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Hydrophilic polymers as stabilisers and flocculants of sulphadimidine suspensions

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Summary

The effect of various grades of polyvinylpyrrolidone (PVP), sodium carboxymethylcellulose (SCMC) and acid and alkaline gelatins on the flocculation behaviour of sulphadimidine suspensions has been studied. These polymers induce both flocculation and stabilization of the suspension depending upon the polymer concentration used. Each polymer exhibited an optimum concentration for flocculation. Higher concentrations of the polymer induced some degree of steric stabilization.

The principles of controlled flocculation were tested by determining the relationship between the electrophoretic mobility and the sedimentation volume of the suspended particles. Although these principles were applicable to the SCMC/sulphadimidine suspensions in that the sediment volume increased as the stability decreased, PVP/sulphadimidine suspensions behaved differently in that the sediment volume decreased with decrease in mobility and this was attributed to steric stabilization by the polymer. It was therefore concluded that by the use of these polymers one can produce the desired degree of flocculation in suspensions by selection of the type, fraction and concentration of polymer.

Introduction

A problem with the formulation of suspensions is the settling of the solid particles to the bottom of the container under gravity and forming a sediment which is difficult to redisperse. This could lead to uneven doses being taken by the patient. Such settling may be modified by controlled flocculation, an established concept which was first developed by Haines and Martin (1961a, b, c).

Several mechanisms are available which can be used to induce flocculation and there are a number of methods for studying the extent of aggregation in suspensions. These methods do not measure the same physical property of the suspensions and so they may not produce comparable results.

In this work, flocculation of sulphadimidine particles induced by PVP, SCMC and acid and alkaline gelatins is examined and 4 techniques are used to measure the extent of flocculation.

Materials and Methods

The sources and characterization of materials have been described previously (Kellaway and Najib, 1980a, b).

Sedimentation volume

Suspensions were prepared by dispersing 5 g of sulphadimidine in 30 ml of either water or polymer solution by means of a Silverson homogenizer (Silverson, London). The suspension was then transferred to a 50-ml measuring cylinder and made up to 50 ml with the required vehicle. The cylinder was then inverted 10 times to ensure complete mixing and placed in a constant temperature water bath at 25 ± 0.1°C. No wettability problems were encountered in the preparation of the suspension. The sediment volume was then recorded at different time intervals until no further change was noted. The value of the sedimentation volume expressed as percentage of the total volume (F) was calculated from the equation:

$$F = \frac{V_u}{V_0}$$

where V_u = the final sediment volume; V_0 = the initial sediment volume.

Settling rate

The settling rate of the particles was calculated by measuring the migration rate of the solid–liquid boundary. A plot was made of the distance moved against time and the slope of the linear portion of the graph was taken as the settling rate.

Settling rate measurements were only possible for suspensions where the boundary was sharp and this precluded the study of deflocculated systems by such a method.

Refiltration rate

A filter cake of the suspended particles was formed by pouring 50 ml of suspension onto a sintered glass filter to form the filter cake. The filtrate was collected and then re-filtered through the cake at a constant pressure head of 7 cm of filtrate. The rate of filtration was calculated from the slope of the linear plot of the volume of filtrate collected against time.

Specific resistance of filter cake

The filter cake of the suspension to be studied was formed as above. A suspension of similar composition was then filtered through the filter cake under the influence of gravity. The filtration rate was calculated from the slope of t/v against v, where v is the volume of filtrate collected in time (t). The filtration rate was then used to calculate the specific resistance (r) from the equation:

$$r = \frac{2PA^2}{\eta c} \cdot \frac{t}{v^2}$$

where P = pressure applied; A = filter area; η = filtrate viscosity; and c = solid content of suspension.

Results and Discussion

Fig. 1 shows the flocculation behaviour of sulphadimidine suspensions in the presence of various concentrations of PVP 24,500. The 4 different techniques mentioned above were used to study the extent of flocculation. The optimum PVP concentration for flocculation was 10^{-6}% w/v as determined by 3 of the techniques, namely re-filtration rate, sedimentation volume and specific resistance of the filter cake. The settling rate determination gave a higher optimum concentration and this may be attributed to the entrapment of air in the floccule resulting in a slower sedimentation rate with the larger floccules which are obtained at optimum polymer concentration indicated by the other methods. Re-filtration rate and sedimentation volume measurements were the techniques selected to assess all other suspensions.

