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Pharmaceutical suspensions: relation between zeta potential, sedimentation volume and suspension stability

J. B. KAYES

Pharmacy Department, Pharmaceutics Research Group, University of Aston, Gosta Green, Birmingham, B4 7ET, U.K.

The effect of added surface-active agents of various ionic types on the sedimentation volume of drug suspensions of betamethasone, griseofulvin, nalidixic acid and thiabendazole has been investigated, and the results correlated with previously measured zeta potentials. Study of the zeta potential/sedimentation volumes versus concentration plots showed that apparently only coagulated, deflocculated or sterically stabilized systems were formed. In most cases the sterically stabilized systems were produced from mixtures of ionic/non-ionic surfactants. These are examples of controlled coagulation, although non-ionic surfactant alone conferred stability against caking. Secondary minimum flocculation was not apparent but this may have been due to the method of examination of suspensions. The work confirmed that the DLVO theory of colloid stability and its modification to include a steric term can be applied to coarse suspension systems.

The so called, 'controlled flocculation' approach to pharmaceutical suspension formulation has been examined by a number of workers (Haines & Martin, 1961a, b, c; Matthews & Rhodes, 1968a, b, 1970; Jones, Matthews & Rhodes, 1970; Short & Rhodes, 1973) and is well established. The concept of 'controlled flocculation' is based on an understanding of the so called DLVO theory of colloid stability. This considers the potential energy of interaction between a pair of particles to be the result of adding an electrical double layer repulsion component, V_R, and van der Waals attraction V_A:

$$V = V_R + V_A \quad \ldots \quad (1)$$

In describing aggregation of particles in suspensions the terms coagulation and flocculation tend to be used indiscriminately in the literature. The most satisfactory way of defining these terms (see, for example, Ottewill, 1973) is to reserve the word coagulation for primary minimum aggregation. Association of particles in the secondary minimum is termed flocculation. The latter term is also used to describe polymer bridging between particles and cross linking of particles produced by metal-ion interactions with polyelectrolytes. It has long been known that substances such as non-ionic surfactants may, if adsorbed at the particle surface, stabilize a dispersion in the absence of a significant zeta potential. An additional term steric stabilization, V_S, has to be included in the potential energy of interaction

$$\text{Thus } V = V_R + V_A + V_S \quad \ldots \quad (2)$$

However the term "controlled flocculation" is perhaps a misnomer, as it covers:—

(a) Secondary minimum flocculation—particularly where the primary maximum is reduced by addition of an electrolyte thus deepening the secondary minimum—this is controlled flocculation. (b) flocculation produced by bridging, either by polymers or by metal ion—polyelectrolyte, this could also be called controlled flocculation; and (c) primary minimum coagulation caused by addition of electrolyte or other charged species, the depth of the primary minimum being restricted by the steric effect of an added surface-active agent or polymer—more correctly termed controlled coagulation. The term "controlled flocculation" could thus with advantage, be replaced by another such as "controlled aggregation". When sedimentation is studied in aggregated systems, it is observed that the aggregates fall together producing a boundary between the sediment and the supernatant liquid. Coagulated and flocculated systems have a greater sediment volume than deflocculated systems, hence this parameter can give an indication of the state of the system. By itself the sedimentation volume is meaningless for lack of a reference value. To

avoid this difficulty Dintenfass (1959) used the ratio of the ultimate settled volume to the original volume:

$$F = Vu/Vo \quad .. \quad .. \quad .. \quad (3)$$

and this expression with F expressed as a percentage is used in this paper. The ratio F thus gives a measure of the aggregated—deflocculated state of the system.

MATERIALS AND METHODS

Materials

See Suspensions, Microelectrophoretic properties (Kayes, 1977).

Methods

Suspensions of the drugs 2% w/v were made as previously. After shaking for 24 h in a constant temperature water bath the suspensions were stored at 25° for 3 days to allow sedimentation to occur. Sedimentation volumes were then measured and the appearance of the settled suspension noted.

