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The effect of sodium lauryl sulphate, cetrimide and polysorbate 20 surfactants on complex coacervate volume and droplet size

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The effects of sodium lauryl sulphate (SLS), cetrimide and polysorbate 20 surfactants at concentrations below, at and above their critical micelle concentration (CMC) on the complex coacervation of varying concentrations of gelatin and acacia have been described. The overall effect of increasing concentration of SLS was to reduce the weight of coacervate formed. The addition of increasing concentrations of cetrimide produced an increase in the weight of coacervate. The two lowest concentrations of polysorbate 20 produced an increase in coacervate weight while the highest concentration, above the CMC, reduced the coacervate weight. These effects have been explained in terms of shielding of electrostatic attractions between gelatin and acacia polyions by adsorption of ionic and non-ionic surfactant molecules onto the polyions. The addition of surfactants influenced the size distribution of the coacervate droplets that were produced. It is believed that the reduction in interfacial tension by the aggregation of surfactant molecules at the coacervate-equilibrium liquid interface permitted the formation of smaller coacervate droplets.

When very finely divided powders are being microcapsulated by complex coacervation, initial wetting of the powder can be a problem. Addition of a dispersing or surface active agent can facilitate wetting by lowering the surface tension of the coacervate droplets, thereby giving increased encapsulation.

The presence of electrolytes has long been known to affect complex coacervation (Bungenberg de Jong 1949) but only relatively recently has interest been shown in the effect of surfactants on microcapsules. Poly (N^{α},N^{ε}-terephthaloyl-L-lysine) {PPL} microcapsules were found to interact electrostatically in aqueous media with poly(diallyl dimethyl ammonium) ions resulting in either aggregation or disintegration of the microcapsules (Suzuki & Kondo 1978). The action of alkylpyridinium chlorides on PPL microcapsules caused them to aggregate at low concentrations of surfactant and to disintegrate when the surfactant cations existed in such amounts that they could solubilize the PPL molecules constituting the microcapsules (Suzuki et al 1979). The interaction between gelatin-acacia microcapsules and octaoxyethyleneglycol lauryl ether, sodium lauryl sulphate and laurylpyridinium chloride at different pH and ionic strengths again resulted in either aggregation or disintegration (Suzuki & Kondo 1982). Siddiqui & Taylor (1983) investigated the effects of cetrimide, sodium lauryl sulphate and hexadecyltrimethylammonium lauryl sulphate on the surface tension of a gelatin simple coacervate and their effect on the surface charge of the simple coacervate droplets and oil core material droplets.

To determine the optimum conditions for microencapsulation it is necessary first to establish the effect of surfactant molecules on the complex coacervation process itself before investigating the effect of surfactants on microencapsulation.

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MATERIALS AND METHODS

Gelatin, acid processed pigskin, isoelectric pH 9·0, Bloom number 200, pH (2%) 4·4, (Richard Hodgson and Sons Ltd, Beverley, Yorks); acacia powder BP (Macarthys); sodium lauryl sulphate, specially pure (BDH); cetrimide BP (Fisons); polysorbate 20 (Tween 20, Atlas Chemicals Ltd), formaldehyde solution, 37–41% HCHO (BDH).

Preparation of coacervate

The surfactant was always dissolved in the acacia solutions and equilibrated to 40 ± 0·5 °C. An equal quantity of gelatin solution, previously equilibrated to the same temperature, was added and stirred. The pH was adjusted with further stirring to the optimum pH for coacervation (4·35).

Weight of coacervate

The coacervate droplets which formed were allowed to sediment out at 40 °C in preweighed tubes. The tube and contents were then cooled until the coacervate phase solidified. The tube and contents were weighed, the equilibrium liquid was decanted and the tube and coacervate reweighed. Thus the percent coacervate by weight was determined. The colloid concentrations used ranged from 1–5% w/w. The surfactants used were sodium lauryl sulphate (0·07, 0·20, 0·35% w/v); cetrimide (0·025, 0·050, 0·075% w/v); polysorbate 20 (0·004, 0·0065, 0·009% w/v). These concentrations are below, at, and above the CMC of the respective surface active agents.