The extent of flocculation of sulphadimidine suspensions in the presence of different concentrations and grades of PVP was examined. A well defined optimum PVP concentration of 10^{-6}% w/v was determined for all grades of PVP assessed by both sediment volume and re-filtration rate measurements. Table 1 shows the

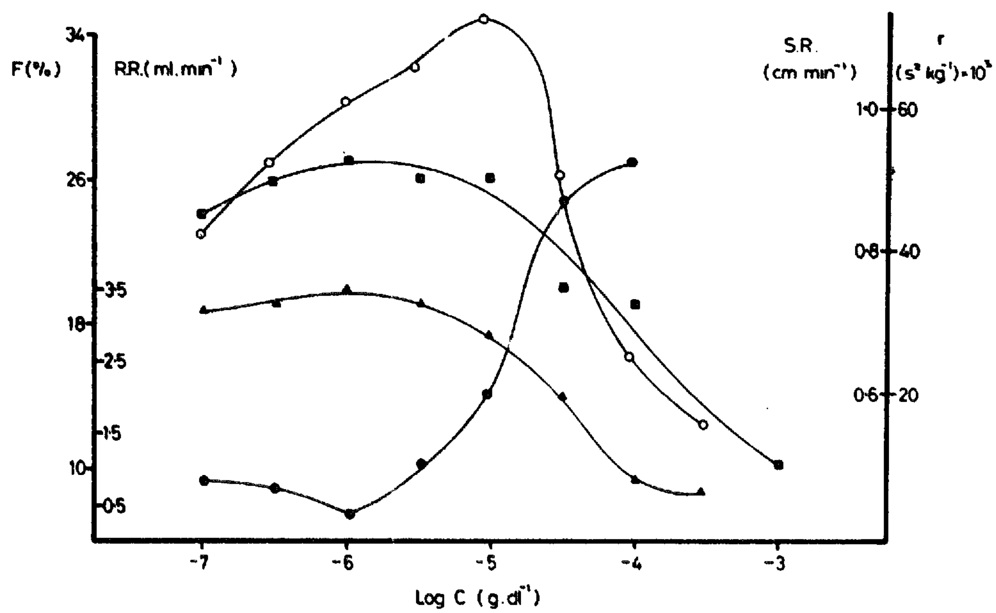

Fig. 1. The flocculation behaviour of sulphadimidine suspensions in the presence of PVP 24,500 as measured by: sediment volume (F, ■), settling rate (SR, O), specific resistance (r, ●) and refiltration rate (RR, ▲).

TABLE 1

THE SEDIMENT VOLUME AND RE-FILTRATION RATE OF SULPHADIMIDINE SUSPENSIONS IN THE PRESENCE OF VARIOUS GRADES OF 10^{-6}% w/v PVP

Molecular weight	Sediment volume (%)	Re-filtration rate (ml min^{-1})
10,000	26.5	3.4
24,500	26.5	3.5
44,000	26	3.2
360,000	27	4.0
700,000	28.5	4.6
Water	22	2.0

sediment volume and refiltration rates obtained for sulphadimidine suspensions in 10^{-6}% w/v PVP solutions. Similar values were obtained for all PVP grades examined, indicating that the flocculation efficiency of PVP was independent of molecular weight. The sediment volume of the suspensions containing PVP 10^{-6}% w/v when compared with the sediment volume of the suspensions in water shows that the degree of flocculation induced by the addition of PVP was small. However, the sediment volume is reduced when more concentrated PVP solutions, e.g. 10^{-1}% w/v, are used. At these relatively high polymer concentrations, surface coverage by the adsorbed polymer is sufficiently high to prevent polymer bridge flocculation. The structured adsorbed polymer film now serves to stabilize the particles against particle–particle interaction presumably by the mechanism of steric stabilization. These data therefore indicate that PVP is a better stabilizer than flocculant of suspended sulphadimidine particles.

The zeta potential of particles is thought to play an important role in the resistance to flocculation and coagulation. Electrophoretic mobility studies had been

