Entropy-driven phase separation in mixtures of small colloidal particles and semidilute polymers

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We study mixtures of polymer solutions with particles whose diameter is much smaller than the radius of gyration of the polymer. They are found to demix when the polymer is semidilute and its correlation length is approximately equal to the particle's diameter. Protein purification using polymer solutions is shown not to be possible without attractive polymer-protein interactions. [S1063-651X(97)13610-8]

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I. INTRODUCTION

Polymers are mixed with suspensions of colloidal particles because the mixture possesses desirable properties that the pure suspension does not, for example, the required degree of viscosity [1,2]. The resulting solution is a mixture of small compact particles, usually roughly spherical, and polymer chains. These polymer chains are, of course, not compact; each chain is spread over a large volume, only a small fraction of which is actually occupied by its segments [3]. The two components of the mixed solution are very different and so the interaction between them is very different from the colloid-colloid and polymer-polymer interactions [4–6]. When the particles are, for example, protein molecules they are typically small in relation to the polymer i.e., they have a diameter much smaller than the radius of gyration of the polymer. Here we derive a simple theory that qualitatively describes the small-particle-polymer mixtures and use this to calculate their phase behavior. We find that the mixture demixes into a particle-rich phase and a polymer-rich phase and that it does so at a volume fraction of particles that is universal and a volume fraction of polymer that varies as $D^{-4/3}$, for D the diameter of the particle.

The colloidal particles may be protein molecules [7,8], surfactant micelles [9,10], or synthetic, polymer, or silica spheres [2]. Both protein molecules and micelles typically have diameters of around 5 nm. The polymer is considered to be in a good solvent and is therefore swollen in dilute solution due to self-interactions [3]. All interactions are assumed to be excluded volume interactions, that is, two polymer segments may not occupy the same volume and likewise for two particles or a particle and a polymer segment. This is reasonable if the solvent is good for the polymer, and the polymer does not absorb onto the particle. The energy of mixing is zero and so demixing can only occur if the entropy of mixing is offset by a decrease in entropy caused by the polymer reducing the particle's translational entropy and the particles reducing the polymer's configurational entropy.

The opposite case to that considered here, when the particle's diameter is larger than the radius of gyration of the polymer, has been considered extensively, both by experiment [1] and by theory [1,11]. In this case the particles are usually synthetic colloidal spheres.

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II. PHASE BEHAVIOR

When the polymer concentration is low enough that the polymer coils do not overlap, the dilute regime, the interaction between a particle and a much larger polymer coil, is weak [4,12,13]. The particle freely penetrates the polymer coils because these coils are mostly solvent, the actual density of polymer segments inside the polymer coil is very low. If a particle is introduced into a coil the probability of it interacting with the polymer is only $(D/R_G)^{4/3} \ll 1$ [4,12], where R_G is the radius of gyration of the polymer (this result is derived below). So, when the polymer is dilute, the polymer and particles are miscible. The situation is different at higher polymer densities when the coils overlap, the semidilute regime [3]. We will show that there the mixture demixes.

All three interactions are excluded volume and therefore there are no energy scales, apart from the temperature T. There remain only length scales and the phase behavior can only depend on ratios of the length scales of the polymer to those of the particles. Obviously, the only length scale of the particles is their diameter D. In a pure semidilute polymer solution there is again only one relevant length scale, the correlation length ξ [3], which is roughly the distance between interactions between segments on different polymer chains. ξ is given by $\xi = a\phi_K^{-3/4}$, where a is the segment length and ϕ_K is the volume fraction of polymer segments. The radius of gyration is not a relevant length scale as it is much larger than ξ and the chain loses its correlations and ''forgets'' which polymer it belongs to over a distance of ξ. A sphere of diameter $D \gg a$ interacts not with each polymer segment individually but with a piece of polymer chain of size D [4]. When $D \gg a$, the piece of a polymer coil of size D is sufficiently large that it behaves as a small polymer coil and then a is irrelevant just as for any other polymer coil [3,4,13]. The mixture then has only two relevant length scales, D and ξ, these are shown in Fig. 1. This means that the particle-polymer interaction, and hence whether or not the mixture demixes, depends only on their ratio D/ξ.

