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Pharmaceutical suspension studies II. The interaction between particles of diloxanide furoate B.P. coated with an adsorbed polymeric layer

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Summary

The stability characteristics of a series of diloxanide furoate suspensions stabilized with an adsorbed layer of polyvinylalcohol have been studied. The determination of the adsorbed layer thickness is attempted and this, in conjunction with data from the mass adsorption isotherms, has been used in correlating the suspension characteristics with potential energy diagrams based upon a mean polymer segment concentration within this layer. Such diagrams have also been constructed allowing for an exponential segment density distribution normal to the interface.

Introduction

A previous paper has dealt with the adsorption of several polyvinyl-alcohol fractions onto diloxanide furoate particles and a polystyrene latex (Rawlins and Kayes, 1982). The present paper attempts to quantify the interaction between drug plates coated with such polymers and to relate this interaction to the type of suspension ultimately observed.

The factor governing the stability of colloidal and supracolloidal particles is the balance between the attractive and repulsive forces operating within the dispersion. In this respect the DLVO theory has successfully been used in interpreting the stability of colloidal dispersions stabilized by electrostatic means. The work of Matthews and Rhodes (1970) has demonstrated the applicability of this theory to

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coarse pharmaceutical suspensions in the presence of electrolyte solutions of varying concentrations.

The repulsion between particles covered with an adsorbed polymeric layer is more difficult to quantify due to the dependence of this steric repulsion upon parameters which cannot readily be determined, e.g. configuration of the adsorbed macromolecules, solvency conditions for the polymer segments within the interfacial layer. However, in the last decade, advances have been made in this field and several authors have formulated expressions for the steric repulsion between particles (e.g. Hesselink et al., 1971: Smitham et al., 1975: Dolan and Edwards, 1974). Use of such expressions in this work permits one quantitative approach for estimating the repulsion to be pursued. An alternative method is to treat the adsorbed layers as non-deformable, rigid shells encasing the drug core and to evaluate the attraction between the coated particles when the polymer sheaths are on the point of contact. This method has been used previously for drug particles coated with adsorbed non-ionic surface active agents (Rawlins and Kayes, 1980). Methods for estimating the adsorbed layer thickness of the polymer fractions are also considered.

Materials and Methods

Diloxanide furoate B.P., polystyrene latex and the polyvinylalcohol fractions have been described previously (Rawlins and Kayes, 1982). Potassium and sodium chlorides were AnalaR grade reagents.

Adsorbed layer thickness

Adsorbed layer thicknesses on polystyrene latex particles were determined by viscosimetric measurement using a Grade A U-tube viscometer for which the flow time for doubly distilled water was 288.4 s. The volume fractions of latex used were < 0.02. Dispersions of known latex volume fraction were prepared by adding the requisite amount of latex to a PVA solution of such a strength as to give maximum coverage of the latex surface. The electrolyte concentration was adjusted to a final concentration of 10^{-2} $mol \cdot dm^{-3}$ potassium chloride in order to suppress the electroviscous effect. This concentration is not high enough to alter the configuration of the macromolecules in solution (Fleer, 1971). Adsorption was carried out over a period of 24 h at 25°C. To reduce flocculation between latex particles the dispersions were passed through a sintered glass filter prior to use. The volume fraction of latex ϕ was then re-evaluated after performing the viscosity experiments by evaporating to dryness and weighing the residue. The weight of adsorbed PVA contributing to this dry weight was determined from the plateau region of the previously determined mass adsorption isotherms (Rawlins and Kayes, 1982). The relative viscocity of the dispersion η_r was found from the flow time ratio of the dispersion to the supernatant. To account for adsorption of polymer onto the glass capillary of the viscometer one set of experiments was performed by allowing a 0.05% solution of the PVA fraction to equilibrate with the glassware for 24 h. The solution was drained and the viscometer rinsed with small portions of the dispersion under test prior to filling. The Einstein equation (1906):

$$\eta_r = 1 + 2.5\,\phi \tag{1}$$

and Mooney equation (1951):

$$\frac{1}{\ln \eta_r} = \frac{1}{2.5\phi} - k_m \tag{2}$$

(where k_m is a constant) were used to interpret the data obtained by this method.