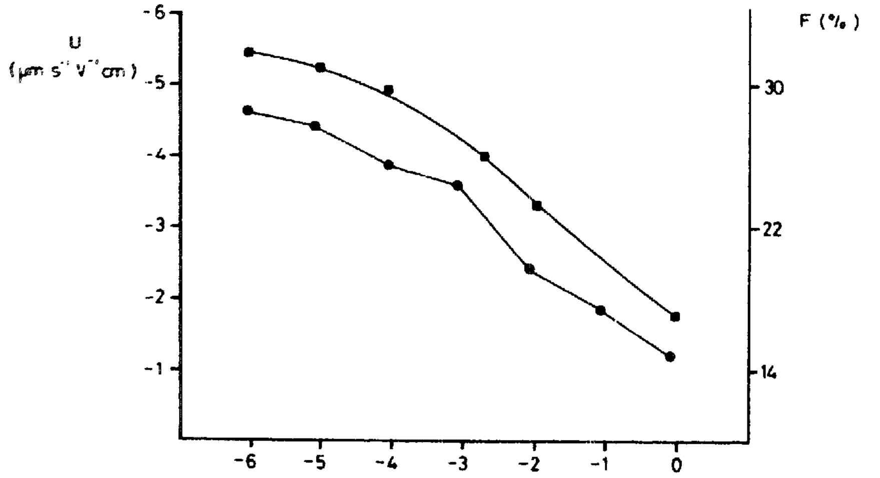

Fig. 2. The relationship between the electrophoretic mobility (U, ●) and the sediment volume (F, ■) of sulphadimidine particles in the presence of various concentrations of PVP 700,000.

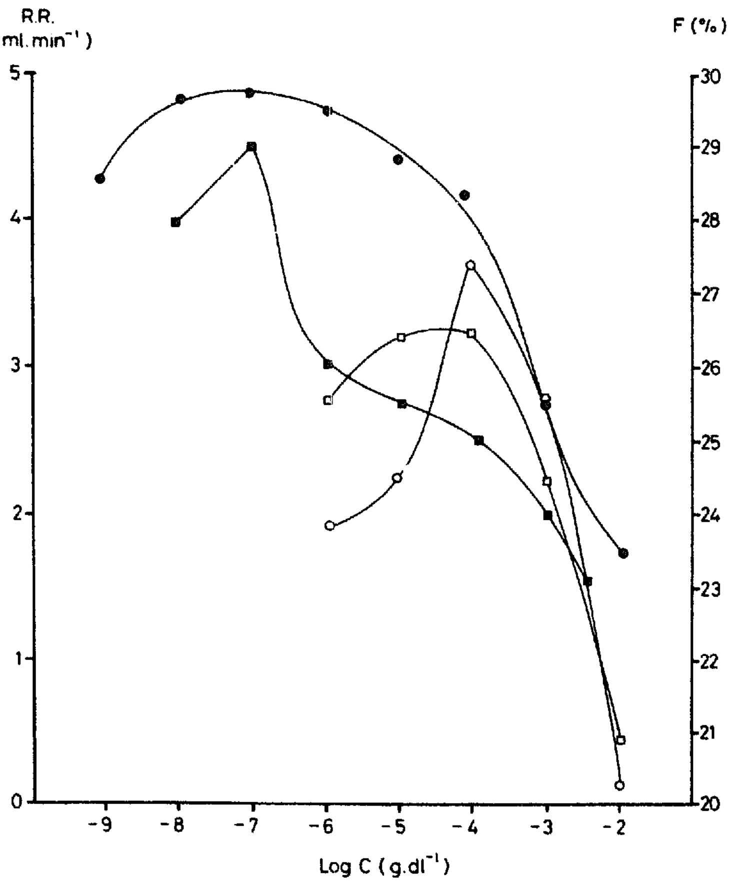

Fig. 3. The influence of acid and alkaline processed ossein gelatins on the flocculation of sulphadimidine suspensions. Acid gelatin—RR(○), F(□). Alkaline gelatin—RR(●), F(■).

carried out previously (Kellaway and Najib, 1980b) for sulphadimidine particles in various concentrations of PVP and SCMC. Fig. 2 shows results extracted from these studies and plotted so as to relate PVP concentration to both electrophoretic mobility and sediment volume. Electrophoretic mobility was found to increase as sediment volume increased. This behaviour has been previously reported (Kayes, 1977), and may be attributed to steric stabilization induced by the adsorbed PVP molecules. The non-ionic PVP molecules, when adsorbed, mask the charge on the particle surface and therefore reduce the electrophoretic mobility. Therefore, although the electrophoretic mobility is low, the system is sterically stable. At the optimum flocculation concentration the drug particles are not fully covered and therefore have a higher mobility.

