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# **Thermodynamic stability condition can judge whether a nanoparticle dispersion can be considered a solution in a single phase**

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## **ABSTRACT**

Establishing that a nanoparticle dispersion can, in fact, be treated as a solution has an important practical ramification, namely the application of solubility theories for solvent selection.

However, what distinguishes a solution and dispersion has remained ambiguously understood.

Based on the recent progress in statistical thermodynamics on multiple-component solutions, here we establish the condition upon which a nanoparticle dispersion can be considered a single-phased solution. We shall provide experimental evidence already found in the literature showing the solution nature of nanoparticle dispersions.

**Keywords:** Dispersion; Stability; Phase separation; Thermodynamics; Nanoparticles

## 1. Introduction

*Dispersions* of nanoparticles and colloids have not only been of scientific interest but also of technological importance. In the literature, the terms such as colloidal dispersion, suspension, and solution have been used interchangeably [1]. IUPAC has provided a definition for dispersion which has evolved over the years [2–4]. The latest definition, in the context of polymer dispersion, is “[m]aterial comprising *more than one phase* where at least one of the phases consists of finely divided phase domains, often in the *colloidal* size range, dispersed throughout a *continuous phase*” (italics have been added for emphasis) [4]. The size of the continuous phase domain is one of the characterizing feature of dispersion [3]. In addition, the term “suspension” is used specially when dispersed phase particles are greater than colloidal in size [1]. However, polymer and protein “solutions” are often treated effectively as colloidal dispersions [1].

Such conflicting statements raise the following questions. What, really, is the difference between a dispersion and a suspension, or a dispersion and a solution? Here, the difference in scale between colloidal (defined as “a state of subdivision, implying that the molecules or polymolecular particles dispersed in a medium have at least in one direction a dimension roughly between 1 nm and 1  $\mu\text{m}$ , or that in a system discontinuities are found at distances of that order” [2]) and molecular (defined as “[a]n electrically neutral entity consisting of more than one atom” [2]) is evident. However, can the phase stability be defined specially in terms of thermodynamic phases and degrees of freedom [5–7]? Indeed, whether a carbon nanotube dispersion is a “true solution” in a thermodynamic sense has been debated in the literature [8–12]. What, really, is the condition upon which a dispersion is considered to be in a stable, single phase?

These questions arise both for a theoretical and applied perspective. Dispersion plays a key role in product formulation which involves nanoparticles, polymers and solid particles [13–16]. A rational approach to nanoparticle dispersion would be beneficial for choosing and screening candidate solvents, if solution models can be applied to dispersions [17–19]. From a theoretical perspective, what distinguishes a solution from surface adsorption has been founded on the Gibbs phase rule, which governs the number of independently-quantifiable interactions via statistical thermodynamics,[5–7], yet the condition for when a mixture (dispersion) can be considered a solution has not been written down in an experimentally-tractable manner. Hence, the chief aim of this paper is twofold:

1. to establish the condition upon which a dispersion can be considered a single phase and, therefore, a solution, and
2. to provide experimental evidence already found in the literature in the light of the criterion.

In the following, we shall establish a universal theoretical criterion upon which a dispersion can be considered a solution, based on recent progress in thermodynamic phase stability condition [20,21] and statistical thermodynamics of fluctuation [5–7,22,23]. The same criterion will be shown to be the foundation for a wide range of experimental techniques. Some techniques, such as gravitational sedimentation and analytical ultracentrifugation, employ an external field (such as gravity and centrifugal force), whereas others, such as osmotic and scattering measurements, do not employ an external field. However, the application of the external field is merely to visualize the same universal criterion, as will be clarified below. The conclusion from gravitational and

centrifugal sedimentation is equivalent to scattering and osmotic measurements, because they all probe the same criterion.

We start the discussion with the behaviour of systems in the presence of gravity or centrifugal forces, because the common notion is that dispersions settle out, whereas solutions remain stable. As we shall show below, phase separation is a *discontinuity* in the concentration profiles under an external field that couples with the mass or density.

## 2. Detecting phase separation via sedimentation under gravity

Whether a system separates or crashes out after standing under gravity has been invoked as the criterion distinguishing a solution from dispersion [11,24]. However, even molecular solutions, under gravity, do exhibit concentration inhomogeneity [21,25]. Hence, it is necessary to write down the condition for gravity-induced phase separation in a quantitative manner.

Consider a vertical column that contains solvent (species 1) and “dispersion” (species 2) in equilibrium and let  $h$  be the height from the bottom. Let us first note that the chemical potential of the solution species,  $\mu_2$ , must be constant everywhere [21,25],

$$d\mu_2 = 0 = \left(\frac{\partial\mu_2}{\partial P}\right)_{h,c} dP + \left(\frac{\partial\mu_2}{\partial h}\right)_{P,c} dh + \left(\frac{\partial\mu_2}{\partial c}\right)_{h,P} dc \quad (1)$$

due to the mutual cancellation of the chemical potential changes due to gravitational potential energy, pressure and the molality composition of the “dispersion”,  $c$ . See Appendix A for more detailed explanation on our derivation. The partial derivatives can be evaluated as the following [21,25]:

$$\left(\frac{\partial \mu_2}{\partial P}\right)_{h,c} = v_2 \quad (2)$$

$$\left(\frac{\partial \mu_2}{\partial h}\right)_{P,c} = M_2 g \quad (3)$$

where  $M_2$  is the molar mass of species 2. Note that the partial molar volume  $v_2$  is now dependent on the height  $h$  and that the changes in  $P$  and  $h$  are related as

$$dP = -\rho g dh \quad (4)$$

where

$$\rho = c_1 M_1 + c_2 M_2 \quad (5)$$

Combining all above, we obtain

$$\left(\frac{\partial \mu_2}{\partial c}\right)_h \left(-\frac{dc}{dh}\right) = (M_2 - v_2 \rho) g \quad (6)$$

