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SOME OBSERVATIONS ON CONDUCTIVITY AND FLOCCULATION IN BISMUTH SUBNITRATE SUSPENSIONS

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ABSTRACT

Bismuth subnitrate suspensions from 2 to 6% solids were flocculated with monobasic potassium phosphate. Their conductivity appeared to follow colloid theory as judged by the linear relationship observed between the suspension conductivity and the supernatant conductivity. However, no correlation was observed between this relationship and flocculation behavior. An alternate plotting technique revealed a correlation between flocculation and conductivity. The onset of flocculation as determined by sediment heights and optical microscopy was observed to coincide with a discontinuity in a conductivity versus electrolyte concentration plot. For bismuth subnitrate suspensions prepared with either potassium or aluminum chloride there was observed a gradual change in the state of aggregation from non-flocculated to flocculated on aging. This change was correlated with changes in the suspension conductivity

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and was interpreted on the basis of a hydrolysis of bismuth subnitrate catalyzed by chloride ions. Previous subnitrate is not flocculated by aluminum chloride. This study suggests that conductivity can be used in evaluating and developing suspensions of pharmaceutical interest.

INTRODUCTION

The importance of the surface charge of a suspended particle in the evaluation and interpretation of suspension behavior is well documented in the literature. This is true for those suspensions where the flocculation mechanism depends on the surface charge (measured by the zeta potential) as outlined by the theory developed by Derjaguin, Landau, Verwey and Overbeek, known as the DLVO theory[1,2]. The zeta potential of these suspensions is most readily controlled or changed by varying the concentration and/or valence of the added electrolyte.

The zeta potential is determined experimentally as a function of the mobility of the charge suspension particle moving in an electrical field. Since the conductivity of an aqueous dispersion is also dependent upon the mobility of charged particles it is proposed that conductivity should be affected by the same variables that affect the zeta potential. It is also proposed that changes in surface charge should be detected by conductivity and therefore that conductivity should be of utility in the interpretation of suspension behavior.

For a dispersion of a solid in an aqueous medium two experimental conductivities can be measured: K, the conductivity of the thoroughly dispersed suspension and, K_1, the conductivity of the supernatant liquid or the dispersion medium. K_1 can be measured following filtration or centrifugation of the dispersed solid.

If the dispersed solid is uncharged the relationship between K and K_1 is given by Maxwell's equation rearranged for plotting purposes as follows[3]):

$$K = \frac{1}{F} K_1 \tag{1}$$

where F is called the formation factor and accounts for the presence of solid in the dispersion. Theory predicts that K should be less than K_1 due to an increase in resistance to the passage of current created by the presence of suspension particles. It follows then that the formation factor, F, is greater than unity. F can be determined from the ratio K_1/K or, alternately, from the slope of a plot of K versus K_1 for a series of dispersions where the concentration of electrolyte is varied.

For a dispersion of solid particles having a charged surface Equation 1 becomes for the most simple case:

$$K = K_s + \frac{1}{F} K_1 \tag{2}$$

The term K_s is the contribution to the total suspension conductivity made by the charged suspension particles. K_s includes both a surface conductivity and a mobility term and should be related to zeta potential. Extensive theoretical expressions exist for K_s[4,5]; however, for the purpose of this work K_s will be treated as an experimental parameter. A plot of K versus K_1 is predicted to be linear for a suspension of charged particles with a slope of 1/F and an intercept of K_s.

The objectives for this work are, in general, to evaluate the use of conductivity as an alternative to zeta potential in the evaluation of suspension behavior and specifically to test the proposed hypothesis by comparing the conductivity of bismuth subnitrate suspensions with their flocculation behavior as reported in the literature[6].

MATERIALS AND METHODS

Bismuth subnitrate in suspensions containing 2 to 6% solids was selected for this study because of its widely documented flocculation behavior[6,9]. Three electrolytes, monobasic potassium phosphate, potassium chloride and aluminum chloride, were used to control flocculation.

Suspension conductivity was measured using a Radiometer CDM3 conductivity meter by immersing the conductivity cell into a well dispersed suspension. The conductivity of the supernatant liquid was measured after centrifugation of the suspension. All conductivities reported are specific conductivities.

Suspensions containing 2, 4 and 6% bismuth subnitrate were prepared by transferring the required amount of an electrolyte stock solution to centrifuge tubes, followed by water and aliquots of 3, 6 and 9% bismuth subnitrate stock suspensions respectively. The order of addition of electrolyte, in the case of potassium chloride, was found to be critical as discussed later. The suspensions were thoroughly dispersed for one minute on a vortex mixer and left to stand for 24 hours prior to evaluation. All concentrations are expressed as percent weight in volume.