RESULTS AND DISCUSSION

The significance of the zeta potential to, and its relation with, the sedimentation volume can be seen by plotting these parameters versus concentration of additive. Consideration of the total potential energy of interaction between the particles, Equations 1 and 2, quantifies the coagulated or deflocculated state of the system; if the height of the potential energy barrier is >20 kT (Napper, 1967) (the zeta potential will then be approximately 50 mV) (k is the Boltzmann constant and T the absolute temperature) then the particles will not be able to get close enough to enter the primary minimum where coagulation occurs.

Making the assumption that the drug particles are monodisperse spheres, an estimate of V the total potential energy of interaction can be made. V_A for distances Ho of less than 15 nm can be calculated from the equation (de Boer, 1936; Hamaker, 1937),

$$V_A = \frac{Aa}{12Ho} \quad .. \quad .. \quad (4)$$

where a is the radius of the particle and A is the Hamaker constant of the particle in water. At distances greater than 15 nm the equation:

$$V_A = \frac{-2{\cdot}45\ Aa\ \lambda o}{120\ \pi\ Ho^2} \quad .. \quad .. \quad (5)$$

where λ_o is the wavelength of intrinsic oscillation of the atoms assumed to be 10^{-7} m (Ho & Higuchi, 1968; Schenkel & Kitchener, 1960) must be used because of retardation effects.

For particle/non-ionic and particle/non-ionic/ionic surfactant mixtures the presence of an adsorbed layer of the non-ionic surfactant entails the use of a modified equation (Vold 1961).

$$V_A = \frac{1}{12}(A_M^{\frac{1}{2}} - A_S^{\frac{1}{2}})^2 H_S + (A_S^{\frac{1}{2}} - A_P^{\frac{1}{2}})^2 H_P + 2(A_M^{\frac{1}{2}} - A_S^{\frac{1}{2}})(A_S^{\frac{1}{2}} - A_P^{\frac{1}{2}})H_{PS}) \quad (6)$$

where A is the Hamaker constant of the medium, adsorbed layer and the particle as designated by the subscripts, M, S, and P respectively.

Ottewill & Walker (1974) have indicated that this equation can be simplified, by putting $A_M = A_S = 3{\cdot}7 \times 10^{-20}$ J, as the error involved is not likely to be great; (for example, the Hamaker constant of the non-ionic Triton X35 (an alkyl aryl polyether alcohol) has a value of $3{\cdot}22 \times 10^{-20}$ J (Visser 1972)).

Equation 6 then becomes:

$$V_A = -\frac{1}{12}(A_S^{\frac{1}{2}} - A_P^{\frac{1}{2}})^2 H_P \quad .. \quad .. \quad (7)$$

The same workers have shown that the function H which is dependent on the radius of the particles, distance of separation and thickness of adsorbed layer can be approximated to

$$H_{(x\ y)} = \frac{y}{x(1+y)} \quad .. \quad .. \quad (8)$$
$$x \to o$$

where for H_p, $x = \frac{\Delta + 2\delta}{2a}$ and $y = 1$

where Δ is the distance between the surface of the adsorbed layers and δ the thickness of the adsorbed layer.

In the case of two approaching particles both covered with an adsorbed layer, as they touch $\Delta \to o$ and $x = \delta/a$.

An estimate of the thickness of the adsorbed layer can be made using one of the equations of the Gouy-Chapman diffuse double layer theory:

$$\kappa x = 1n\left[\frac{(\exp ze\psi/2kT+1)}{(\exp ze\psi/2kT-1)}\frac{(\exp ze\psi o/2kT-1)}{(\exp ze\psi o/2kT+1)}\right] \quad .. \quad (9)$$

If ζ (the zeta potential) replaces ψ in this equation then x is the distance of the plane of shear from the

particle surface of potential ψo; e is the unit of electronic charge and z the valency of the counter ions; κ is the reciprocal length parameter of Debye-Huckel theory. The distance x therefore represents δ the thickness of the adsorbed layer.