What is important here is that the composition  $c$  depends on  $h$ . Nevertheless, we can show that the following stability condition, reminiscent of the one for homogeneous solution, is applicable at each  $h$ :

$$\left(\frac{\partial \mu_2}{\partial c}\right)_{T,P} > 0 \quad (7)$$

To derive Eq. (7), let us introduce the free energy of mixing in a horizontal-slice subsystem at the height  $h$ , defined as

$$g^{mix} = (1 - x_2)\mu_1 + x_2\mu_2 - (1 - x_2)\mu_1^o - x_2\mu_2^o \quad (8)$$

where  $x_i$  is the mole fraction of the species  $i$ . Note that  $\mu_i$  is independent of  $h$  but  $x_i$  is dependent on  $h$ . Here we generalize the stability condition in the absence of an external field [20] to the solution under gravity, as

$$\frac{\partial^2 g^{mix}}{\partial x_2^2} > 0 \quad (9)$$

Since the Gibbs-Duhem equation at constant temperature and pressure applies to the horizontal-slice subsystem at every  $h$ , within which the pressure (gravity) is taken as constant,

$$x_1 d\mu_1 + x_2 d\mu_2 = 0 \quad (10)$$

Using Eq. (10), Eq. (9) can be rewritten as

$$\frac{\partial^2 g^{mix}}{\partial x_2^2} = \frac{\partial \mu_2}{\partial x_2} - \frac{\partial \mu_1}{\partial x_2} = \left(1 + \frac{x_2}{x_1}\right) \frac{\partial \mu_2}{\partial x_2} = \frac{1}{x_1} \frac{\partial \mu_2}{\partial x_2} > 0 \quad (11)$$

Since  $c$  increases monotonously with  $x_2$  because  $c = x_2/x_1$ , Eq. (11) is equivalent to Eq. (7).

Now we have the stability condition at hand in the presence of gravity (Eq. (7)). Eq. (6) shows that, because its left-hand side is always finite, the stability condition is broken ( $(\frac{\partial \mu_2}{\partial c}) \rightarrow 0$ ) only when  $-\frac{dc}{dh}$  diverges. Thus, whether the dispersion really “separates” should be judged thermodynamically, by the discontinuous change in nanoparticle concentration  $c$  along the height. The chief role of gravity here is to make the thermodynamic stability condition (Eq. (7)) visible through the continuity / discontinuity of concentration profile along the height.

Let us apply our stability theory to gold nanospheres dispersed in water, whose diameter range from 13 to 150 nm, reported by Midelet et al. [26], who have obtained the equilibrium distribution  $c(h)$  at  $t \rightarrow \infty$  based on their sedimentation kinetic that has been shown to follow the classical Mason-Weaver theory [27],

$$c(h) = Bc_0 \exp\left(-\frac{h}{h_0}\right) \quad (12)$$

where  $c_0$  is the initial concentration,  $h_0 = \frac{kT}{M_2 - v_2 \rho}$  is the characteristic height, and  $B$  is a constant arising from the conservation of mass within a system of finite size, all reported in Ref [26]. Hence the stability condition is whether

$$-\frac{dc(h)}{dh} = \frac{Bc_0}{h_0} \exp\left(-\frac{h}{h_0}\right) \quad (13)$$

is finite. Figure 1 shows that  $-\frac{1}{c_0} \frac{dc(h)}{dh}$  is obviously finite for smaller-sized nanoparticles.

However, as the particle diameter increases  $-\frac{1}{c_0} \frac{dc(h)}{dh}$  increases drastically, bringing the system

closer to phase separation. Based on the above, how can we judge if the system is phase separated?

A possible practical criterion would be when  $h_0$ , the characteristic length in the variation of concentration profile, becomes in the same order as the particle size. In our example in Figure 1, the largest particle has  $h_0 = 12 \mu\text{m}$ , which is still two order of magnitude larger than its diameter (150 nm). However, these two values are much closer than for the smallest nanoparticle, 13 nm in diameter with  $h = 18 \text{ mm}$ .

Note that our stability condition, namely the convergence of  $dc/dh$ , is a general condition that can be used regardless of the model, whereas its application to gold nanoparticle dispersions have relied upon the Mason-Weaver theory [27] which pre-supposes particles in dilution, in which  $h = 0$  as “bottom” of the dispersion. However, for sufficiently large  $c$ , there is a sediment phase in  $h < 0$  region where  $c(h)$  is expected to be near-constant. Incorporating such a case would be difficult, yet even in such cases we can still take  $h = 0$  as the bottom of the “dispersion” phase (i.e. the top of the sediment phase) and look for the characteristic length  $h_0$  in the exponential evolution of  $c(h)$  in the dispersion region ( $h > 0$ ).