Particle size analysis

In a separate series of experiments, after the adjustment of pH, stirring was continued for 40 min. 10 ml of 40% formaldehyde solution were added to produce cross-linking of the gelatin and stirring was continued for a further 10 min. The temperature of the system was rapidly reduced to 5 °C by replacing the water bath with an ice bath. Samples were then removed and a coacervate droplet size analysis carried out using the Coulter Counter Model TA II. The electrolyte used was 0·9% w/v sodium chloride. The size distributions of the droplets were recorded at various time intervals after addition to the electrolyte. The concentration of colloids used was 2% w/w.

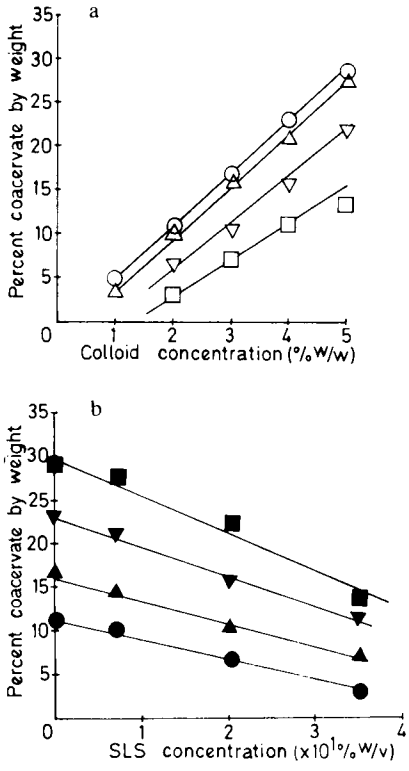

FIG. 1. Effect of (a) colloid concentration and (b) sodium lauryl sulphate (SLS) concentration on coacervate weight. ○ No surfactant; △ 0·07% w/v SLS; ▽ 0·20% w/v SLS; □ 0·35% w/v SLS; ● 2% w/w colloids; ▲ 3% w/w colloids; ▼ 4% w/w colloids; ■ 5% w/w colloids.

RESULTS AND DISCUSSION

Coacervate weight

Figs 1–3 show the effect of colloid concentration and the presence of surfactants on the weight of coacervate.

The results in the absence and presence of 0·07, 0·20 and 0·35% w/v sodium lauryl sulphate (SLS) are shown in Fig. 1(a) and (b). It is seen that the weight of coacervate increases linearly with colloid concentration, 1–5% w/w, both when prepared without surfactant and with SLS. The two higher concentrations of SLS prevent coacervation of the 1% w/w colloids, this effect probably being caused by the presence of sodium cations and lauryl sulphate anions shielding oppositely charged groups on gelatin and acacia molecules. A concentration of 0·20% w/v SLS provides approximately 7 mmol litre^{-1} of sodium ions and of lauryl sulphate ions which, together with calcium and chloride ions from the acacia and gelatin respectively, is probably sufficient to prevent or restrict electrostatic attractions between gelatin and acacia polyions.

Alternatively, the presence of SLS micelles may prevent or suppress coacervation. This effect cannot be one of solubilization of gelatin and acacia molecules within spherical micelles however, since the micelles are considered to have a diameter equal to approximately twice the length of the surfactant molecules comprising them and both gelatin and acacia are macromolecules of much larger dimensions. Instead, solubilization of these macromolecules by surfactants has been considered to take place by adsorption of surfactants onto their surface (Suzuki & Kondo 1978, 1982; Suzuki et al 1979) with orientation of polar groups outwards towards the bulk aqueous phase. This necessitates double-layer adsorption since the first layer is adsorbed by electrostatic interaction of surfactant polar head groups and the second layer by hydrophobic tail to tail bonding. This adsorption has been shown to occur at SLS concentrations well below the CMC value (Suzuki & Kondo 1982) therefore it is probably fair to assume that at the CMC concentration (0·20% w/v) and above (0·35% w/v) very few, if any