An estimate of V_R can be obtained from the equation (Hogg, Healy & Fuerstenau, 1966).

$$V_R = \frac{\epsilon a \zeta^2}{2} \ln (1 + \exp^{-\kappa Ho}) \quad .. \quad (10)$$

where ϵ is the permittivity of the medium.

The stabilizing effect of steric and solvation layers V_S can be calculated using an equation (Ottewill & Walker, 1974) in the form:

$$\frac{V_S}{kT} = \frac{4\pi NC^2}{3V_1\rho_2^2} \quad (0{\cdot}5 - \chi)\left(\delta - \frac{Ho}{2}\right)^2 \left(3a + 2\delta + \frac{Ho}{2}\right) \quad .. \quad .. \quad .. \quad .. \quad (11)$$

where N is Avogadros number, C is the concentration of non-ionic surfactant in the adsorbed layer, V_1 is the partial molar volume of water, ρ_2 is the density of the adsorbed layer and χ is an interaction parameter arising from the enthalpy of interaction of water with the adsorbed layer.

Characteristics of the zeta potential/sedimentation volume versus concentration of surface-active agent plots, and calculation, in selected cases, of the total potential energy of interaction between particles.

(a) *Drug particle, non-ionic surfactant systems.* Results for thiabendazole/C_{16} E_{30} and griseofulvin/C_{16} E_{30} are shown in Figs 1 and 2. The results are similar, examination of the plot for thiabendazole shows a fall off of F and zeta potential as concentration of non-ionic is increased, so that, for example, at a concentration of 10^{-4} mol dm^{-3}

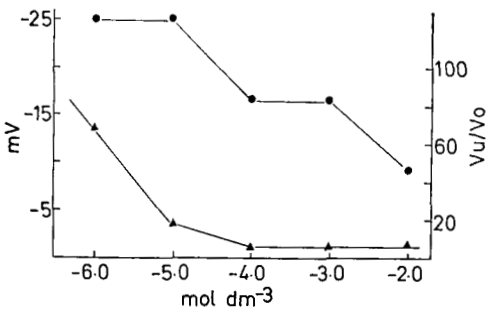

FIG. 1. Zeta potential (mV)—●, sedimentation volume Vu/Vo %)—▲, thiabendazole—$\log_{10}$ concentration $C_{16}E_{30}$ (mol dm^{-3}).

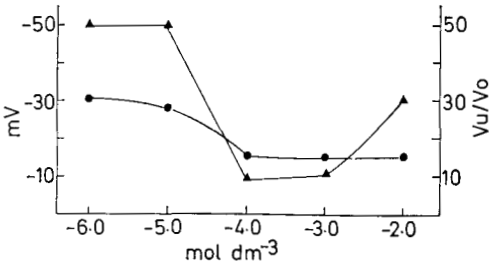

FIG. 2. Zeta potential (mV)—●, sedimentation volume (Vu/Vo %)—▲, griseofulvin—$\log_{10}$ concentration $C_{16}E_{30}$ (mol dm^{-3}).

C_{16} E_{30} the system is deflocculated even though the zeta potential is only −16·5 mV. It is likely therefore that the particles are sterically stabilized.

If a full layer of C_{16} E_{30} is present on the thiabendazole particles V_A can be calculated from equation 7. The thickness of the adsorbed layer, calculated using equation (9) at $\zeta = -16{\cdot}5$ mV, is 4·7 nm. The mean radius of the thiabendazole particles is 5·5 μm so that the value of H_P is $5{\cdot}9 \times 10^2$. The value of the Hamaker constant for thiabendazole is taken as $8{\cdot}55 \times 10^{-20}$ J (Schenkel & Kitchener, 1960, Ho & Higuchi 1968, have indicated that 1×10^{-20} J is a reasonable value for the Hamaker constant of an organic substance in water, and Visser, 1972, quotes values for hydrocarbons of 6–7 $\times$ 10^{-20} J so the above value would seem reasonable). V_A is then evaluated as −102 kT.