### 3. Evidence from osmotic stability via ultracentrifugation and scattering

Gravity-induced sedimentation is a slow process which can take weeks before reaching equilibrium [26–29]. Hence, a quicker evaluation of phase stability is needed in practice. Sedimentation equilibrium using analytical ultracentrifuge (AUC) [30–32] and light, X-ray or neutron scattering [23,33,34], despite their apparent difference, provides an equivalent route to evaluating phase stability. Note also that the same formalism can be applied to the centrifugal forces (with the angular velocity  $\omega$  and radius  $r$  from the axis of rotation) to derive a well-known relationship,

$$\left(\frac{\partial\mu_2}{\partial c}\right)_r \left(-\frac{dc}{d(r^2)}\right) = \frac{1}{2}(M_2 - v_2\rho)\omega^2 \quad (14)$$

in which the divergence of  $-\frac{dc}{d(r^2)}$  breaks the phase stability [21,31,35]. Thus, the chief role of the centrifugal field is to visualize the thermodynamic stability condition (Eq. (7)) through the continuity / discontinuity concentration profile,  $c(r)$ , along the radius.

What is particularly useful is that the thermodynamic stability condition (Eq. (7)) can be expressed in a different yet equivalent expression, in terms of the osmotic pressure  $\Pi$ , as

$$\left(\frac{\partial\Pi}{\partial c}\right)_{T,\mu_1} > 0 \quad (15a)$$

$$\left(\frac{\partial\Pi}{\partial c_2}\right)_{T,\mu_1} > 0 \quad (15b)$$

The equivalence between Eqs. (7) and (15) is shown in Appendix B. It is through the osmotic representation of the stability condition that a close relationship between AUC and scattering, unexpected as it may seem, becomes apparent. Both techniques can probe how the osmotic pressure  $\Pi$  depend on the particle concentration. AUC probes this via [36,37]

$$\left(\frac{\partial\Pi}{\partial c}\right)_{T,\mu_1} = \frac{\left(\frac{\partial\rho}{\partial c}\right)_{P,\mu_1}}{\omega^2 \frac{d \ln c}{dr^2}} \quad (16)$$

Scattering probes this condition via

$$\left(\frac{\partial \Pi}{\partial c_2}\right)_{T, \mu_1} = \frac{RT}{\lim_{q \rightarrow 0} S(q, c_2)} \quad (17)$$

where the structure factor,  $S(q, c_2)$ , as a function of the wavenumber  $q$ , can be obtained from the scattering intensity,  $I(q, c_2)$ , as

$$S(q, c_2) = \frac{I(q, c_2)}{P(q)} \quad (18)$$

where  $P(q)$  is the form factor [38–40]. Under this condition, the well-known relationship between the divergence of  $\lim_{q \rightarrow 0} S(q, c_2)$  and phase separation can be seen clearly in Eq. (17). The stability condition expressed osmotically in Eq. (18) is more complex than the approach in Section 2 for the need to consider both  $\left(\frac{\partial \rho}{\partial c}\right)_{P, \mu_1}$  and  $\frac{d \ln c}{dr^2}$ . In fact, the former is related to the condition of phase separation without the external force (centrifugal force) whereas the latter is expressed as a profile of  $c$  as a function of  $r$  and is concerned with centrifugal sedimentation. The relationship to the virial coefficients will turn out to be useful in our discussion below.

What is common between AUC and scattering is a link to the osmotic pressure  $\Pi$  and its particle concentration dependence. It is common in the literature to report the osmotic second osmotic virial coefficient. However, there are two types of virial coefficients: molality ( $c$ )-based  $A_{22}$  and molarity ( $c_2$ )-based  $B_{22}$ , each related to  $\Pi$  as

$$\frac{\Pi}{RT} = c_1 c + A_{22} c^2 + o(c^2) \quad (19)$$

$$\frac{\Pi}{RT} = c_2 + B_{22} c_2^2 + o(c_2^2) \quad (20)$$

Even though, a direct conversion of  $B_{22}$  to  $A_{22}$  [35] involves the partial molar volume of the particle which may not be available in the literature, we can exploit an equivalent form of the

stability condition, Eq. (15b), which comes from the monotonous relationship between  $c$  and  $c_2$  [41]. Hence, both molarity- and molality-based virial coefficients can be used as the measure of stability.