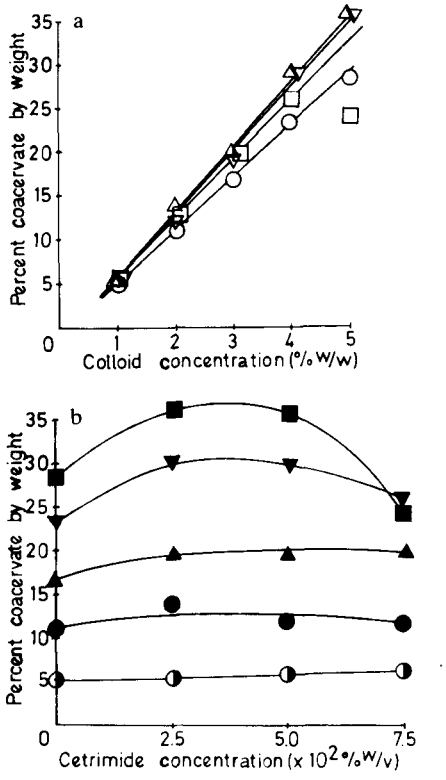

FIG. 2. Effect of (a) colloid concentration and (b) cetrimide concentration on coacervate weight. ○ No surfactant; △ 0·025% w/v cetrimide; ▽ 0·05% w/v cetrimide; □ 0·075% w/v cetrimide; ◑ 1% w/w colloids; ● 2% w/w colloids; ▲ 3% w/w colloids; ▼ 4% w/w colloids; ■ 5% w/w colloids.

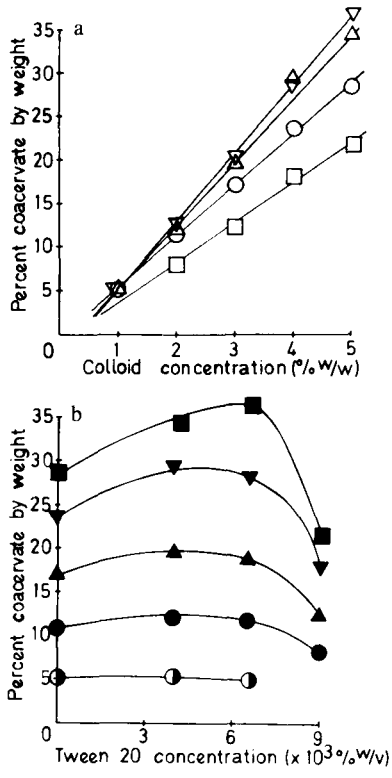

FIG. 3. Effect of (a) colloid concentration and (b) polysorbate (P) 20 concentration on coacervate weight. ○ No surfactant; △ 0·004% w/v P 20; ▽ 0·0065% w/v P 20; □ 0·009% w/v P 20; ◑ 1% w/w colloids; ● 2% w/w colloids; ▲ 3% w/w colloids; ▼ 4% w/w colloids; ■ 5% w/w colloids.

micelles will be present, the concentration of SLS molecules in the bulk phase being below the CMC value. Thus, there is left a complex picture of macromolecule-surfactant molecule interaction and inorganic ion-macromolecule interaction, together preventing coacervation.

The effect of cetrimide on coacervation is the reverse of SLS (Fig. 2a, b). The addition of increasing concentrations of cetrimide produced an increase in the weight of coacervate. However, the effect is not so clear cut as for SLS. Addition of 0·025% w/v and 0·05% w/v cetrimide produced an increased weight of coacervate for all colloid concentrations studied. However, the effect of 0·075% w/v cetrimide is seen to be dependent on colloid concentration.

Cationic surfactants have been shown to adsorb onto gelatin and acacia microcapsules by electrostatic interaction of the polar head groups with anionic sites on the gelatin and acacia macromolecules (Suzuki & Kondo 1982). However, since cetrimide was added before coacervation an explanation of the above effects must be sought in ionic interactions before coacervate droplets have been formed. A concentration of 0·05% w/v cetrimide provides about 0·15 mmol litre^{-1} of cetyltrimethylammonium cations (CTA^+) and bromide ions, an approximate fiftyfold smaller concentration of inorganic ions than provided by the CMC of SLS. Hence these concentrations are probably far too small to produce any marked adverse effect on the coacervation process. Adsorption of CTA^+ ions onto gelatin and acacia macromolecules will occur, but the extent of adsorption will be much less since they are present in much lower concentrations. Furthermore, the attraction between the highly sterically hindered CTA^+ ions (with adjacent methyl groups) and charged groupings on gelatin and acacia polyions is probably much smaller than that of the SLS anions. It may well be that electrostatic interaction between oppositely charged groupings on gelatin and acacia polyions is energetically more favourable than