The thickness of the adsorbed layer of C_{16} E_{30} is 4·7 nm, if interpenetration of layers is assumed to a small extent then Ho the distance between the particles will be say $2 \times 4{\cdot}7 - 1{\cdot}0 = 8{\cdot}4$ nm. The particle radius is 5·5 μm, 2δ and Ho/2 are small compared with this value so that $3a + 2\delta + Ho/2$ of equation 11 can be modified to 3a without great error. Florence & Rodgers (1971) have reported values for the interaction parameter χ, for aqueous solutions of polyoxyethylene compounds and give for C_{16} E_{21} a value of 0·497, using these figures a value of +118 kT is obtained for V_S. V_R evaluated from equation (10) at Ho 8·4 nm is +43 kT. Hence V = +50 kT signifying, as found, a deflocculated system. However, at 10^{-6} mol dm^{-3} C_{16} E_{30} (Fig. 1), assuming no contribution from V_S (i.e. V_A is unmodified), so that equation (4) can be used, then at Ho = 10 nm.

$$V = V_A + V_R$$
$$= -112{\cdot}5 + 88 = -24{\cdot}5 \text{ kT}$$

i.e. the system should be coagulated. Experimentally the particles formed light fluffy aggregates and it is

possible that flocculation due to polymer bridging had occurred because of the low concentration of non-ionic surfactant, rather than coagulation.

The plot for griseofulvin Fig. 2 differs at concentrations of C_{16} E_{30} above 10^{-3} mol dm^{-3} when the sedimentation volume increases. This suspension was easily resuspended and the particles were not aggregated into groups, it is probable therefore that this suspension is showing controlled coagulation. Whilst the layer of adsorbed non-ionic surfactant will prevent coagulation of the particles deep in the primary minimum there will be a large enough attractive force to cause aggregation as soon as the distance between particles is greater than twice the thickness of the adsorbed layer. For example with griseofulvin at Ho = 15 nm, $V_R = +3{\cdot}6$ kT, $V_A = -36$ kT, V_S will not be effective at this distance—it contributes a "cut off" effect at 9·4 nm (i.e. twice the thickness of the adsorbed layer). V is therefore −31·4 kT which is a large enough attraction for aggregation to occur.

(b) *Drug particle, cationic surfactant systems.* Results for griseofulvin, nalidixic acid and thiabendazole are of the same pattern and can be discussed by examining the plot for thiabendazole/C_{12}TAB. (Fig. 3). This shows a rise in F as the zeta potential passes from the negative value to zero, at zero F is at a maximum, then falls to a minimum as the positive zeta potential increases. At concentrations

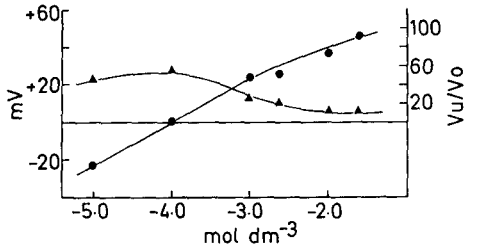

FIG. 3. Zeta potential (mV)—●, sedimentation volume (Vu/Vo %)—▲, thiabendazole—$\log_{10}$ concentration C_{12} TAB (mol dm^{-3}).

of 10^{-5} and 10^{-4} mol dm^{-3} C_{12}TAB light fluffy aggregates were present but as the zeta potential increased the system gradually became deflocculated. The suspension at 10^{-2} mol dm^{-3} C_{12}TAB was deflocculated but easily dispersed.

At zero zeta potential V_R is zero hence $V = V_A \rightarrow -450$ kT as Ho→2·5 nm and the system is coagulated, shown by a maximum in the sedimentation volume.