Bismuth subnitrate stock suspensions were prepared by transferring the corresponding weighed amount of the solid into a 1000 mL volumetric flask and made to volume with fresh distilled water. The suspension was immediately transferred into a 1000 mL three neck flask and stirred continuously by use of a glass stirrer.

In order to measure sediment heights, 3.8 mL aliquots of the suspensions were transferred immediately

TABLE 1.

Preparation and Conductivity of 2% Bismuth Subnitrate Suspensions with 0.42 mM Potassium Chloride.

Sample Number	Method of Preparation	Potassium Chloride Stock Solution (mM)	Specific Conductivity (mmhos/cm) 2 hrs	48 hrs	144 hrs	336 hrs
1	A[a]	0.025	0.96	1.66	8.70	8.75
2	A	0.005	0.96	1.38	8.65	8.70
3	A	0.0025	0.96	1.20	2.58	8.85
4	A	0.00125	0.96	1.18	3.35	8.75
5	B[b]	0.025	0.96	1.25	3.18	8.65
6	B	0.005	0.96	1.24	3.00	8.70
7	B	0.0025	0.96	1.24	3.04	8.65
8	C[c]	0.025	0.96	1.39	8.81	8.85
9	C	0.005	0.96	1.19	2.74	8.85
10	C	0.0025	0.96	1.17	2.28	8.79

[a] - An aliquot of a 3% bismuth subnitrate suspension was added to a centrifuge tube first, followed by the potassium chloride stock solution, then water.

[b] - The potassium chloride stock solution was added to a centrifuge tube first, followed by water, then an aliquot of a 3% bismuth subnitrate suspension.

[c] - An aliquot of a 3% bismuth subnitrate stock suspension was added to a centrifuge tube first, followed by water, then the potassium chloride stock solution.

after vortexing into 5 mL plastic disposable cuvets and the cuvets sealed. Sediment heights were measured using a cathetometer after the dispersions were left to stand for a period of time, in general, 24 hours.

RESULTS AND DISCUSSION

Suspension Preparation

Studies carried out with bismuth subnitrate suspensions containing 0.42 mM potassium chloride demonstrated the importance of at least one processing variable in suspension preparation and led to the adoption of the procedure B as indicated in Table 1, to prepare all the suspensions.

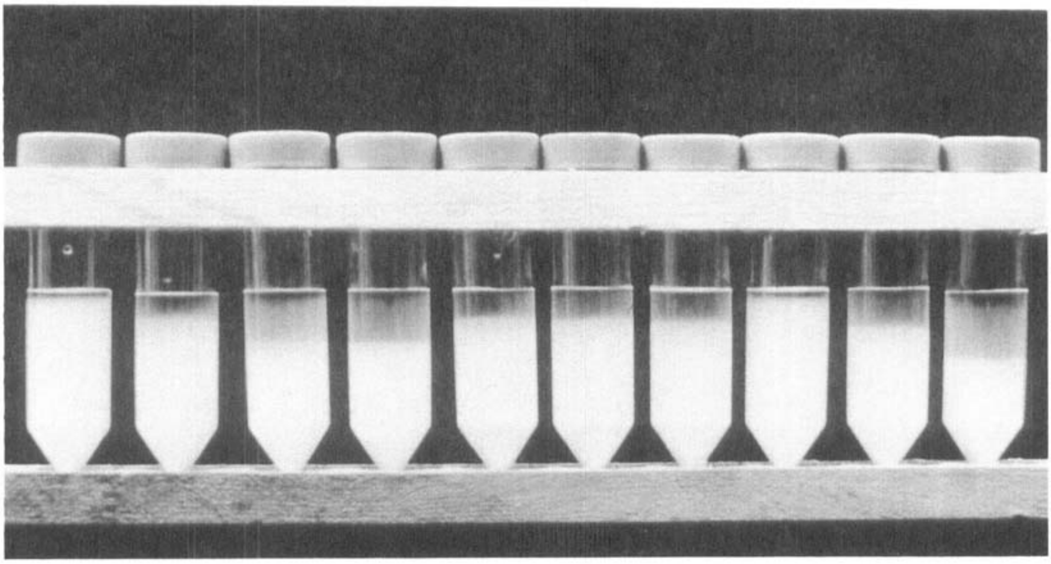

FIGURE 1.

2% Bismuth subnitrate suspensions prepared according to the procedures outlined in Table 1.