The free energy per unit volume of a semidilute polymer solution scales with ξ as $\sim T/\xi^3$ [3], essentially the density of intrachain interactions. The free energy of colloidal particles modeled as hard spheres is well described by a virial series [14]. However, in a mixture of the spherical particles and the polymer there are particle-polymer interactions that are qualitatively different from either the polymer-polymer or
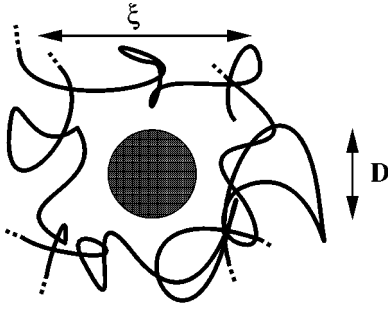
FIG. 1. A schematic picture of a small colloidal sphere, a micelle, or a protein molecule, in a semidilute polymer solution.

particle-particle interactions; their contribution to the free energy must be estimated in order to determine the phase behavior of the mixture.

In the limits $D \ll \xi$ and $D \gg \xi$, the particle-polymer interaction is straightforward. When $D \ll \xi$ we scale the polymer segment length from a to D. Then if N_D is the number of these segments of size D in a piece of polymer of length ξ, ξ is related to N_D by $\xi = D N_D^{3/5}$; on length scales smaller than ξ the polymer is swollen. These segments are spread over a volume of ξ^3 but only exclude a particle of diameter D from a volume of order $N_D D^3$; now that the segments are of the same size as the particle we can consider them as interacting independently with the particle. Using $N_D = (\xi/D)^{5/3}$, the fraction of volume denied by the polymer to particle is then $(D/\xi)^{4/3}$. The work done w ($=$ the difference in excess chemical potential) in taking a particle from a pure solvent and inserting it into the polymer solution is just given by the expression of Widom [13,15]:

$$\frac{w}{T} \sim -\ln\left[1 - \left(\frac{D}{\xi}\right)^{4/3} \right] \sim \left(\frac{D}{\xi}\right)^{4/3}, \quad D \ll \xi, \quad (1)$$

where the logarithm is of the fraction of volume available to the particle. Note that by replacing ξ by R_G we obtain the equation quoted earlier for the particle-polymer interaction when the polymer is dilute. The notation ''$\sim$'' indicates that we are neglecting (unknown) coefficients of order unity; here we derive only the scaling behavior of the interactions with respect to the relevant length scales. When $D \gg \xi$, the work done in inserting the particle is just that done in clearing the polymer solution from a volume of D^3, i.e., ΠD^3, where Π is the osmotic pressure of the polymer solution. The osmotic pressure of a polymer solution is related to ξ by $\Pi/T = \xi^{-3}$, so

$$\frac{w}{T} \sim \left(\frac{D}{\xi}\right)^3, \quad D \gg \xi. \quad (2)$$

Although Eqs. (1) and (2) have been derived in the two limits of D much larger or much smaller than ξ, they do agree that for $D \sim \xi$, $w \sim T$ [5]. This result must be correct as here the only relevant dimensionless parameter D/ξ is unity. We approximate the work done in inserting a particle of arbitrary diameter $D \gg a$ by the sum of Eqs. (1) and (2).

Straightaway we can derive an approximation for the partitioning of small spheres between a pure solvent phase and a semidilute solution; the two phases separated by a membrane

permeable to the spheres but not the polymer, at least on the time scale of the experiment. The ratio of the density of the spheres in the pure solvent to that in a semidilute polymer solution is simply $\exp(w/T)$, which is

$$\sim \exp\left[\left(\frac{D}{\xi}\right)^{4/3} + \left(\frac{D}{\xi}\right)^3 \right]. \quad (3)$$