The virial expansion establishes a formal analogy between osmotic pressure and gas pressure. This is why a “gas-like” phase reported in dispersed hydrophobic silica particles [42] and a “colloidal gas” phase for the mixtures of colloid and non-adsorbing polymers [43] both signify single-phase behaviour, where the former used up to the fourth virial coefficient to demonstrate phase stability. However, a positive second virial coefficient without higher-order contributions is a sufficient piece of evidence for phase stability, because  $\Pi$  is an increasing function of concentration (either  $c$  or  $c_2$ ) in the concentration region in which the measurement took place, hence the phase stability condition (Eq. (15) or Eq. (20)) is satisfied. A finite, positive  $B_{22}$  has been reported for magnetic nanoparticle (oleic acid-coated iron oxide), dispersed in decalin using AUC [44,45]; silica nanoparticles in aqueous polyethylene oxide solutions exhibits an increasing  $\Pi$  along the nanoparticle concentration [46]; a large positive yet finite  $B_{22}$  via turbidity has been reported from PDMS-grafted silica nanoparticles in octamethyltrisiloxane solvent [47]. For SAXS, most of the experiments aim at determining the size and shape of nanoparticles using the Porod region of  $q$  [48–51], unlike the case of biological macromolecules and their assemblies [38,52] for which the  $q \rightarrow 0$  behaviour has mainly been studied. Yet a finite, positive  $B_{22}$  for carbon nanotubes in NMP evidences its phase stability [8].

We emphasise that that our main concern here is not the sign of  $B_{22}$ , which infers the tendency for nanoparticles towards aggregation or repulsion [38,52]. Rather, the thermodynamic stability

condition is the finiteness of  $\left(\frac{\partial \Pi}{\partial c_2}\right)_{T, \mu_1}$ , namely, the finiteness of  $\lim_{q \rightarrow 0} S(q, c_2)$  according to Eq. (17).

Hence a finite  $B_{22}$  determined from a convergent series in Eq. (18) is therefore a guarantee for the finiteness of  $\left(\frac{\partial \Pi}{\partial c_2}\right)_{T, \mu_1}$  at small  $c_2$ . Thus, we can extend the range of available evidence further by

noting that the finiteness of  $\left(\frac{\partial \Pi}{\partial c_2}\right)_{T, \mu_1}$  as the thermodynamic stability condition, based on Eqs. (17)

and (18), is equivalent to the convergence of scattering intensity  $I(q, c_2)$  at the  $q \rightarrow 0$  limit.

When the radius of gyration  $R_g$  of a nanoparticle is calculated from the Guinier plot,  $\ln I(q) = \ln I(0) - \frac{q^2 R_g^2}{3}$ , pre-supposes the convergence of  $I(0)$ . Even though interparticle interference, arising from nanoparticle aggregation or repulsion between them, makes  $I(q)$  deviate from the form factor, the deviation due to interparticle interference, namely the structure factor [38,52], remains finite at  $q \rightarrow 0$  when the thermodynamic stability condition is satisfied, as can be seen from Eqs. (17) and (20). The question here is not about the accuracy of fitting  $R_g$  in the presence of interparticle interference but about the fact that  $R_g$  can be determined as a finite parameter, which comes from the fact that the concentration effect is indeed a correction to the form factor, and that the structure factor,  $1/\left(\frac{\partial \Pi}{\partial c_2}\right)_{T, \mu_1}$ , is finite, hence did not make  $I(q)$  diverge at  $q \rightarrow 0$ .

Thus, a report of  $R_g$  from the Guinier plot provides evidence for phase stability. Consequently, the routine report of  $R_g$  for nanoparticles [48–51] serves as the evidence for a single-phase behaviour of nanoparticle dispersions.

#### 4. How a degree of freedom is lost in fluctuation

All the discussion so far were based on the thermodynamic stability condition, which also has the following relationship to concentration fluctuation,  $\langle(\delta c)^2\rangle$  [53,54]:

$$\left(\frac{\partial\mu_2}{\partial c}\right)_{T,P} = \frac{k_B T}{\langle N_1 \rangle} \frac{1}{\langle(\delta c)^2\rangle} \quad (21)$$

This relationship provides a complementary insight into phase stability and how it is broken via the order of magnitude of  $\langle(\delta c)^2\rangle$  [22,23,33,54–56]. To this end, expressing the relative error of  $c$  in terms of the Kirkwood-Buff integrals (KBIs),  $G_{ij}$ , between the species  $i$  and  $j$  [22,54,55] is helpful.

$$\sqrt{\frac{\langle(\delta c)^2\rangle}{c^2}} = \sqrt{\frac{1}{c_1 x_2 + G_{22} + G_{11} - 2G_{12}}} \frac{1}{V} \quad (22)$$

See Appendix C for derivation. Now we perform an order-of-magnitude analysis of Eq. (22), whose significance is explained also in Appendix C. According to Eq. (22),

- if the system is in a single phase, the KBIs are all convergent with the magnitude of  $O(1)$ ,

hence  $\sqrt{\frac{\langle(\delta c)^2\rangle}{c^2}}$  is  $O(1/\sqrt{V})$  and  $\langle(\delta c)^2\rangle$  is  $O(1/V)$ ;

- if the system is phase separated, the KBIs are divergent with the magnitude of  $O(V)$ , [5]

hence  $\sqrt{\frac{\langle(\delta c)^2\rangle}{c^2}}$  and  $\langle(\delta c)^2\rangle$  are both  $O(1)$ .

Thus, under phase stability,  $c$  is allowed the error (fluctuation)  $\langle(\delta c)^2\rangle$  of the order  $O(1/V)$  [56]. When the stability condition is broken, the fluctuation reaches the same order as  $c$  (namely,  $O(1)$ ), which means that  $c$  can no longer be determined within the required precision.