It was observed that suspensions prepared with the same concentration of bismuth subnitrate and the same concentration of electrolyte were not identical if electrolyte stock solutions of different concentration and different orders of mixing were used. These differences are shown in Figure 1 for 10 suspensions two hours after preparation, all containing 0.24 mM potassium chloride. The concentration of electrolyte stock solution and the order of mixing are described in Table 1; the sample number in the table corresponds to the tubes in Figure. 1 counting from left to right.

The first four suspensions were prepared with four electrolyte stock solutions of decreasing concentration by adding the electrolyte solution to the stock suspension aliquot and finally making up to volume with

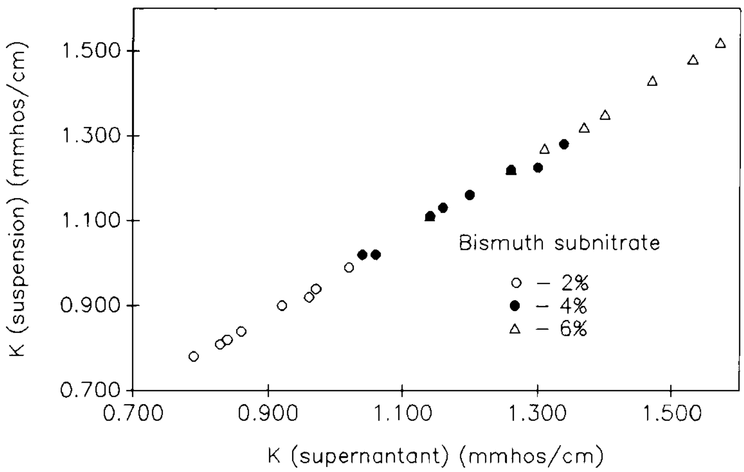

FIGURE 2.

The conductivity of bismuth subnitrate suspensions containing 0 to 4.8 mM monobasic potassium phosphate plotted according to Equation 2.

water. The suspensions exhibited different degrees of aggregation as evidenced by their sedimentation behavior. The same variation in degree of aggregation was observed in the last three tubes in which the electrolyte stock solution was added last.

Only in suspensions 5, 6 and 7 was the degree of aggregation constant and independent of electrolyte stock solution concentration. In these tubes the stock suspension aliquot was added last, i.e., the stock suspension aliquot was added to a mixture of electrolyte stock solution and water in which the concentration of electrolyte was constant. It appears that the initial state of aggregation is dependent on the concentration of the electrolyte to which the bismuth subnitrate is exposed. This is consistent with literature reports[7,8] of a hydrolysis reaction of bismuth subnitrate in aqueous medium catalyzed by various ions.

As seen from the data in Table 1 all of the suspensions had identical conductivity values initially and that the conductivity changed on aging eventually reaching a similar limiting value. The rate of change, however, was dependent on the order of mixing, i.e., on the concentration of electrolyte to which the bismuth subnitrate is initially exposed. At the end of the aging period all of the suspensions were flocculated.

These observations lead to the use of procedure B in Table 1 in order to prepare equivalent suspensions independent of the order of mixing.

<u>Colloid Theory</u>

The bismuth subnitrate suspensions containing 0 to 4.8 mM monobasic potassium phosphate as reported by Martin[6] were prepared and their conductivity measured. Suspension conductivity was plotted as a function of supernatant conductivity as suggested by Equations 1 and 2. The data for three series of suspensions containing 2, 4 and 6% bismuth subnitrate all fall on the same straight line (Figure 2) even though the range of concentration of monobasic potassium phosphate was the same for each series. Bismuth subnitrate itself affects the conductivity of both the suspension and the supernatant concomitantly; therefore increasing the concentration of bismuth subnitrate leads to an increase of both conductivities.

It would be expected that the plots of suspension conductivity vs supernatant conductivity for different concentrations of bismuth subnitrate would have different slopes since the formation factor, F, has been suggested to depend on the volume fraction or concentration of solids. The value of the formation factors are 1.10, 1.10 and 1.06 for 2, 4 and 6% bismuth subnitrate respectively and suggests that either the formation factor is a constant or that this plotting technique is not sensitive enough to detect changes in the formation factor.

The linear relationship in Figure 2 also suggests, from Equation 2 that the surface conductivity is constant. However, it is known that the zeta potential or surface charge changes with electrolyte concentration for bismuth subnitrate suspensions[6]; it would also be expected that the surface conductivity would also change with electrolyte concentration. Furthermore, each of the series of suspensions in this study contained both non-flocculated as well as flocculated samples, experimental evidence of a change in surface charge.