Hamaker constant of polyvinylalcohol

An optical dispersion technique was used as previously described (Rawlins and Kayes, 1980). In this instance a film of PVA was prepared by evaporating a thin film of concentrated aqueous solution onto a microscope slide and gradually increasing the thickness by repeating the process. The film obtained was clamped between the prisms of an Abbé refractometer and the refractive index measured using monobromonaphthalene as the contact liquid.

Potential energy diagrams

(1) Attraction. Vincent (1973) has given expressions for the attractive potential V_A between semi-infinite plates of core material separated by a distance z with an adsorbed layer of thickness δ which allows for the effects of electromagnetic retardation:

$$-12V_A = H_f(A_f^{1/2} - A_m^{1/2})^2 + H_i(A_i^{1/2} - A_m^{1/2})^2 + 2H_{if}(A_i^{1/2} - A_m^{1/2})(A_f^{1/2} - A_m^{1/2}) \tag{3}$$

where A_f, A_m and A_i correspond to the respective Hamaker constants of the core material, dispersion medium and adsorbed layer, respectively. The retarded H functions for semi-infinite plates are given by

$$H_S = \frac{a}{\pi\Delta^2} - \frac{4b}{\Delta\pi} \tag{4}$$

$$H_L = \frac{a'}{2.5\pi\Delta^3} - \frac{b'}{5\pi\Delta^4} \tag{5}$$

The critical separation point at which the cross-over from the short-range function H_S to the long-range function H_L occurs is taken to be 10 nm (Vincent, 1973). The values in the derived H functions are given by

$a = 1.01$
$b = 0.14\,(2\pi/\lambda)$
$a' = 2.45\,(\lambda/2\pi)$
$b' = 2.04\,(\lambda/2\pi)^2$

H_i: $\Delta = z - 2\delta$
H_f: $\Delta = z$
H_{if}: $\Delta = z - \delta$

where λ represents the characteristic wavelength of the molecules.

(2) Repulsion. The repulsion afforded by an adsorbed polymer physically bound in the form of equal loops at a flat interface was evaluated using the HVO theory (Hesselink et al., 1971). In this analysis the rise in free energy on overlap of the layers is divided into two sections. The first is the volume restriction term ΔG_{VR} which accounts for the loss of segmental configurations on approach of a second surface and is given by:

$$\Delta G_{VR} = 2vkTV_{(i,z)} \tag{6}$$

where v is the number of loops per unit area and $V_{(i,z)}$ is given by

$$V_{(i,z)} = -2(1 - 12z^2/il^2)\exp(-6z^2/il^2) \tag{7}$$

Here i is the number of segments per unit area, l represents the length of a polymer segment and z is the interparticulate surface separation.

The mixing or osmotic term ΔG_{mix} produced on overlap was originally given by Meier (1967):

$$\Delta G_{mix} = 2(2\pi/g)^{3/2}(\alpha^2 - 1)\,kTV^2\,\langle h^2\rangle M_{(i,z)} \tag{8}$$

α being the polymer expansion coefficient and $\langle h^2\rangle^{1/2}$ being the root mean square end-end distance of the chain in solution. For equal loops and $z \gg \sqrt{il^2}$, $M_{(i,z)}$ approximates to

$$M_{(i,z)} = (3\pi)^{1/2}(6z^2/(il^2) - 1)\exp(-3z^2/il^2) \tag{9}$$

Preparation of diloxanide furoate suspensions

All suspensions were prepared by dispersing 1 g of drug in 25 ml of polymer solution which was adjusted, with sodium chloride, to give an ionic strength of 10^{-2} mol · dm^{-3}. Results have shown that at this electrolyte concentration, electrostatic stabilization is insufficient to overcome the long-range van der Waals forces of attraction and changes in suspension stability will therefore reflect the influence of adsorbed layers (Rawlins and Kayes, 1980).