At 10^{-2} mol dm^{-3} C_{12}TAB, the zeta potential is +35·5 mV; hence $V = V_A + V_R$ and the magnitude of V depends on distance such that this system was deflocculated with a value for Vm of the order of +66·5 kT at Ho about 10 nm.

(c) *Drug particle, cationic/non-ionic systems.* Suspensions examined were thiabendazole, nalidixic acid and griseofulvin with C_{12}TAB and 10^{-2} mol dm^{-3} C_{16} E_{30}, and griseofulvin with C_{12}TAB and 10^{-2} mol dm^{-3} C_{16} E_{10} and C_{16} E_{60}.

The results for thiabendazole, Fig. 4 are representative. The sedimentation volume stays constant with increase in concentration of C_{12}TAB as the zeta potential moves from the value of −5 mV

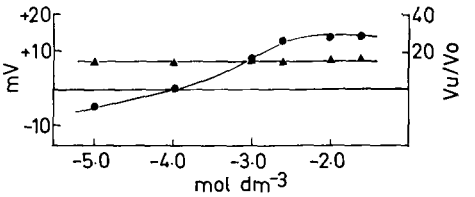

FIG. 4. Zeta potential (mV)—●, sedimentation volume (Vu/Vo %)—▲, thiabendazole with 10^{-2} mol dm^{-3} $C_{16}E_{30}$—$\log_{10}$ concentration C_{12} TAB (mol dm^{-3}).

at 10^{-5} mol dm^{-3} C_{12}TAB to +14 mV at 10^{-2} mol dm^{-3} C_{12}TAB, thus showing that the presence of 10^{-2} mol dm^{-3} C_{16} E_{30} confers stability upon the particles. Calculation of V at 10^{-4} mol dm^{-3} C_{12}TAB, i.e. at zero zeta potential, where V_R is zero, can be made from:—

$$V = V_A + V_S = -102 + 118$$
$$= +16 \text{ kT, at Ho} = 8{\cdot}4 \text{ nm.}$$

This value of positive potential energy would not alone be sufficient to prevent coagulation, however this will dramatically increase as the particles get closer together so that at 8·0 nm V_S will be approximately doubled.

This is therefore an example of controlled coagulation i.e. Primary minimum coagulation restricted by the steric layer.

Changing the ethylene oxide chain length with griseofulvin/C_{16} E_{10}, C_{16} E_{30} and C_{16} E_{60}, respectively it was found that as the ethylene oxide chain length was increased, so was the steric stabilizing effect, i.e. C_{16} E_{10} at zero zeta potential gave a coagulated system whilst C_{16} E_{30} and C_{16} E_{60} sterically stabilized. Increasing stability with increasing ethylene oxide chain length has been reported previously (see for example Elworthy & Florence, 1967).

(d) *Drug particles anionic surfactant systems.* The behaviour of all four drugs in solutions of varying concentrations of SDS was investigated. Exami-

nation of the zeta potential/sedimentation volume versus concentration SDS plot for thiabendazole, Fig. 5, shows a lowering of F as the zeta potential increases, this plot is typical of the group.

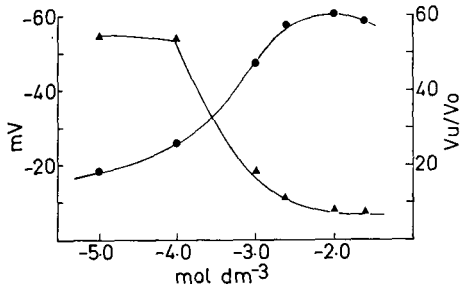

FIG. 5. Zeta potential (mV)—●, sedimentation volume (Vu/Vo %)—▲, thiabendazole—$\log_{10}$ concentration SDS (mol dm^{-3}).