It would appear that experiment follows theory as judged by the linear plot according to Maxwell's theory (Equations 1 and 2). On the other hand, the constant formation factor, the suggestion of constant surface charge and the lack of any corarelation with flocculation concludes that simple colloid theory does not properly describe the physical behavior of the bismuth subnitrate suspensions.

An Alternate Conductivity Plot

The conductivity data for the bismuth subnitrate suspensions were not as continuous as suggested by the Maxwell plot. The data for the 6% bismuth subnitrate series was plotted in Figure 3, according to Equation 2 with the data points numbered in order of increasing concentration of electrolyte. It can be seen that the conductivity increases with electrolyte concentration but reaches a point where the conductivity decreases then increases again. This discontinuity in the conductivity plot was found to coincide with the onset of flocculation as determined from sediment heights. Since it is known from the literature that the onset of flocculation occurs when the the zeta potential approaches zero, it is

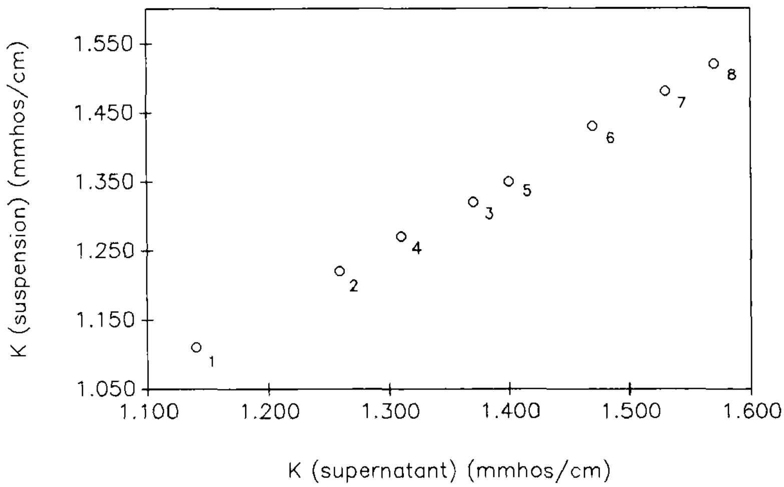

FIGURE 3.

The conductivity of 6% bismuth subnitrate suspensions plotted according to Equation 2. The data points are numbered in order of increasing concentration of monobasic potassium phosphate from 0 to 4.8 mM.

concluded that the discontinuity in the conductivity plot corresponds to the reduction of zeta potential or surface charge.

This observation led to presenting the data in a different format, i.e., plotting the conductivity of the suspension as a function of the concentration of monobasic potassium phosphate. Such a plot for the three series of suspensions containing 2, 4 and 6% bismuth subnitrate is shown in Figure 4. The lower curve represents the conductivity of monobasic potassium phosphate solutions over the same concentration range as that used in the suspensions; it is apparent that the bismuth subnitrate contributes the larger part of the total conductivity of the suspension.

The discontinuity observed in Figure 3 appears as a break in the conductivity vs electrolyte plot. For each

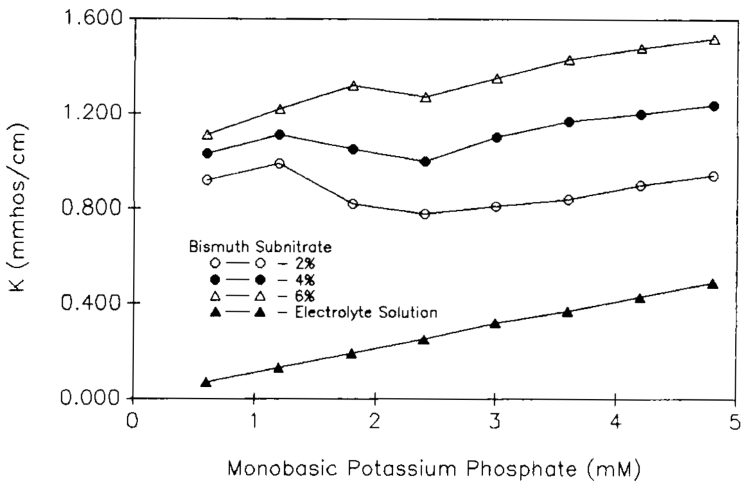

FIGURE 4.

The conductivity of bismuth subnitrate suspensions as a function of electrolyte concentration.

series of suspensions this break coincides with the onset of flocculation. This relationship is shown in Figure 5 for the series of 6% bismuth subnitrate suspensions where both conductivity and sediment heights are plotted as a function of the electrolyte concentration. It is apparent that the maximum sediment height corresponding to the onset of flocculation coincides with the break in the conductivity plot. The correlation between the conductivity data and the sediment height is similar to that demonstrated by Haines and Martin[6] between zeta potential and sediment heights.