Results and discussion

The equilibrium plateau adsorption levels for the PVA fractions adsorbed onto latex in this work are greater than values found where true monolayer adsorption takes place (Rawlins and Kayes, 1982). These relatively large levels of polymer at the latex interface indicate: (a) the molecules adsorb with a small interfacial area of contact combined with a large extension of polymer segments normal to the particle surface; or (b) adsorption occurs as a multilayer. The determination of the adsorbed layer thickness δ on the latex can be used to assist in the identification of the most probable adsorption process. Additionally, as it is far more difficult to estimate values of δ found at the drug–solution interface, experimentally determined values of δ on the model polystyrene latex may be substituted providing it is established that adsorption on both surfaces is similar.

In interpreting the viscosity data it has been assumed that the increase in the apparent phase volume on adsorbing polymer onto the latex surface is due solely to the presence of the solvated interfacial films. Alternative explanations of particle asymmetry and particle flocculation can be discounted. Electron photomicrographs of the colloids show the existence of smooth, uniform-sized spheres both before and after adsorption of the polymer. Dilutions of the dispersions in a PVA solution of concentration equivalent to that of the undiluted system showed no evidence of aggregation when viewed under a high resolution optical microscope.

To obtain values of the adsorbed layer thickness from Eqns. 1 and 2 plots of ηr against ϕ and $1/\ln \eta r$ against $1/\phi$ were constructed. The resulting graphs are shown in Figs. 1 and 2. The slope of the graphs represent 2.5 f and 1/2.5 f, respectively. The factor f accounts for the increase in particle volume fraction caused by polymer adsorption and is equal to the ratio of the covered and uncovered particle volumes

$$f = \frac{(a+\delta)^3}{a^3}$$

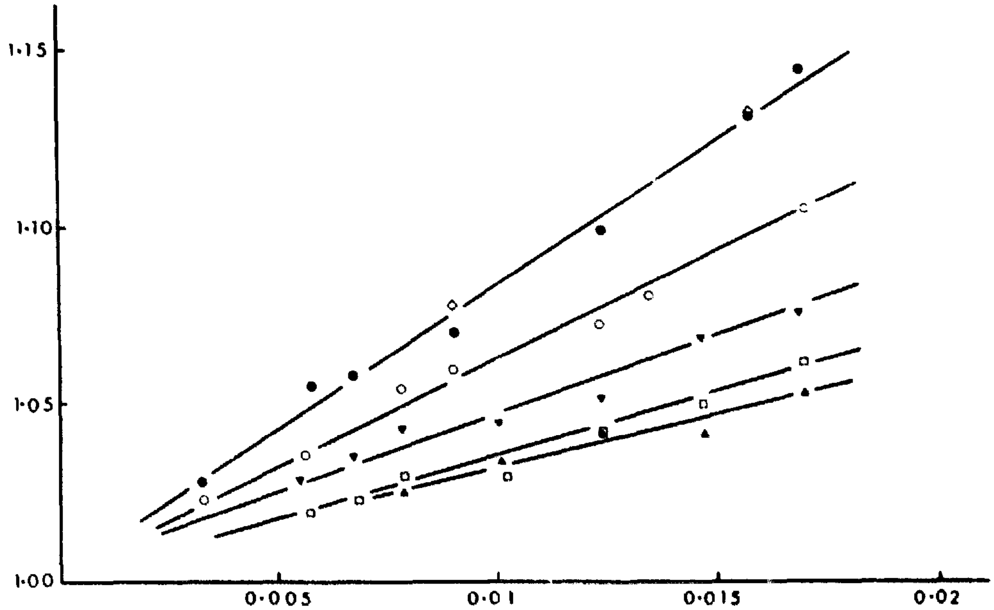

Fig. 1. Relative viscosity data for latex coated with adsorbed polymer plotted according to the Einstein equation. Ordinate: relative viscocity, ηr. Abscissa: volume fraction of latex ϕ. Key: ●, M = 95,900; ◇, M = 95,900 allowing for adsorption onto viscometer; ○, M = 76,200; ▼, M = 36,700; □, M = 22,400; ▲, M = 13,700.

