R.V. to plateau R.V. will take place gradually as shown in Fig. 4.

Matthe vs and Rhodes (1968) prepared suspensions of griseofulvin and assessed their degree of redispersibility after 9 months storage. The systems used were all coagulated and it was found that no significant change in sedimentation volume and redispersibility occurred over this period. The same is true of all the aggregated systems studied in this work irrespective of the method of aggregation, i.e. bridging flocculation with low concentrations of PVA or primary minimum coagulation with

very low NPE concentrations. All these systems redispersed within 1-5 revolutions of the suspensions.

The redispersibility data for the suspensions stored for one year at room temperature are shown in Figs. 6 and 7 for the adsorbed nonylphenylethoxylates and polyvinylalcohols, respectively. The curves are essentially similar to those obtained after 3 days storage although in each case the redispersibility value is higher after prolonged storage. A probable explanation for this is the crystal growth of the particles in intimate contact during storage at an uncontrolled temperature (Carless and Foster, 1966; Tadros, 1973).

It was of interest to relate the redispersibility values to the ease of dispersion by hand. Suspensions corresponding to the plateau region of the redispersibility curve were shaken manually and the relative ease with which complete dispersion was accomplished was noted. Suspensions stabilized by NPE8 or NPE13 and stored for 3 days were readily dispersed despite being deflocculated with small sedimentation volumes. It would appear that over short storage periods some deflocculated suspension systems may be usefully employed as formulated products. However, the possibility of physical changes such as crystal growth between particles in the sediment over long time periods should not be ignored.

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