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Anticipating colloidal instabilities in cationic vesicle dispersions by measuring collective motions with dynamic light scattering

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Abstract

Vesicle dispersions are useful for many applications from medicinal to consumer products. However, using these dispersions requires some knowledge of and control over their colloidal properties. Measuring interparticle interactions between vesicles should allow framing the problem in terms of Smoluchowski kinetic models and consequently anticipating time-dependent aggregation and coalescence for the dispersions. However, this can be a difficult task for many complex mixtures. A primary goal of this paper is to show that it is possible to measure interparticle potential between small vesicles by measuring the concentration-dependent collective motion using dynamic light scattering. These measurements allow determination of the second virial coefficient for the dispersion, providing a convenient platform for summing all contributions to the interaction potential over all vesicle conformations, thus making the analysis of complex mixtures more tractable. As a verification of the approach, a comparison is made to dispersions in which the stability is governed solely by electrostatics, using existing techniques to anticipate instabilities. A second goal of this paper is to build a simple potential model in which the Smoluchowski model can be used to quantitatively anticipate the aggregation behavior of the small vesicle dispersion. Together, these observations constitute a convenient approach to anticipating the behavior of vesicle (and other) dispersions in complex mixtures.

Keywords: Vesicles; Dynamic light scattering; Collective motions; Hydrodynamic virial coefficient; Second virial coefficient; Aggregation; Coalescence

1. Introduction

Vesicles are composed of surfactant bilayers that are bent into the form of balloon-like aggregates entrapping large volumes of solutions. They are used for microencapsulation by keeping entrapped active solution separated from exterior solution, achieving systematic or localized sustained release. Vesicles can be biocompatible, biodegradable, and administered intravenously, orally, or intramuscularly. They are used in medical imaging to improve contrast in CT scans and MRI, as well as to reduce toxicity in anticancer and gene therapies [1,2]. They are also used to contain oil pollution, making the clean up more efficient and manageable. In the food industry, they are used to emulsify, improve control, and shorten fermentation time in cheese and beer making. In the cosmetics industry, they are used to simultaneously dissolve water-soluble and water-insoluble substances in skin care and sunscreen lotions [3]. They play an important role in the plastic, pesticide, and paint industries. Finally, they are used to mimic biological systems [4,5]. All these applications require control over the colloidal properties of vesicle dispersions.

Anticipating the colloidal properties of vesicle dispersions is difficult, particularly for complex mixtures. Smoluchowski kinetic models [6] are often used to define the kinetics of colloidal stability, but require knowledge of the interaction between vesicles. At a rudimentary level, we can describe the interaction in terms of the Derjaguin–Landau–Verwey–Overbeek (DLVO) theory [7–9], which sums electrostatic and van der Waals potentials to arrive at an effective potential. It should be noted that even at this rudimentary level, contemporary debates focus on whether these contributions are sufficient to accurately describe the potential or if it necessary to include of additional terms such as hydration. At a higher level, other contributions can

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arise, for example, from the presence of nonabsorbing polymer (depletion) or specific ion effects. In addition, potential associated with vesicle dispersions requires modification to account for nonspherical shapes, polydispersity, and bilayer structure. It is desirable to measure the potential, directly minimizing assumptions about contributions to the potential and yielding results that sum over all orientations and shapes. Achieving this end should make it possible to anticipate the colloidal properties of these mixtures more accurately in the context of Smoluchowski kinetic models.

The second virial coefficient is a direct measurement of interparticle interactions between dispersed particles, proteins, and polymers, which has proven effective in anticipating colloidal properties. The osmotic pressure of a solution is expressed as a virial expansion in concentration [10],

$$\Pi = \frac{kTn}{V}\left(1 + B_{22}\frac{n}{V} + \cdots\right), \tag{1}$$

where (n/V) is the number density of the particles and B_{22} is the second virial coefficient, reflecting deviation from ideal solution behavior. In a moderately concentrated solution, third- and higher-order terms are negligible, so positive values of the second virial coefficient reflect the magnitude of attractive interparticle interactions and negative values reflect the magnitude of repulsive interparticle interactions. The second virial coefficient is an intrinsic property of the mixture, reflecting interactions averaged over all orientations, shapes, and sizes including, electrostatic, dispersion, and depletion force contributions to the potential, and thus is ideal for this endeavor.