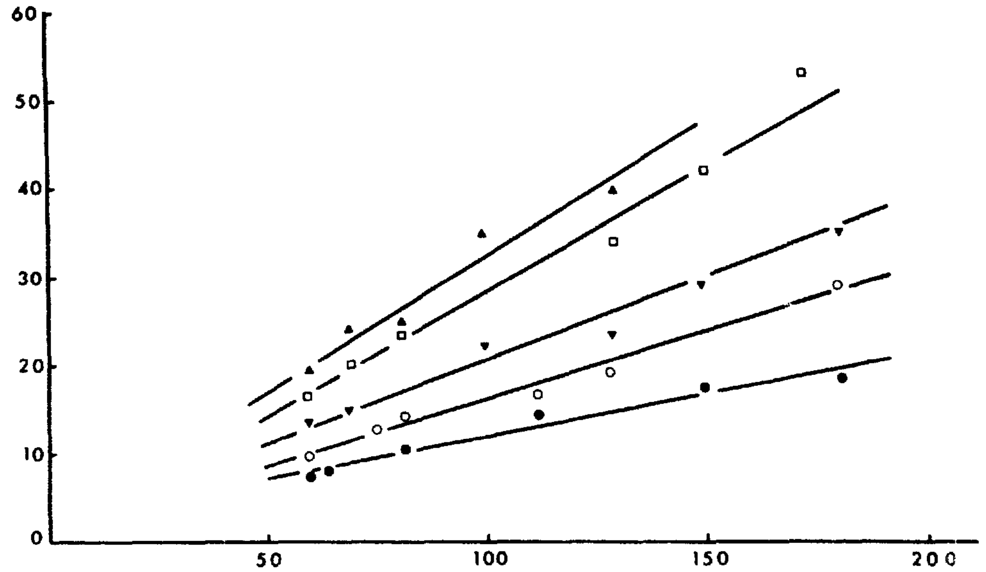

Fig. 2. Relative viscocity data for latex coated with adsorbed polymer plotted according to the Mooney equation. Ordinate: reciprocal of the logarithm of relative viscosity $1/\ln \eta r$. Abscissa: reciprocal of latex volume fraction. Key: ●, M = 95,900; ○, M = 76,200; ▼, M = 36,700; □, M = 22,400; ▲, M = 13,700.

where a represents the radius of the latex particle. The derived values of δ are given in Table 1 together with the estimated errors based on 95% confidence limits of the regression coefficients. The regression lines in Fig. 1 were constructed to intercept the vertical axis at $\eta_r = 1$ in accordance with the Einstein equation. This restraint results in narrower confidence limits than those obtained from Fig. 2 where unconstrained regression lines are drawn. From Fig. 1 equilibration of PVA solution with the viscometer gave essentially the same data points as when this correction was not applied. Reduction in capillary bore-size due to polymer adsorption can therefore be neglected.

Included in Table 1 are the adsorbed layer thicknesses calculated by equating the

TABLE 1

VALUES OF ADSORBED LAYER THICKNESS FOR PVA AT THE POLYSTYRENE LATEX-WATER INTERFACE

Molecular weight	Adsorbed layer thickness (nm)		
	Einstein Eqn.	Mooney Eqn.	Calculated from coil dimensions
95,900	78.8 ± 3.2	78.0 ± 11.1	131.0
76,200	56.0 ± 4.4	63.9 ± 18.6	79.4
36,700	35.8 ± 4.8	42.1 ± 12.4	37.2
22,400	18.9 ± 4.4	19.4 ± 16.8	13.5
13,700	11.8 ± 4.9	23.8 ± 24.0	4.0

volume of the polymer molecule at the interface to the volume of the polymer coil in dilute solution. Thus $\delta = 4/3 \cdot \pi R_h^3/A$ where R_h is the hydrodynamic radius of the random coil in solution and A represents the area occupied by each polymer molecule at the latex–water interface. Values of R_h and A were obtained from previous data (Rawlins and Kayes, 1982).

Values of the adsorbed layer thickness determined experimentally are in excess of those observed where monolayer coverage on polystyrene latex occurs (Garvey et al., 1974). Multilayer adsorption has been shown to occur with a similar system and results presented in this work are more in accord with values of adsorbed layer thickness determined by these authors (van den Boomgaard et al., 1978). No clear trend is found on comparing the adsorbed layer dimensions obtained experimentally with those found by equating the molecular volume of the coils in solution to that at the interface. The experimental results substantiate the adsorption measurements where multilayer formation was considered to have occurred (Rawlins and Kayes, 1982).