Acid- and alkaline-processed ossein gelatins behaved in a similar manner to PVP (Fig. 3). The peaks on the sediment volume graphs coincided with the re-filtration rate optimum in each case, although the greatest extent of flocculation was obtained at a concentration of 10^{-7}% w/v for alkaline gelatin and 10^{-4} w/v for acid gelatin. This concentration difference may be attributed in part to molecular weight difference in the two samples (Robinson et al., 1975). It is, however, more likely to

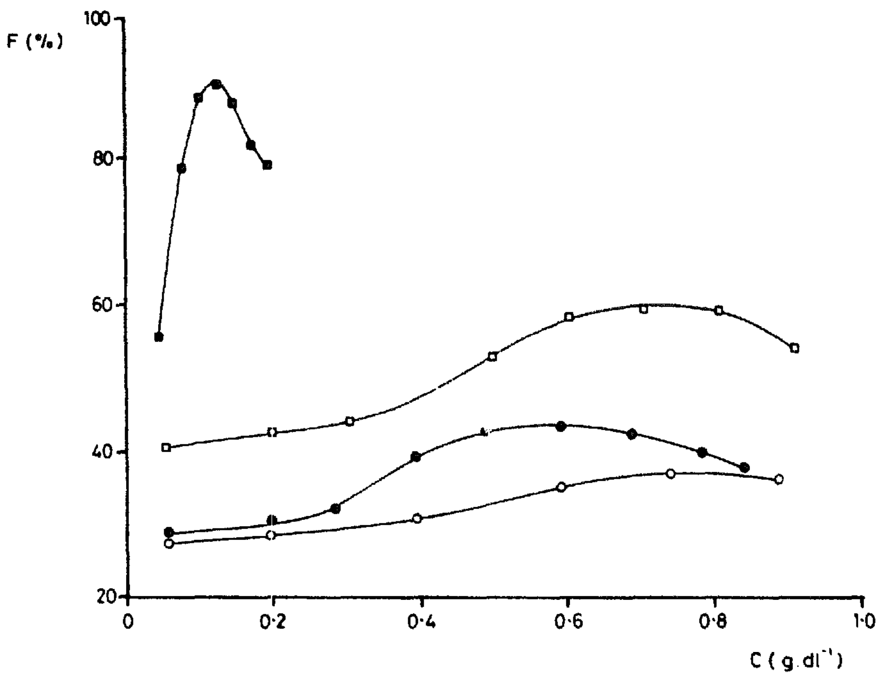

Fig. 4. The effect of SCMC grade and concentration (C) on the sediment volume (F) of sulphadimidine suspensions. pH 7.0–7.4. SCMC P20(○), SCMC P40(●), SCMC P75(□), SCMC P1,000(■). For C=0, F=22%.

reflect differences in amino acid composition resulting from the different methods of manufacture (Eastoe and Leach, 1977). The pH had been adjusted to the isoelectric point of the gelatin samples in order to eliminate differences due to charge effects. Like PVP, gelatin is a more efficient stabilizer than flocculant of sulphadimidine particles.

SCMC addition caused a marked change in the flocculation behaviour of the drug suspensions. All grades of SCMC caused a high degree of flocculation which increased with increasing molecular weight of the polymer. However, unlike PVP or gelatin, SCMC produced flocculation at high concentrations ($>0.1\%$ w/v). For P20, 40 and 75, the largest sediment volumes were obtained in the concentration range of 0.6–0.8% of SCMC (Fig. 4). For P1000, the highest degree of flocculation was obtained at 0.125% w/v. It has been reported previously (Ash and Clayfield, 1976) that the concentration producing the optimum degree of flocculation shifts to lower values with increasing polymer molecular weight. Since both the SCMC molecules and the particles are negatively charged, it is surprising to find that SCMC induces flocculation of sulphadimidine. However, it has been noted previously (Nemeth and Matijevic, 1968) that negatively charged polymers do induce flocculation in negatively charged particles but only at relatively high concentrations; the above results confirm these findings. Although molecular weight is a factor in the flocculation efficiency of a polymer, conformation and adsorption mechanisms are of greater importance. The flocculation by SCMC may be attributed to the linear conformation of the polymer chain in solution which is maintained on adsorption at an interface. The linear conformation results in more favourable conditions for polymer

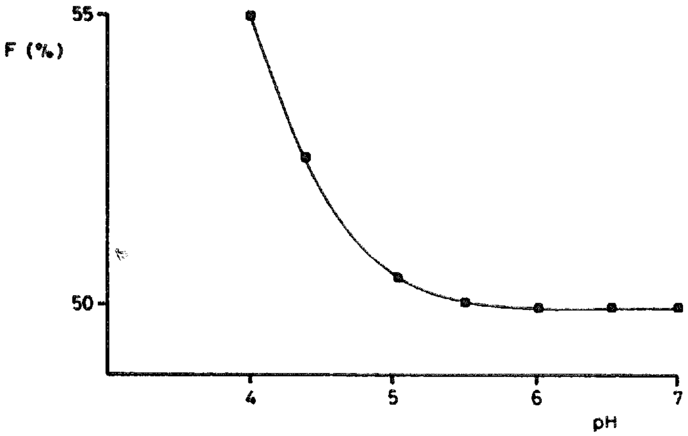

Fig. 5. The relationship between sediment volume (F) and pH for sulphadimidine suspensions in the presence of SCMC P75 0.5% w/v.