Fig. 6 shows how V, calculated from equation 1, varies with distance Ho between particles. At $\zeta = -18$ mV the system shows negative potential energy at all distances, the suspensions should therefore be coagulated and this was found experimentally.

With $\zeta = -34$ mV, V is positive at distances less than 50 nm, a maximum of potential energy is reached of *ca* +64 kT which should be sufficient to prevent primary minimum coagulation. A shallow secondary minimum is seen at *ca* 70 nm of about −2 kT, this suspension showed a sedimentation volume of 33%, aggregation of particles had occurred but these were easily dispersed, it is possible that this is secondary minimum flocculation, although a value of 5–10 kt would be expected before such flocculation occurred. However Verwey & Overbeek (1948) give an example of a suspension of 1 μm particles in a solution of 10^{-3} mol dm^{-3} 1 : 1 electrolyte where there was a secondary minimum of 6 kT and where loose aggregation occurred. In view of the approximations made in calculating V it may well be that the true secondary minimum was larger than that calculated. At $\zeta = -60$ mV, V is always positive to *ca* 60 nm. A maximum of +558 kt is reached at 5 nm. The depth of the secondary minimum barely reaches −1 kT and as expected the suspension was completely deflocculated and caked.

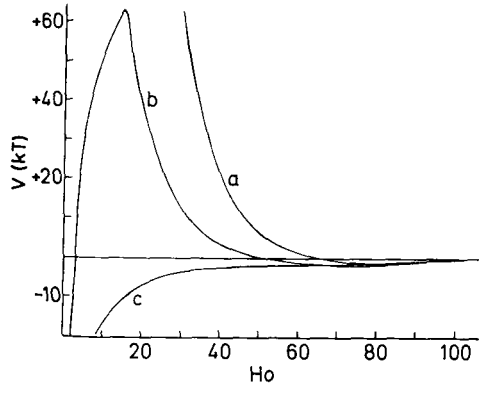

FIG. 6. Potential energy $V = V_R + V_A$ for thiabendazole with varying concentration of SDS; zeta potential a = −60 mV 10^{-2} mol dm^{-3} SDS; b = −34 mV at 5×10^{-4} mol dm^{-3} SDS and c = −18 mV at 10^{-5} mol dm^{-3} SDS. Abscissa—Distance Ho between particles (nm).

(e) *Drug particle anionic/non-ionic surfactant systems.* Here results are similar in pattern to those found for cationic/non-ionic surfactant mixtures. The plot for thiabendazole/SDS/C_{16} E_{30} is representative of this group (Fig. 7). The sedimentation volume F stays virtually constant as the concentration of

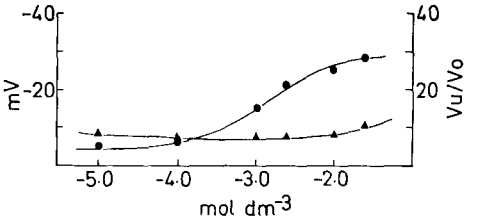

FIG. 7. Zeta potential (mV)—●, sedimentation volume (Vu/Vo %)—▲, thiabendazole with 10^{-2} mol dm^{-3} C_{16} E_{30}—$\log_{10}$ concentration SDS (mol dm^{-3}).

SDS is increased. This indicates that this concentration of $C_{16}E_{30}$ is adsorbed sufficiently to sterically stabilize the suspension. Results for griseofulvin/SDS/$C_{16}E_{10}$, $C_{16}E_{60}$ and $C_{16}E_{60}$ confirm those found with similar cationic non-ionic systems that as the ethylene oxide chain length is increased so does the steric stabilizing effect of the non-ionic surface-active agent.

It can be concluded that the non-ionic surface-active agents used were successful as steric stabilizers of pharmaceutical suspensions and prevented caking. The work supports the concept of controlled flocculation by means of mixed ionic/non-ionic surface-active agents and the application of the DLVO theory to coarse suspension systems.

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