Due to the absence of a suitable model system for the drug, an alternative approach was adopted to provide an estimate of the extension of the adsorbed polymer from the drug surface into solution. Garvey et al. (1974) have postulated that in a good solvent environment the volume of a molecule at the interface is similar to the hydrodynamic volume in solution. In further work by the same authors the validity of this approach was questioned (van den Boomgaard et al., 1978). The lack of a model for the drug–PVA system necessitates the adoption of this approach to gain approximate values for the adsorbed layer thickness and the values obtained are shown in Table 2. These values are of similar magnitude to those found by Garvey et al. for monolayer adsorption of PVA onto latex. Adsorption into the drug pores has been demonstrated for the two lower fractions which causes an apparent increase in adsorbed polymer (Rawlins and Kayes, 1982). To determine δ for these fractions by the above method the quantity adsorbed on the external drug surface was estimated by extrapolation of the adsorption data in Fig. 3 of the previous reference.

A value of 8.72×10^{-20} J was obtained for the Hamaker constant of the dried PVA film and this value was used for all six PVA fractions studied. The Hamaker

TABLE 2

ADSORBED LAYER THICKNESS (δ) OF PVA ADSORBED ON DILOXANIDE FUROATE B.P. DERIVED FROM MOLECULAR DIMENSIONS

Molecular weight	Hydrodynamic volume (nm^3)	δ(nm)
95,900	3591	52.0
76,200	2438	38.5
36,700	648	13.8
22,400	301	9.2
13,700	141	4.6
5,100	26	1.6

constant of an adsorbed layer composed of polymer and solvent was determined from the expression (Vincent, 1973):

$$A_{p+s} = \left(F_p(A_p)^{1/2} + (1 - F_p)(A_s)^{1/2}\right)^2 \tag{10}$$

where F_p is the volume fraction of component p and A_p and A_s are the Hamaker constants of materials p and s. (Using this equation it is found that the Hamaker constant of the dispersion medium-saturated drug solution is not measurably different to that of water.)

The potential energy diagrams for the suspensions were constructed using a previously described technique which does not rely on the quantitative estimation of the steric term V_s (Rawlins and Kayes, 1980). Values of potential energy minima, adsorbed layer polymer concentration and suspension type are listed in Table 3.

Reasonable agreement between suspension type and energy minimum depth was previously found with adsorbed non-ionic surfactants if a value of about -5×10^{-3} $kT \cdot nm^{-2}$ was taken as the critical depth above which aggregation would not occur. With the polyvinylalcohols this correlation is not so reliable as PVA 13,700 gives an aggregated system of calculated potential energy minimum -3.27×10^{-3} $kT \cdot nm^{-2}$. Several explanations may be forwarded for this discrepancy.

(1) The accurate determination of adsorbed layer thickness is essential particularly for short-chain polymers as it controls the polymer concentration of the adsorbed phase and through this the Hamaker constant of this layer and hence V_A. The measurement of this thickness for the PVAs was not performed directly but was obtained from the amount adsorbed and the polymer dimensions in solution.

(2) Based upon the amount of polymer adsorbed and the adsorbed layer thickness the mean concentration of polymer at the interface is given in Table 3 for each of the 6 fractions studied. In terms of the classical equations for steric stabilization (Ottewill and Walker, 1968; Hesselink, 1971) complications arise due to the concentration dependence of the polymer–solvent interaction parameter χ. Peppas and Merrill (1976) have shown that at 20°C, χ for PVA increases from 0.475 to 0.495 as the volume fraction of polymer is increased from 0.05 to 0.10. From Table 3 the