between CTA^+ ions and gelatin and acacia polyions. Hence, the slight increase in coacervate weight for the 1, 2 and 3% w/w colloids prepared in the presence of cetrimide may result from an increase in the amount of water of occlusion in the coacervate phase because the water content of the complex coacervate is reciprocally related to the magnitude of the electrostatic attractions. In the absence of surfactant the coacervate phase has been found to contain about four to five times as much water as colloids (Agyilirah 1978). Effectively nearly all of the gelatin and acacia is contained within the coacervate phase and hence any increase in coacervate weight produced by the addition of cetrimide must result from an increased water content. For the 5% w/w colloids the coacervate prepared with 0·025% w/v cetrimide contains approximately six times as much water as colloids.

The dramatic change in coacervate weight seen for the 4 and 5% w/w colloids prepared with 0·075% w/v cetrimide can only be explained by assuming that the sum of inorganic ions from this concentration of cetrimide and from these relatively high concentrations of gelatin and acacia, together with some degree of solubilization by the surfactant molecules, is sufficient to reduce the Gibbs free energy change upon coacervation making coacervation less favourable energetically, i.e. that coacervation is not actually being totally suppressed but that the equilibrium liquid becomes richer in colloids.

The effect of polysorbate 20 on coacervate weight is very similar to that of cetrimide, i.e. the two lowest concentrations studied produced an increase in coacervate weight whilst the highest concentration, which is above the CMC, reduced the coacervate weight but in this instance for all colloid concentrations studied (Fig. 3a, b). In fact coacervation of the 1% w/w colloid was totally suppressed by 0·009% w/v polysorbate 20. This cannot result from a screening of charged groups on adjacent gelatin and acacia molecules by introduction of ionic species, since polysorbate 20 is a non-ionic surfactant. But because polysorbate 20 is a much larger molecule than either cetrimide or SLS, steric hindrance from the bulk of the molecule may possibly contribute to suppression of electrostatic attractions. Solubilization may also play a part at high polysorbate 20 concentrations. Whatever the true molecular mechanism it is fairly certain that micelles do not play a significant role unless the whole micelle, again by virtue of its bulk, after adsorption onto gelatin and acacia macromolecules prevents their close approach.

Thus the 0·004 and 0·0065% w/v polysorbate 20 concentrations increase the coacervate weight by increasing the water content through partial suppression of electrostatic attractions while the 0·009% w/v polysorbate 20 concentration, which is above the CMC, decreases coacervate weight by suppression of coacervation through solubilization.

Coacervate droplet size analysis

Coulter Counter particle size analysis of the cross-linked coacervate droplets initially produced a bimodal distribution for the sample without surfactant. As the time of exposure to normal saline progressed, so the position of the secondary maximum shifted to smaller particle size ranges and became narrower and the percentage of particles by number in the primary maximum increased (Fig. 4). This change in the position of the secondary maximum was found to be linearly related to time (Fig. 5). After 18·5 min exposure the distribution became unimodal with a maximum at or below 1 μm.

This changing distribution may be due to the changes in the state of aggregation of the cross-linked droplets. Low electrolyte concentrations would stabilize the microcapsules in accord with the Derjaguin-Landau and Verwey-Overbeek theory,

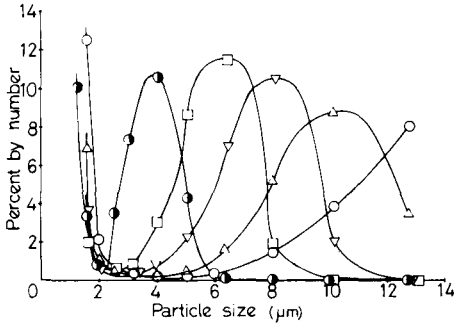

FIG. 4. Effect of time of sampling on coacervate droplet size distribution for sample without surfactant. ○ 1·5 min; △ 4·5 min; ▽ 7·5 min; □ 10·5 min; ◑ 14·5 min.