Thus, when the KBIs reaches the order of the system volume, the fluctuation (error) of concentration becomes in the same order of magnitude as the concentration itself. Concentration,

therefore, ceases to be a thermodynamic variable, that is to say, one thermodynamic degree of freedom is lost. This is the microscopic interpretation of phase instability via Eqs. (21) and (22).

## **5. Connection to phase diagram, solubility and particle-particle interaction**

So far, we have focused on a direct observation of phase stability condition via scattering and osmotic pressure, as well as via visualisation using external fields (gravity and centrifugal forces). Another piece of evidence for the single-phased nature of nanoparticle dispersion comes from the temperature dependence of nanoparticle solubility [57], taken together with evidence that solubility is reversible and thermodynamic [57], and that nanoparticle concentration below saturation concentration can be attained as indicated with the phase diagram [58]. According to the Gibbs phase rule, when a dispersion (consisting of solvent and nanoparticles, i.e., 2 components) is in a single phase, its degree of freedom is  $2 - 1 + 2 = 3$ . Under constant pressure, the system still has 2 degrees of freedom, meaning that the temperature and nanoparticle concentration can be changed independently below the phase boundary. This is consistent with the degrees of freedom for a mixture in a single phase calculated from the Gibbs phase rule. The same degrees of freedom remain even when solvent mixtures with fixed composition are used, allowing the independent change of temperature and nanoparticle concentration, evidencing again the single-phase nature of nanoparticle dispersion.

However, care must be taken when applying the concept of solubility, or solvation free energy, directly to the modelling of phase stability. The transfer free energy of a nanoparticle from its pure phase to dispersion could be modelled as the difference in nanoparticle's solvation free energy

between the two phases [59]. Yet, contrary to their assumption [59], a positive free energy of transfer does not automatically mean phase separation, because it can simply be from low solubility. However, at a nanoparticle concentration, transfer free energy becomes concentration-independent, which has been referred to as “saturation nanoparticle concentration” [59]. This is equivalent to the concentration at which the thermodynamic phase stability (Eq. (7)) is broken. Thus, the existence of saturation concentration can indeed be used to infer phase separation.

In addition to solvation free energy, pairwise interaction free energy between two nanoparticles as a function of separation,  $\Phi(r)$ , have been modelled using the DLVO theory and its extension, xDLVO theory [60,61]. The basic premise of this approach is that the nanoparticle is stable when the minimum of pairwise interaction energy is more than the thermal energy. However, there are two reasons as to why this supposition is fundamentally different from the stability condition in the thermodynamic sense. Firstly, to judge whether the thermodynamic stability condition is broken, calculating higher-order virial coefficients is indispensable, as has already been discussed in Section 3. Secondly, even the second virial coefficient, which is a contributor to the thermodynamic stability condition, involves contributions not only from the free energy minimum but also from all particle-particle distances from zero to infinity, as can be seen from its definition [62,63],

$$B_{22} = -\frac{1}{2} \int_0^\infty dr \left[ \exp\left(-\frac{\Phi(r)}{k_B T}\right) \right] 4\pi r^2 \quad (23)$$

It is for these reasons that the DLVO theory cannot probe the thermodynamic stability condition. However, if there is any correlation between the thermodynamic stability condition and the suppositions of DLVO theory is a worthwhile question for further investigation.

The solution-like nature of nanoparticles in solvents makes it possible to use the tools and insights from the statistical thermodynamics of solutions and to apply them to rationalize experimental observations. Size-selective precipitation of nanoparticles is important not only in fabricating uniform-sized nanoparticle samples but also as a support for the single-phase nature of dispersions [64–67]. Especially important is the establishment of the partition coefficient, regardless of dispersant concentration, between dispersed and flocculated phases [66,67]. Consequently, the modulation of the partition coefficient, or equivalently the transfer free energy, upon the addition of poor solvents (referred to as species 3) can be described as [5,68]

$$-\left(\frac{\partial\mu_2^*}{\partial\mu_3}\right)_{T,P,c_2\rightarrow 0} = c_3(G_{23} - G_{21}) \quad (24)$$

where  $G_{21}$  and  $G_{23}$  are the Kirkwood-Buff integrals describing nanoparticle-poor solvent and nanoparticle-good solvent interactions, respectively. Even though this equation is exact under dilute nanoparticle concentration, it is applicable when the effect of poor solvent on a nanoparticle is much stronger than nanoparticle-nanoparticle interaction [69].  $G_{21}$  and  $G_{23}$  can be quantified when Eq. (24) is solved simultaneously with the volume of nanoparticle,

$$V_2 = -c_1V_1G_{21} - c_3V_3G_{23} + RT\kappa_T \quad (25)$$

where  $V_1$  and  $V_3$  are the partial molar volumes of good and poor solvents in the bulk phase, respectively, and  $\kappa_T$  is the isothermal compressibility of the bulk solvent mixture, which makes a negligibly small contribution [5,68].