We now construct a simple approximate free energy A by adding together the free energy of a pure semidilute polymer solution, the free energy of a pure fluid of hard spheres, and the work done in inserting the particles into the polymer solution. It is

$$\frac{A}{T} = N_K \phi_K^{5/4} + N_S[\ln(\phi_S) - 1] + N_S \phi_S + N_S \phi_S^2$$

$$+ N_S\left[\left(\frac{D}{\xi}\right)^{4/3} + \left(\frac{D}{\xi}\right)^3 \right], \quad (4)$$

where N_K, N_S, and V are the number of polymer segments, the number of particles, and the volume, respectively. The volume fractions of polymer ϕ_K and of the particles ϕ_S are given by $\phi_K = N_K a^3/V$ and $\phi_S = N_S D^3/V$. The second, third, and fourth terms are the ideal and second and third virial coefficient terms of a fluid of hard spheres. The numerical coefficients of the virial terms are omitted along with the higher order virial coefficients as our theory is purely qualitative. The third virial term could, of course, be neglected but as the particle densities are not very low it does have a significant effect and the cost in complexity of including it is very low. The assumptions underlying Eq. (4) are those underlying the theory of the pure components [3,14] plus the assumption that the free energy change in adding N_S particles is just N_S times the free energy of adding one: a low ϕ_S approximation.

The phase diagram for a mixture with $D/a = 10$ is shown in Fig. 2(a); the two-phase region where the particles and polymer demixes is clear. The behavior at the level of the individual particles and polymer molecules that is driving the phase separation could hardly be simpler. As the concentration of the polymer increases the correlation length ξ and hence the space available for the particles decreases until when $D \sim \xi$ inserting a particle requires of order T free energy to push the polymer out of the way. Then the free energy cost of the particle-polymer interaction is of the same order as the ideal free energy of mixing the spheres and polymer, and this ideal free energy is no longer enough to keep the mixture miscible. This free energy cost is the last term of the Eq. (4), it is this term that is large and positive in mixtures when D/ξ is large and so it drives phase separation. At the critical point, then $D \sim \xi = a \phi_K^{-3/4}$ and the polymer volume fraction at the critical point is $\sim (a/D)^{4/3}$. The calculations made with the free energy (4) give $D/\xi \simeq 1.5$ at the critical point so at the critical point ϕ_K is about twice this value. Although the phase diagram in the ϕ_S-ϕ_K plane changes when the ratio D/a is changed, there is essentially only one generic phase diagram. This can be seen if the phase diagram is plotted with D/ξ replacing ϕ_K [see Fig. 2(b)]; then the diagram is the same for all values of D/a.
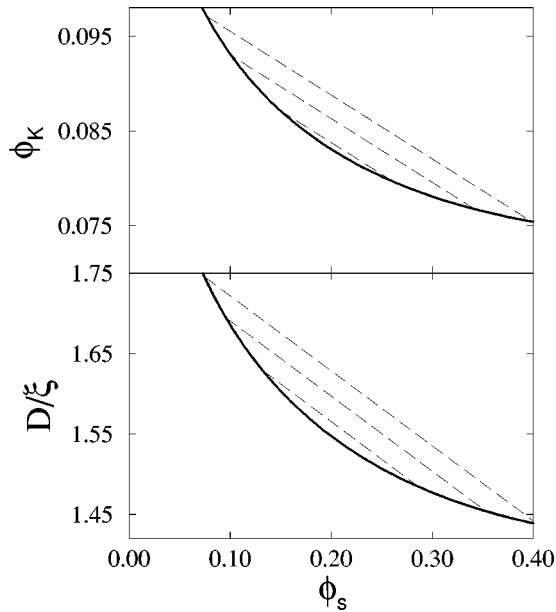
FIG. 2. Phase diagrams for a mixture of small colloidal particles and polymer. (a) is the phase diagram in the ϕ_K-ϕ_S plane for $D/a = 10$ and, (b) is the generic phase diagram in the D/ξ-ϕ_S plane. The thick curves separate the coexistence and single phase regions, and the dashed lines are tie lines. At high densities hard spheres freeze to form a solid phase and so fluid-fluid coexistence shown will terminate at a triple point. Beyond this triple point there will be only fluid-solid coexistence.