TABLE 3

STABILITY CHARACTERISTICS OF DILOXANIDE FUROATE B.P. SUSPENSIONS IN THE PRESENCE OF PVA

Molecular weight	Potential energy minimum ($kT \cdot nm^{-2}$)	Suspension characteristic	Mean interfacial polymer concentration (%w/v)
95,900	-0.22×10^{-3}	Deflocculated	4.4
76,200	-0.31×10^{-3}	Deflocculated	5.2
36,700	-1.04×10^{-3}	Deflocculated	9.6
22,400	-1.60×10^{-3}	Deflocculated	12.2
13,700	-3.27×10^{-3}	Aggregated	17.0
5,100	-17.60×10^{-3}	Aggregated	35.1

volume fractions of the two lowest molecular weight species at the interface are in excess of 0.10. It is conceivable that in these cases χ is greater than 0.50 resulting in an attraction due to the polymer interaction alone as V_s would be negative. This effect may also explain why aggregated systems are found with the two lower molecular weight polymers. Equations for V_s allowing for segment concentration dependence have been proposed by Smitham et al. (1975). Due to the poorer solvent conditions experienced by the lower molecular weight fractions at the interface the mechanism of steric action previously proposed (i.e. a rapid rise in V_s on the point of contact of the adsorbed sheaths) will not apply.

(3) The relationship between suspension type and potential energy minima assumes uniform segment concentration of polymer within the adsorbed layer. This assumption is reasonable for short-chain ethylene oxide condensates where the chains extend a few nanometres from the surface. For long-chain polymers including PVA the segment concentration decreases exponentially away from the surface (Hoeve, 1965; Roe, 1965: Hesselink, 1969) and the above model becomes unrealistic.

As an alternative method of constructing potential energy diagrams the equations of Hesselink et al. (1971) have been used in combination with those of Vincent (1973), for polyvinylalcohol adsorbed onto flat plates of diloxanide furoate allowing for the exponential segment density distribution of polymer normal to the surface (Eqs. 6 and 8). Equations for an equal loop size distribution were used for their ease of application. Both the volume restriction and osmotic contributions to V_s for equal loops are less than those predicted for a coverage of equal tails or copolymer

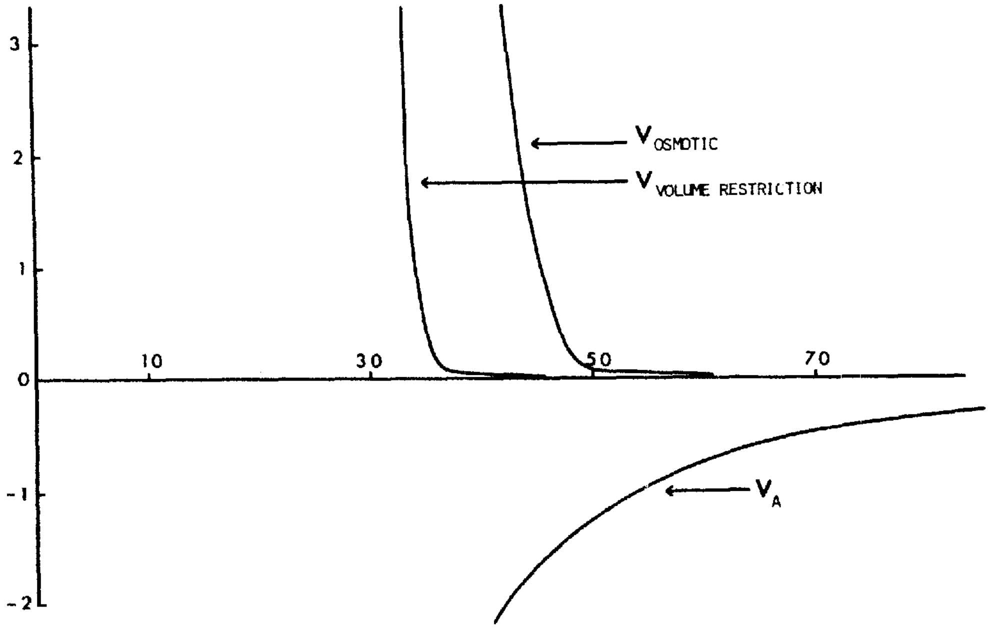

Fig. 3. Potential energy curves for semi-infinite plates of drug coated with PVA, M = 36,700, illustrating the components of the total interaction curve calculated using the theory of Hesselink et al. Ordinate: V_{TOTAL} (kT·nm^{-2} × 10^{-6}). Abscissa: surface separation (nm).

coverage under comparable conditions. In a qualitative sense the use of such a distribution for an adsorbed polymer is more likely to predict the occurrence of aggregated suspension systems.