Clarification of the mechanism of precipitation requires the calculation of  $G_{21}$  and  $G_{23}$ , just like many other chemical and biochemical processes whose mechanisms have been elucidated via such calculations. However, qualitative insight can be drawn already from Eq. (24). The addition of poor solvents increases  $\mu_3$  while the chemical potential of nanoparticle,  $\mu_2$ , goes up. Therefore,

$-\left(\frac{\partial \mu_2^*}{\partial \mu_3}\right)_{T,P,c_2 \rightarrow 0}$  is negative and is more so for a poorer solvent. Consequently, according to Eq.

(24),  $G_{23} - G_{21} < 0$ , showing that the poor solvent is more excluded overall from the nanoparticle compared to the good solvent. The question of size-dependent precipitation could thus be quantified via the Kirkwood-Buff integrals, directly from experimental data, in a model-free manner. Note that there is a large excluded volume effect to the Kirkwood-Buff integrals, which are dependent on particle size; this may give rise to the discrimination based on size.

Thus, upon the establishment of dispersion phase stability, state-of-the-art tools from the statistical thermodynamics of solutions can be applied to rationalize nanoparticle solubility and its modulation by poor solvents. Hence “dispersion phase stability” is a subset of “solution stability”.

## 6. Conclusion

This paper has established the condition upon which a “nanoparticle dispersion” can be considered as a solution in a single phase and how this condition can be probed using experimental measurements from diverse techniques. The key was the stability condition, a universal thermodynamic condition applicable to wide-ranging and seemingly unrelated experimental techniques, such as gravitational sedimentation, ultracentrifugation, osmotic pressure, turbidity and scattering. The thermodynamic stability condition is universally applicable regardless of whether an external field, such as gravity or centrifugal force, has been applied. The role of the external field is chiefly to visualise thermodynamic stability condition via the continuity of concentration profile. We have thus established a universal guideline for establishing a nanoparticle dispersion as a solution.

Prior to this paper, no such universal guideline was established. In addition to the previous evidence supporting the solution nature of nanoparticles based on phase diagrams [42] [43], our new guideline has increased the available evidence from experimental observations, previously not expected or intended to be the evidence. Moreover, conditions based on solvation free energy difference [59] and the xDLVO theory [60,61] are shown not have a direct connection to the stability condition.

Having established the universal criterion for the solution nature of a nanoparticles in solvents, the future work focuses not only on systematic experimental investigation to probe nanoparticle phase stability which is currently underway but also to apply the statistical thermodynamics theory of preferential solvation (as outlined in Section 4) to the quantification of interactions underpinning dispersion stability and size-selective precipitation.

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## Appendix A

Here we present derivations and justifications for needed to derive Eq. (6).

To derive Eq. (1), it is necessary to observe that the chemical potential  $\mu_2$ , being an intensive thermodynamic quantity (which does not depend on system size), depends only on intensive thermodynamic quantities [20]. In the absence of the gravity, a single-phase system consisting of two components has three degrees of freedom, according to the Gibbs phase rule [20]. Under constant temperature, the remaining degrees of freedom is two. This means that  $\mu_2$  is a function of two intensive parameters. Here we choose  $P$  and  $c$  as the two intensive parameters. In the presence of the gravity,  $\mu_2$  depends also on the height  $h$ . Therefore, we can express the change of  $\mu_2$ ,  $d\mu_2$ , in terms of  $dP$ ,  $dc$ , and  $dh$  as,

$$d\mu_2 = \left(\frac{\partial\mu_2}{\partial P}\right)_{h,c} dP + \left(\frac{\partial\mu_2}{\partial h}\right)_{P,c} dh + \left(\frac{\partial\mu_2}{\partial c}\right)_{h,P} dc \quad (\text{A1})$$

Combining Eq. (A1) with the constancy of  $\mu_2$ , namely,  $d\mu_2 = 0$ , yields Eq. (1).

Eqs. (2) and (3) come from the definition of the partial molar volume as well as gravitational potential energy. Eq. (4) can be justified from the fact that the lower the position the larger the pressure, and the increment in the pressure  $dP$  upon the reduction of height ( $-dh$ ) comes from per-area gravity of the solution,  $\rho g dh$ . Eq. (6) can be derived straightforwardly from Eqs. (1)-(5).

## Appendix B

Here we show that the phase stability under isobaric condition is equivalent to that under osmotic equilibrium. To do so, we need to convert an isobaric system  $\mu_2(c, P)$  to an osmotic system  $\mu_2(c, \mu_1)$ , via

$$d\mu_2 = \left(\frac{\partial\mu_2}{\partial c}\right)_{T,P} dc + \left(\frac{\partial\mu_2}{\partial P}\right)_{T,c} dP = \left(\frac{\partial\mu_2}{\partial c}\right)_{T,P} dc + v_2 dP \quad (\text{B1})$$

together with the following relationship from the Gibbs-Duhem equation

$$\left(\frac{\partial\mu_2}{\partial c}\right)_{T,\mu_1} = \frac{1}{c_2} \left(\frac{\partial P}{\partial c}\right)_{T,\mu_1} \quad (\text{B2})$$

Eq. (B1) can be justified by the fact that the chemical potential,  $\mu_2$ , is an intensive physical quantity independent of system size. Hence  $\mu_2$  depends only on intensive physical quantities. According to the Gibbs phase rule, there are  $2 - 1 + 2 = 3$  independent intensive parameters for a two-component, single-phase system. Under constant temperature, the remaining degrees of freedom is two. Consequently, when  $c$  and  $P$  are chosen as the intensive parameters,  $\mu_2$  is dependent upon them, i.e.,  $\mu_2(c, P)$ ; when  $c$  and  $\mu_1$  are chosen, the same logic leads to  $\mu_2(c, \mu_1)$ . Eq. (B1) is obtained from the total differentiation for  $\mu_2(c, P)$ . Eq. (B2) comes from the Gibbs-Duhem equation under constant  $T$ ,  $c_1 d\mu_1 + c_2 d\mu_2 = dP$ . Differentiating this equation with respect to  $c$  while keeping  $\mu_1$  constant ( $d\mu_1 = 0$ ) yields Eq. (B2).