The break in the conductivity plot could be brought about by several possible mechanisms; the contribution to the conductivity by the suspension particles decreases as the particles change from charged to uncharged or the conductivity may decrease due to the limited mobility of flocs compared to that of single monodispersed particles.

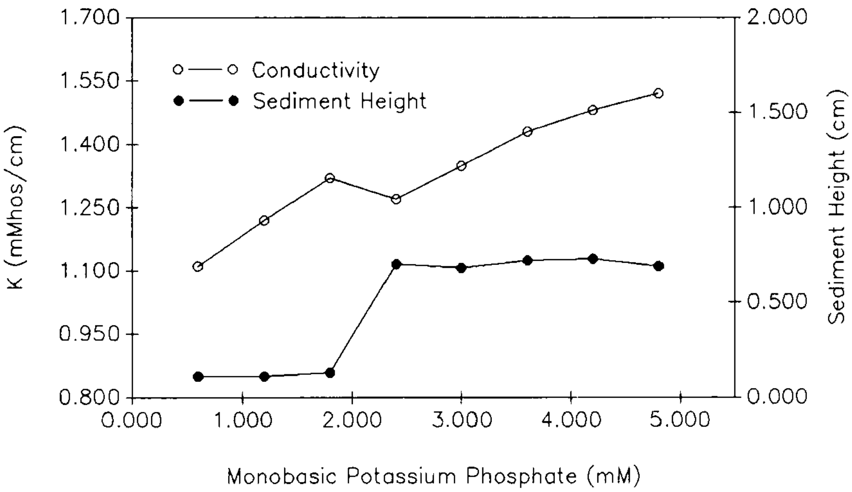

FIGURE 5.

The conductivity and sediment heights of 6% bismuth subnitrate suspensions as a function of electrolyte concentration.

Neither of these arguments explains the fact that the conductivity of the supernatant also shows the same break at the onset of flocculation when the supernatant conductivity is plotted as a function of monobasic potassium phosphate concentration. This observation may suggest that the electrolyte is entrapped in the floc structure and consequently sequestered from the medium.

The effect of potassium chloride and aluminum chloride on the flocculation behavior of bismuth subnitrate was also investigated. It was observed in each case that the suspensions changed from non-flucculated to flocculated on aging as described previously under "Suspension Preparation". No aging effects were observed with monobasic potassium phosphate.

This aging process is supported by reports in the literature of the hydrolysis of bismuth subnitrate catalyzed by various ions[7,8] particularly chloride. Flocculation of bismuth subnitrate suspensions by either potassium or aluminum chloride is suggested to be a function of the products of hydrolysis several of which are ionic. The hydrolysis reaction, hence, the flocculation process can be followed by conductivity since both processes contribute to the total conductivity of the suspension.

The reports in the literature with regard to flocculation of bismuth subnitrate with aluminum chloride are somewhat conflicting. It has been reported[9] that aluminum chloride has no effect on the flocculation of bismuth subnitrate. The results of this study suggest that bismuth subnitrate suspensions do flocculate with chloride ion but only after an aging period.

CONCLUSIONS

The general observations made in this study regarding conductivity and suspension behavior support the following conclusions:

1. Conductivity is sensitive to changes in the composition of a suspension, namely the concentration of both solid and electrolyte, and the degree of aggregation.
2. A correlation exists between the conductometric behavior of a suspension and the onset of flocculation.

This study suggests that conductivity has utility in following and predicting the flocculation conditions for other suspensions of pharmaceutical interest.

REFERENCES

1. B. A. Matthews and C. T. Rhodes, J. Pharm. Sci., 59, 521 (1970).

2. W. Schneider, S. Stavchansky, and A. Martin, Am. J. Pharm. Educ., 42, 280 (1978).

3. S. S. Dukhin and B. V. Derjaguin, in "Surface and Colloid Science," Vol. III, E. Matijevic, ed., Wiley Interscience, New York, 1971, p. 212.

4. N. Street, Aust. J. Chem., 9, 333 (1956).

5. N. Street, J. Phys. Chem., 64, 173 (1960).

6. B. A. Haines and A. N. Martin, J. Pharm. Sci., 50, 753 (1961).

7. F. Pellerin, J. P. Goulle and D. Dumitrescu, Ann. Pharm. Fr., 35, 281 (1977).

8. P. S. Anand and D. R. Baxi, Indian J. Technol., 16, 189 (1978).

9. B. A. Haines and A. N. Martin, J. Pharm. Sci., 50:228 (1961).