-bridging than when, as in the case of PVP, the polymer is coiled.

As mentioned previously, the pH of minimum molecular charge was selected for the flocculation studies employing gelatin. A study of the effect of pH on flocculation was carried out using SCMC P75. Fig. 5 shows that when the SCMC is unionized, the sediment volume was higher than when the ionization of the SCMC carboxyl groups was complete. For pH > 5.5, that is when ionization is complete, the sediment volume remained constant. The pH dependency of flocculation by ionic polymers is due to the ionization state of both drug particles and polymer molecules and its influence on polymer adsorption to the drug particles.

The addition of SCMC to sulphadimidine (Fig. 6), resulted in increased flocculation as the electrophoretic mobility decreased. The reduced mobility is indicative of a lower zeta potential and a reduction in the repulsive barrier. Therefore the particles tend to aggregate and produce a higher sediment volume.

In conclusion, the findings confirm the following general characteristics of

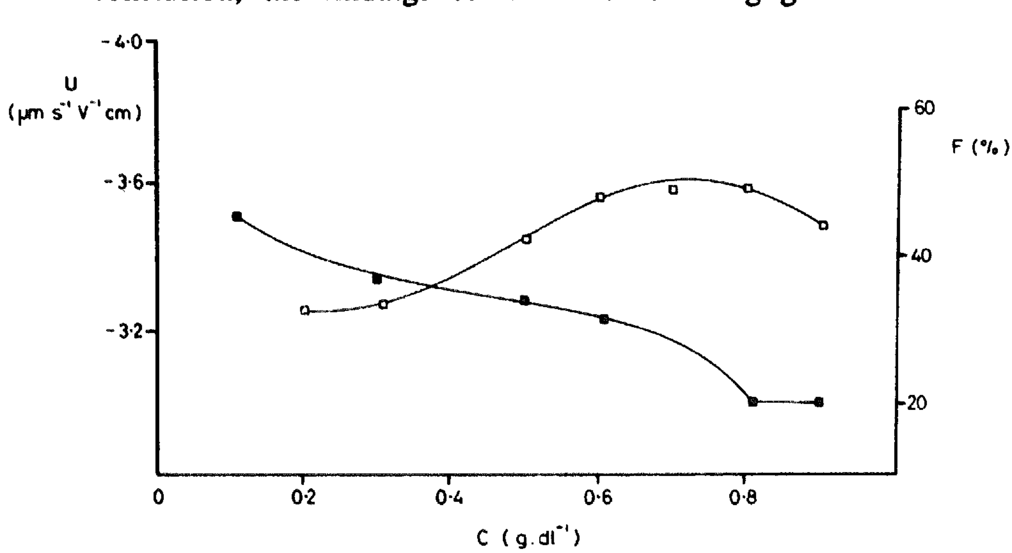

Fig. 6. The relationship between the electrophoretic mobility (U, ■) and the sediment volume (F, □) of sulphadimidine particles in the presence of various concentrations of SCMC P75, pH 7.0–7.4. In the absence of SCMC P75, $U = -2.6\ \mu m\ s^{-1}\ V^{-1}\ cm$ and $F = 22\%$.

polymer flocculation: (1) the polymers induced flocculation at very low concentrations and in the case of negatively charged polymers the concentration is much higher when the particles to be flocculated are also negatively charged; (2) an optimum flocculation concentration exists at which a polymer produces the highest degree of flocculation. For higher concentrations the system becomes sterically stabilized, but at lower concentrations the particles are not sufficiently covered to achieve optimum flocculation. For SCMC and gelatin the higher the molecular weight of the polymer, the lower is this concentration; (3) for ionic polymers such as SCMC, the efficiency of flocculation is pH dependent; (4) linear polymers such as SCMC are more effective flocculants than coiled ones such as PVP; (5) the lower the electrophoretic mobility of the suspended particles, the higher is the sediment volume. Deviation from this occurs due to steric stabilization induced by polymers as in the case of PVP; (6) this work supports the suggestion of La Mer (1966) that re-filtration rate measurements through the settled sediment can be used to study the flocculation behaviour of suspensions; and (7) the findings of this work support the 'polymer bridging theory' proposed by La Mer and Smellie (1956a and b), La Mer et al. (1957a and b) and Smellie and La Mer (1956).

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