Combining Eqs. (B1) and (B2), we obtain

$$\frac{1}{c_2} \left(\frac{\partial P}{\partial c}\right)_{T,\mu_1} = \left(\frac{\partial\mu_2}{\partial c}\right)_{T,P} + v_2 \left(\frac{\partial P}{\partial c}\right)_{T,\mu_1} \quad (\text{B3})$$

Finally, the Gibbs-Duhem equation ( $c_1 v_1 + c_2 v_2 = 1$ ), when used in conjunction with Eq. (B3), can simplify Eq. (B3) to the following form:

$$\left(\frac{\partial\mu_2}{\partial c}\right)_{T,P} = \frac{c_1 v_1}{c_2} \left(\frac{\partial P}{\partial c}\right)_{T,\mu_1} = \frac{c_1 v_1}{c_2} \left(\frac{\partial\Pi}{\partial c}\right)_{T,\mu_1} \quad (\text{B4})$$

where the osmotic pressure  $\Pi$  in the rightmost term comes from the physical meaning of  $\left(\frac{\partial P}{\partial c}\right)_{T,\mu_1}$ ; the constant  $\mu_1$  signifies the presence of the semi-permeable membrane which passes through water only. Accordingly, the change of pressure that accompanies the change of  $c$  is in fact that of the osmotic pressure. Thus, Eq. (B4) shows that the phase stability condition can be written in two different yet equivalent manner

$$\left(\frac{\partial \mu_2}{\partial c}\right)_{T,P} > 0 \quad \text{or} \quad \left(\frac{\partial \Pi}{\partial c}\right)_{T,\mu_1} > 0 \quad (\text{B5})$$

The stability condition for a binary system (Eq. (B5)) can be readily generalized to multiple-component systems. Here, let us only consider a three-component system for simplicity. Let  $i = 3$  be an additional component. When the solvent composition (the ratio between components 1 and 3) are fixed, Eq. (B5) is still valid, provided that  $c$  be extended to  $c = \frac{N_2}{N_1+N_3}$ . This requires a semi-permeable membrane which passes through components 1 and 3 but not 2. When nanoparticle concentration is dilute, keeping the ratio between  $N_1$  and  $N_3$  together with  $\mu_1$  is equivalent to the constancy of both  $\mu_1$  and  $\mu_3$ , under which condition Eq. (B5) is still valid.

## Appendix C

First, we derive Eq. (22) from Eq. (21). Eq. (21) comes from Eq. (30) of Ref [22]. We need to rewrite  $\langle(\delta c)^2\rangle$  in terms of the Kirkwood-Buff integrals (KBIs), defined as [56]

$$G_{ij} = V \frac{\langle \delta N_i \delta N_j \rangle - \delta_{ij} \langle N_j \rangle}{\langle N_i \rangle \langle N_j \rangle} \quad (\text{C1})$$

where  $N_i$  is the number of component  $i$  and  $\delta_{ij}$  is Kronecker's delta. This necessitates us to link the concentration fluctuation  $\langle(\delta c)^2\rangle$  in terms of the number fluctuations. The link between the two is provided by the following equation (see Eq. (17) of Ref [22]).

$$\langle(\delta c)^2\rangle = \frac{1}{\langle N_1 \rangle^2} \left[ \langle(\delta N_2)^2\rangle - \frac{2\langle N_2 \rangle}{\langle N_1 \rangle} \langle \delta N_1 \delta N_2 \rangle + \frac{\langle N_2 \rangle^2}{\langle N_1 \rangle^2} \langle(\delta N_1)^2\rangle \right] \quad (\text{C2})$$

From Eq. (C1), it follows that

$$\langle(\delta N_1)^2\rangle = \frac{\langle N_1 \rangle^2}{V} G_{11} + \langle N_1 \rangle \quad (\text{C3})$$

$$\langle(\delta N_2)^2\rangle = \frac{\langle N_2 \rangle^2}{V} G_{22} + \langle N_2 \rangle \quad (\text{C4})$$

$$\langle \delta N_1 \delta N_2 \rangle = \frac{\langle N_1 \rangle \langle N_2 \rangle}{V} G_{12} \quad (\text{C5})$$

Substituting Eqs. (C3)-(C5) into Eq. (C2) yields

$$\langle(\delta c)^2\rangle = \frac{\langle N_2 \rangle^2}{\langle N_1 \rangle^2} \frac{1}{V} \left[ \frac{V}{\langle N_1 \rangle} + \frac{V}{\langle N_2 \rangle} + G_{11} + G_{22} - 2G_{12} \right] \quad (\text{C6})$$