The only effect of changing D/a is to scale the polymer volume fractions at which the mixture phase separates.

Comparison with experiment is not easy as our scaling theory is only qualitative and its predictive value lies mainly in predicting trends in miscibility when the size of either the particle or the polymer is varied [3]. Experiments in which these have been systematically varied have not, to the author's knowledge, been performed. The theory qualitatively agrees with experiments performed on polymer-micelle mixtures [9,10,16], and it correctly predicts that the particle-rich phase has a higher density of particles and polymer and therefore a lower solvent (water) density. The experiments of Ref. [16] do, however, seem to indicate quite strong partitioning of polymer between the coexisting phases whereas the partitioning in Fig. 2 is quite weak. This may be due to inadequacies of the theory but it may also be due to interactions not taken account of by our simple model, for example, water may not be a very good solvent for either the polymer or the micelles.

III. PROTEIN−ATHERMAL POLYMER MIXTURES

Mixtures of dilute and semidilute polymers and spherical or quasispherical protein molecules have also been studied [7,17,18], due to their use in protein purification. Partitioning of protein molecules between two phase separated (aqueous) polymer solutions is used to purify proteins without destroying the native conformation of the protein. The protein molecules [7,17,18] are roughly spherical and show little or no attractive interaction towards each other. As semidilute polymer solutions of large polymer molecules have a very low

volume fraction of polymer the solution can be mostly saline solution and so this provides an environment in which the native comformation of the protein is maintained.

The two coexisting polymer solutions are the result of a binary mixture of polymers phase separating to form two almost pure phases [3,7]. The two coexisting polymer solutions are each nearly pure and, of course, must be at the same osmotic pressure. But they are at the same osmotic pressure and are (almost) pure, so the correlation length ξ in each phase is (almost) the same if they are both semidilute. Hence, the density of the protein will be almost the same in both phases, if all interactions are athermal. The ratio of the protein densities in the two phases when the the protein density is low (which it is under experimental conditions) is given by the ratio of Eq. (3) in the two phases. As ξ is almost the same in both phases the ratio is near to 1. Thus partitioning of protein molecules between coexisting semidilute polymer solutions requires attractive polymer-protein interactions; one of the polymers must adsorb onto the surface of the protein in order to achieve partitioning. This does not seem to be fully appreciated [7,17]. If one of the coexisting polymers adsorbs onto the protein and the other does not, the partitioning of the protein may be calculated from the free energy of this adsorption. The ratio of the density of the protein in the phase of the adsorbing polymer to the density in the phase of the nonadsorbing polymer is $\sim \exp(F_a/T)$, where F_a is the free energy change when the polymer adsorbs onto a protein molecule. To be more specific, it is the excess free energy of a polymer plus a protein molecule mixture with the attractive interactions minus the excess free energy of the mixture with the attractive interactions "turned off," leaving only excluded volume interactions. F_a could be estimated using, for example, the appraoch of Alexander [19]. The simple form of the expression for the ratio of densities is due to the cancellation of the contributions of the excluded volume parts of the interaction.

If the polymers are dilute, not semidilute, and the radius of gyration of the polymer is still larger than the diameter of the protein molecules ($\simeq 5$ nm) then the polymer-protein interaction is weak; it is given by Eq. (1) with ξ replaced by the polymer's radius of gyration. So, protein partitioning driven by excluded volume interactions is not possible at all for polymers larger than the protein. For polymers with radii of gyration less than the diameter of the protein [11], excluded volume (entropy) driven partitioning may be possible in dilute solution but polymers that are highly immiscible in dilute solution are required.

IV. CONCLUSION

Small colloidal spheres and larger polymers are miscible when the polymer is dilute but demix when the polymer is semidilute and its correlation length ξ is of the same order as the diameter D of the colloid. The demixing is entropy driven. We predict that the volume fraction of particles at the demixing critical point is a constant independent of the size of the particle, or of the nature or size of the polymer, as long as the polymer's radius of gyration is much larger than the particle's diameter and there are no attractive interactions. Also, protein partitioning between semidilute polymer solutions has been shown to require attractive interactions.

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