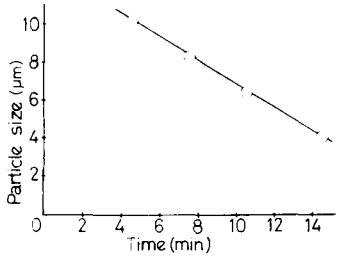

FIG. 5. Particle size at peak of secondary maximum as a function of time for sample without surfactant.

but the concentration of 0·9% w/v sodium chloride is far in excess of that required to produce stability of the droplets, hence aggregation of droplets occurs which would bring the very small droplets into the lowest particle size range studied, thereby increasing the percentage in the primary maximum. Aggregation of these small particles may also have produced a greater number of aggregates with smaller diameters than those of the initially observed secondary maximum, hence the shift to smaller size ranges of the secondary maximum. The remarkable feature of this effect is the precise linear change in the position of the secondary maximum with time from which one might conclude that the rate of aggregation is also linearly related to time. Breakup of larger aggregates may also contribute to the overall observed effect so that the state of the system is constantly changing. Another factor which may contribute to the changing secondary maximum which should not be overlooked is the osmotic withdrawal of water from the droplets caused by the electrolyte medium, followed by shrinkage of the droplets.

A similar changing size distribution was observed for cross-linked droplets prepared with 0·025% w/v cetrimide. The change in the position of the secondary maximum was more rapid in this instance. The effect of 0·05% w/v cetrimide (the CMC concentration) on the particle size distribution of the cross-linked coacervate droplets was by no means so straightforward. Initially, the secondary maximum shifted to small size ranges and the percentage of particles in the primary maximum increased, but just when a unimodal distribution resulted with the two previous samples, in this instance a new secondary maximum appeared at the largest size range studied. This effect on the overall size distribution is minimal since only 1–2% by number of the particles lie in the secondary maximum.

Obviously these results are characteristic of the individual system studied and alteration of the preparation of the droplets and concentration of surfactant will affect this dynamic aggregation, breakdown and reaggregation which must be continuously occurring.

Droplets prepared in the presence of 0·075% w/v cetrimide, 0·004, 0·0065 and 0·009% w/v polysorbate 20 did not display this time-dependent size distribution in 0·9% w/v sodium chloride. It may well be that, at the high concentration of cetrimide used, adsorption of double layers of cetrimide cations onto the droplets occurs which acts to sterically prevent aggregation of the droplets. This would also be true of the concentrations of polysorbate 20 used, especially as the molecules are much larger than those of cetrimide. This is supported by Maierson (1969) who used the surfactant to prevent aggregation during recovery of microcapsules.

The effect of sodium lauryl sulphate on the size of the cross-linked coacervate droplets could not be observed using the Coulter Counter since upon introduction into 0·9% w/v sodium chloride immediate aggregation and precipitation resulted, a contributing factor no doubt being the sodium ions from the SLS. Microscopic observations showed that increasing concentrations of SLS do affect the particle size distribution. For the lowest SLS concentration the size range is similar to that observed in the presence of cetrimide and polysorbate 20 and also without surfactant, the largest droplets being about 16 μm and the smallest, less than 1 μm. Increasing the SLS concentration to the CMC value produced a significant decrease in the size of the largest droplets (approximately 6 μm). Further increase in SLS concentration caused aggregation of the droplets but no apparent alteration to the size distribution.

The considerable suppression of coacervate weight caused by increasing concentration of SLS has already been commented upon. As conditions move away from the optimum it has been observed that droplet size decreases. The lowest SLS concentration had little effect on coacervate weight, hence the similar size distribution to that without surfactant.

In conclusion, the effects that surfactants have on complex coacervation are dependent not only on the concentration of the surfactant, whether above or below the CMC, but also on the character of the surfactant molecule, whether anionic, cationic or non-ionic. Each type of surfactant and its particular concentration must be considered together with the concentrations of colloids before any firm conclusions can be drawn about how the coacervation process will be affected.

REFERENCES

Agyilirah, G. A. (1978) M.Sc. Thesis, London University

Bungenberg de Jong, H. G. (1949) in: Kruyt, H. R. (ed.) Colloid Science. Elsevier, New York, Vol. II

Maierson, T. (1969) U.S. Patent 3, 436, 452

Siddiqui, O., Taylor, H. (1983) J. Pharm. Pharmacol. 35: 70–73

Suzuki, S., Kondo, T. (1978) J. Colloid Interface Sci. 67: 441–447

Suzuki, S., Kondo, T. (1982) Colloids and Surfaces 4: 163–171

Suzuki, S., Nakamura, T., Arakawa, M., Kondo, T. (1979) J. Colloid Interface Sci. 71: 141–146