Fig. 3 shows the 3 components of the total interaction curve. The attraction term V_A was calculated by neglecting the effect of the adsorbed layer upon V_A and choosing an arbitrary composite value for the Hamaker constant of the particle plus adsorbed polymer of 4.5×10^{-20} J. These results are based on data obtained for PVA 36,700. The osmotic term operates well before the volume restriction term and in further calculations ΔG_{VR} has been neglected.

Total potential energy diagrams for the PVAs using the HVO theory for an equal loop size distribution are given in Fig. 4. Increasing energy minima are found on decreasing the molecular weight which is in agreement with calculations based on a

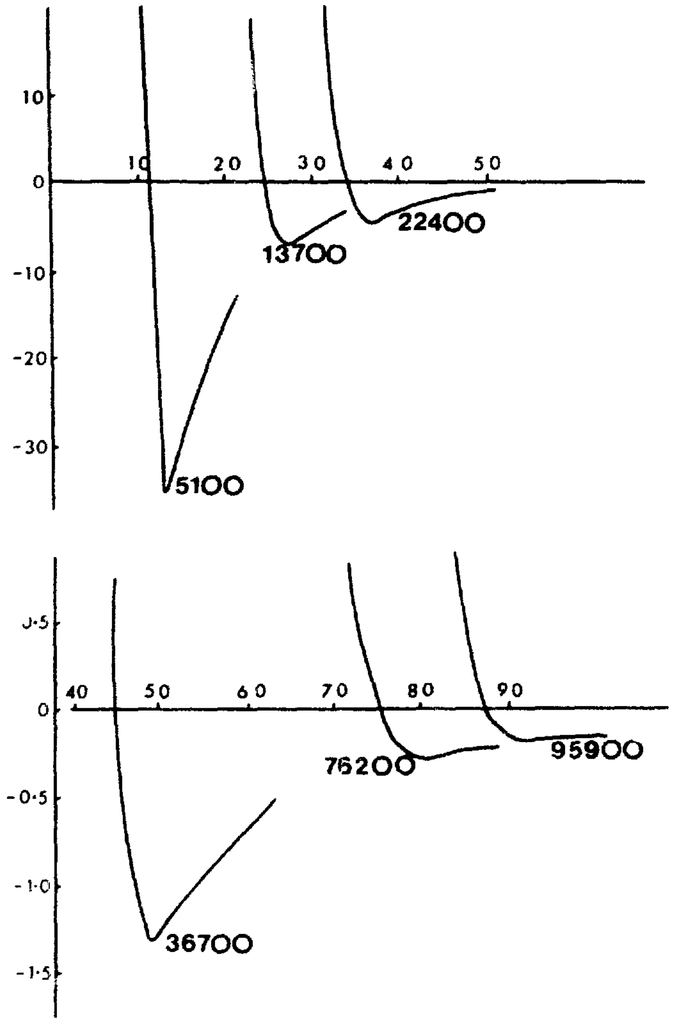

Fig. 4. Total potential energy diagrams for semi-infinite plates of drug coated with adsorbed PVA fractions calculated using the theory of Hesselink et al. Ordinate: V_{TOTAL} ($kT \cdot nm^{-2} \times 10^{-6}$). Abscissa: surface separation (nm).

mean segment density distribution (Table 3). Although expressions for an equal loop distribution of polymer have been used, the general trend of greater energy minima as M decreases is not dependent upon the mode of segmental adsorption chosen. For the smaller molecular weight polymers the interparticulate distance at which repulsion occurs is greater than twice the estimated thickness of the adsorbed layer while for higher fractions the reverse applies. This arises in part because of the exponential decrease in segment density which according to theory only becomes zero at an infinite distance from the interface. This is obviously incorrect as adsorbed layers possess finite dimensions. The quantitative use of these equations is therefore limited and the energy minima calculated in this manner should be viewed with caution. The trend of a greater tendency for aggregation to occur as M decreases is, however, demonstrated.

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