Using  $c = \langle N_2 \rangle / \langle N_1 \rangle$ ,  $\frac{1}{\langle N_1 \rangle} + \frac{1}{\langle N_2 \rangle} = \frac{\langle N_1 \rangle + \langle N_2 \rangle}{\langle N_1 \rangle \langle N_2 \rangle} = \frac{1}{\langle N_1 \rangle x_2}$  (where the mole fraction  $x_2 = \frac{\langle N_2 \rangle}{\langle N_1 \rangle + \langle N_2 \rangle}$ ),

and  $c_1 = \langle N_1 \rangle / V$ , Eq. (C6) can be rewritten as

$$\frac{\langle(\delta c)^2\rangle}{c^2} = \frac{1}{V} \left[ \frac{1}{c_1 x_2} + G_{11} + G_{22} - 2G_{12} \right] \quad (\text{C7})$$

which yields Eq. (22) straightway.

The second aim of this Appendix is to explain how to perform the order-of-magnitude analysis. As a first step, let us remember that there are two types of thermodynamic quantities: extensive and intensive. Extensive quantities (such as  $N_i$ ,  $V$ , energy and free energy) scales with system size whereas intensive quantities (such as  $P$ ,  $T$  and  $\mu_i$ ) are independent of the system size. Here, we incorporate concentrations, such as  $c = N_2/N_1$  and  $c_i = N_i/V$ , as intensive quantities. Note that the extensive quantities, such as  $N_i$  and  $V$ , are macroscopic in scale; this is expressed as  $O(V)$ , in

the same order of magnitude as the system size,  $V$ . Consequently,  $c$  and  $c_i$ , following their definitions, are  $\frac{O(V)}{O(V)} = O(1)$ , which do not scale with the system size.

Based on this setup, let us carry out an order of magnitude analysis of Eq. (22). When the dispersion is in a single phase,  $\mu_2$ , being free energy per mole, by definition, is  $O(1)$ , hence  $\left(\frac{\partial \mu_2}{\partial c}\right)_{T,P} = O(1)$ . Consequently, the right-hand side of Eq. (22) must also be  $O(1)$ . Since  $\langle N_1 \rangle = O(V)$ ,  $\langle (\delta c)^2 \rangle = O\left(\frac{1}{V}\right)$ , as has been employed in the main text.

When the phase stability condition is broken,  $\left(\frac{\partial \mu_2}{\partial c}\right)_{T,P} = 0$ , meaning that its order of magnitude becomes smaller than  $O(1)$ , which is denoted as  $o(1)$ . As discussed in the main text, this takes place when  $\langle (\delta c)^2 \rangle = O(1)$ , as can be seen in Eq. (22).

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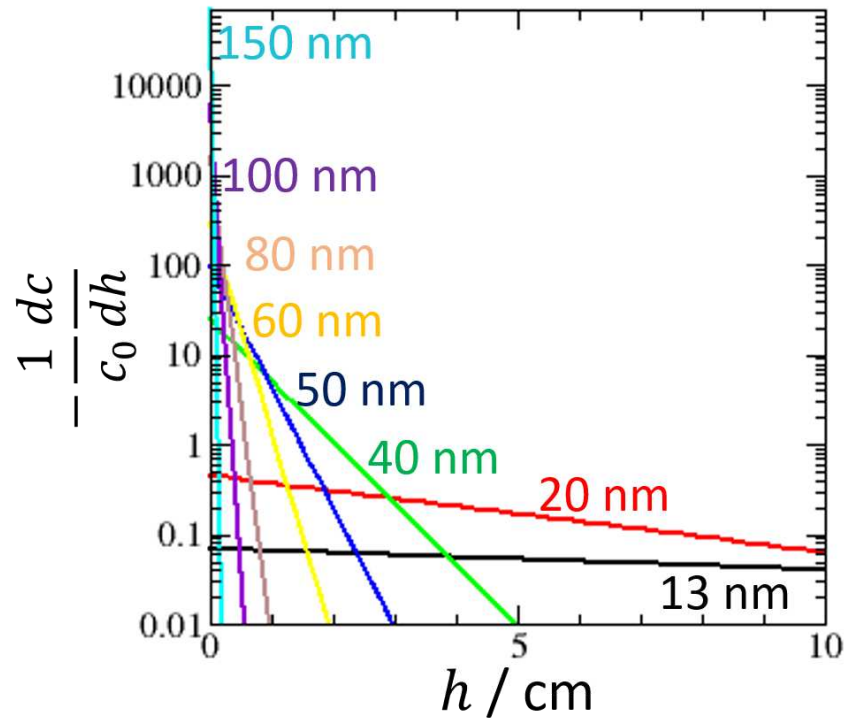
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**Figure 1.** Phase stability of gold nanoparticles with different diameters (13–150 nm), based on the experimental data in Ref [26]. Phase stability under gravity is guaranteed by the convergence of  $-\frac{dc}{dh}$ . As the nanoparticle diameter increases  $-\frac{dc}{dh}$  becomes closer to divergence.