The second virial coefficient is often measured with static light-scattering techniques. Rayleigh scattering from solutions of small molecules originates from spontaneous concentration fluctuations and is captured in the familiar Rayleigh expression [11]

$$\frac{KC_\mathrm{p}}{R_\theta} = \frac{1}{M} - B_{22}C_\mathrm{p}, \tag{2}$$

where K incorporates several optical constants, R_θ is the Rayleigh ratio for the instrument, and M is the molecular weight of a molecule. If the constants are accurately known, it is possible to determine the second virial coefficient from the concentration dependence of the scattering intensity in the small-particle limit, where the size of the molecule is less than $1/20$ the wavelength of the light. Velev et al. [12] present an elegant example of using static light-scattering measurements to determine the second virial coefficient in protein solutions. They demonstrate that the rate and quality of protein crystals formed under different solution conditions critically depends on the magnitude of the second virial coefficient. These results are based on accurate knowledge of the refractive index, accurate intensity measurements, and some knowledge of the intraparticle form factor. These constants are often difficult to obtain for dispersions of small vesicles.

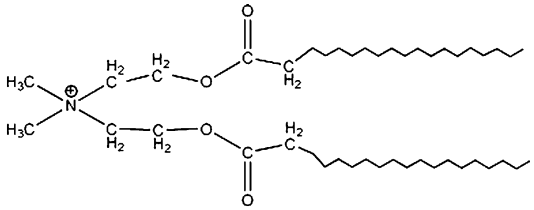
Dynamic light scattering (DLS) provides an alternative method for obtaining the second virial coefficient that does not require acute knowledge of optical constants. Diffusing particles cause intensity fluctuations in scattered light, which are analyzed to determine particle diffusivity [13]. The movement of diffusing particles may be influenced by other particles, altering the intensity fluctuations. This interdependency of particle motion is often referred to as *collective* diffusion. It can be measured in the small-q limit, where $qa \ll \pi$, a being the radius of the particle, and q is the scattering vector. Intuitively, the interaction between particles influences collective diffusion. The hydrodynamic virial coefficient (K_d) is the proportionality constant between changes in the collective diffusion resulting from changes in the particle concentration. In the small-q limit, K_d is proportional to the second virial coefficient. Pusey and Tough [14] provide an excellent summary of these principles. DLS measurements provide the added advantage of measuring particle dynamics, providing additional information about temporal changes of the system.

A primary goal of this paper is to show that it is possible to measure interparticle potential between small vesicles by measuring their concentration-dependent collective motion using DLS techniques. For verification of this approach, these measurements are compared to simplified systems in which interparticle interactions can be independently measured. These measurements allow determination of the hydrodynamic virial coefficient and consequently the second virial coefficient for the dispersion, which sums over all contributions to the interaction potential over all particle conformations. A second goal of this paper is to build a simple potential model so that the Smoluchowski model can anticipate the colloidal properties of the vesicle dispersion. Together, these observations constitute a convenient approach to anticipating the behavior of other vesicle dispersions.

2. Materials and methods

2.1. Materials

The surfactant used in these experiments, di(tallowethylester) dimethyl ammonium chloride,



was purchased from Goldsmith. Calcium chloride powder was purchased from Aldrich (Catalog No. 499609). Distilled water was first passed through a Millipore system ($R > 18$ MΩ) and then twice through a 0.2-μm particle filter.

2.2. Preparation of vesicles

A stock solution of small vesicles was prepared by mixing ∼20 ml of 1 wt% cationic surfactant in water and sonicating with a sonic horn followed by a bench-top ultrasonicator (Bransonic 2000) for 24 h. This process produces 30-nm-sized unilamellar vesicles (Fig. 1), as confirmed by cryo-TEM measurements with no discernable turbidity. No residual large chunks