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Short Communication

Preformulation information for suspensions

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The formulation of pharmaceutical dosage forms frequently requires the balancing of competing objectives. In terms of suspensions, it is usually desirable to maximize the volume fraction of solids in order to minimize the volume of the dose. However, the apparent viscosity of suspensions is very sensitive to particle–particle interactions (Feldkamp et al., 1981) and a suspension may gel when a critical volume fraction is reached. The development of fiber optic Doppler anemometry (FODA) for monitoring particle–particle interactions (Wu et al., 1986) has provided a new tool to assist in the formulation of suspensions. The area under the curve (AUC) of the modified Lorentzian power spectrum as determined by FODA is directly related to the number of freely diffusing particles. The AUC approaches zero with increasing volume fraction when an extensive particle network forms which dampens the random motion of the particles. The volume fraction at which the AUC approaches zero is termed the critical volume fraction, ϕ_c , and serves as an accurate definition of the gelation point. The utility of FODA for monitoring particle interactions in suspensions has been confirmed by correlations of

AUC with rheology. Feldkamp et al. found that the maximum apparent viscosity of an amorphous carbonate-containing aluminum hydroxide suspension occurred when the pH was adjusted to the PZC. Wu et al. observed that a yield value was first exhibited when the AUC approached zero. The purpose of this communication is to demonstrate how information obtained by FODA can aid in the formulation of suspensions by optimizing the solid content (volume fraction) and rheology

Amorphous carbonate-containing aluminum hydroxide will serve as a model suspension. Because amorphous carbonate-containing aluminum hydroxide has a pH-dependent surface charge (Feldkamp et al., 1981), particle–particle interactions can be conveniently controlled by adjusting the pH in relation to the point of zero charge (PZC). Although pharmaceutical suspensions are usually prepared on a weight basis, particle interactions are related to the volume occupied by the solid phase. Thus, the solids content of the suspensions will be expressed as the volume fraction. The volume fraction, ϕ , was calculated by the following equation:

$$\phi = X \cdot d \cdot \frac{MW}{102} \cdot \frac{1}{100} \quad (1)$$

where X is the w/w percent equivalent aluminum

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oxide, d is the density of the suspension at 25°C, and MW is the molecular weight of $Al(OH)_3 \cdot R(HCO_3)_R$, where R is the carbonate to aluminum ratio. The typical relationship of AUC to volume fraction is shown in Fig. 1 for a sample adjusted to pH 6.0, having a PZC of 6.7. At low volume fractions, the AUC was linearly related to the volume fraction indicating that all of the particles are randomly moving and therefore, are contributing to the AUC. The onset of particle interactions is indicated by deviation from the initial linear relationship. In the example, this occurred at a volume fraction of approximately 0.025. At volume fractions greater than 0.025, the AUC was less than the extrapolated value, with a maximum occurring at a volume fraction of 0.040–0.045. The AUC decreased when the volume fraction was greater than 0.045 and approached zero when the volume fraction was greater than 0.088. Thus, in the example shown in Fig. 1, a particle network which is extensive enough to stop the random motion of the suspended particles formed when the volume fraction was greater than 0.088, i.e. $\phi_c = 0.088$. Knowledge of ϕ_c would be very useful in optimizing the solids content and the apparent viscosity during suspension formulation.

Fig. 2 illustrates the relationship between surface charge as characterized by (PZC-pH) and ϕ_c . When the pH was equal to the PZC, the net

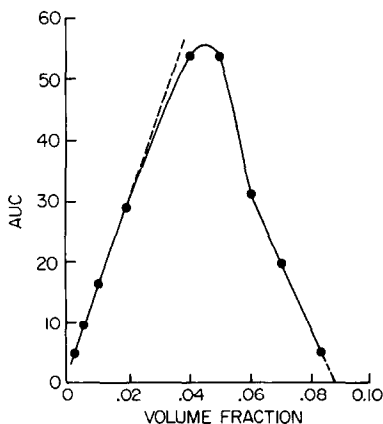


Fig. 1. Effect of volume fraction on the area under the curve (AUC) of the modified Lorentzian power spectrum for an amorphous carbonate-containing aluminum hydroxide suspension at pH 6.0 (point of zero charge, 6.7).

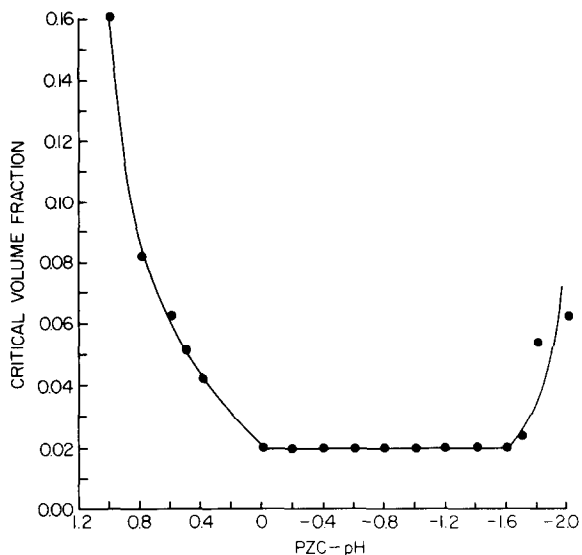


Fig. 2. Relationship between surface charge as characterized by PZC-pH and the critical volume fraction, ϕ_c , for an amorphous carbonate-containing aluminum hydroxide suspension (point of zero charge 6.7).

surface charge was zero and attractive particle interactions predominated. Under these conditions a volume fraction of only 0.02 was possible before a particle network formed. Thus, a volume fraction of 0.02 represents the maximum solids content possible before the apparent viscosity increases sharply due to the formation of a particle network. In contrast, ϕ_c was 0.16 when the pH was 1 unit below the PZC. Thus, the volume fraction can be increased by a factor of 8 without a significant increase in the apparent viscosity if the (PZC-pH) relationship is adjusted to 1.

The critical volume fraction was not symmetrical in terms of the PZC as ϕ_c remained at 0.02 until the pH was 1.6 units above the PZC. Although not understood, this behavior is consistent with a previous study (Feldkamp et al., 1981) of the effect of pH on the apparent viscosity of a suspension of a solid having a pH-dependent surface charge. The volume fraction was held constant but the apparent viscosity increased sharply as the pH was increased to reduce (PZC-pH). The viscosity decreased as the pH was raised above the PZC but the apparent viscosity did not decrease

as rapidly when the pH was above the PZC as when the pH was below the PZC. In addition, FODA revealed that the attractive particle network did not disaggregate as readily when the pH was above the PZC as when the pH was below the PZC (Wu et al., 1986).

Data such as presented in Fig. 2 can be used by the formulator of pH-dependent suspensions to determine the pH necessary to achieve the desired volume fraction without gelation. For example, if a suspension of this carbonate-containing aluminum hydroxide was desired which had a volume fraction of 0.04, i.e. 4% solids content by volume, and also a low viscosity, examination of Fig. 2 reveals that the pH would have to be at least 0.4 units below or 1.8 units above the PZC in order to avoid gelation. The particle-particle interactions responsible for the behavior seen in Fig. 2 are also affected by particle size and polydispersity (Feldkamp et al., 1982). Thus, the critical volume fraction-surface charge relationship for each pH-dependent solid will have to be investigated. However, this information will provide a rational basis for balancing the solids content and apparent

viscosity when formulating suspension dosage forms.

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