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The diffusion of latex nanospheres and the effective (microscopic) viscosity of HPMC gels

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Abstract

Dynamic light scattering (DLS) has been used to measure the diffusion coefficients of 108 ± 7 (±S.D.) and 495 ± 23 nm positively charged amino latex nanospheres (ALNs) and negatively charged carboxyl latex nanospheres (CLNs) (48 ± 7, 91 ± 9.8 and 483 ± 10 nm) in three different media, water, glycerol aqueous solutions and hydroxypropyl methylcellulose (HPMC) gels. The translational diffusion coefficients (*D*) of these latex spheres in water were found to be 13.00 (±0.12), 5.11 (±0.06), 0.89 (±0.01) $\mu m^2/s$ for 48, 91 and 483 nm CLN, and 3.26 (±0.01) and 0.88 (±0.03) $\mu m^2/s$ for 108 and 495 nm ALN, respectively. In Newtonian glycerol aqueous solutions as anticipated the diffusion could be predicted by the Stokes–Einstein relationship over a range of system viscosities. In HPMC gels the results show the deviation of the diffusion coefficient from the Stokes–Einstein equation when the viscosity of the medium is increased. In addition, there was an increase in the polydispersity index (PI) from 0.217 to 0.928 with 108 nm ALN on increasing HPMC concentrations from 0.2% to 0.8% (w/v), which implied an interaction between the positively charged nanospheres and the gel. From the *D* values, the "effective" or "microscopic" viscosities of the HPMC medium were calculated, and ranged from 0.899 to 0.925 mPa s.

Keywords: Diffusion coefficient; Effective viscosity; Nanospheres; Diffusion in gels

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The diffusion and transport of nanoparticles in simple and complex media is an important element in understanding their behaviour as drug carriers and targeting agents. Using photon correlation spectroscopy (PCS), the translation diffusion coefficient (*D*) of nanoparticles can be directly measured from the decay rate of the time autocorrelation function (Pecora, 2000) and transformed into a hydrodynamic diameter using the Stokes-Einstein equation. Many studies of the diffusion of particles and macromolecules have been made in aqueous isotropic and Newtonian systems (Masaro and Zhu, 1999). Understanding the movement of nanoparticles in viscous and complex media is a prelude to understanding the diffusion and translocation of nanoparticles inside cells and tissues. Several attempts have been made to increase

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the viscosity of the continuous phase of particle dispersions to imitate the viscosity of cellular content (Masaro and Zhu, 1999; Bremmell et al., 2001; Westrin and Axelsson, 1991). We have carried out diffusion experiments with negatively and positively charged polystyrene latex nanospheres in aqueous glycerol solution and HPMC gels using PCS. In gels the bulk viscosity does not, as is well known, reflect the viscosity of the medium in which the particles move. This is rather the intrinsic viscosity or effective viscosity (Florence et al., 1973; Westrin and Axelsson, 1991) which we have estimated here in HPMC gels.

The diffusion of macromolecules in gels has been reviewed elsewhere (Lauffer, 1961; Crank, 1975; Muhr and Blanshard, 1982; Westrin and Axelsson, 1991; Masaro and Zhu, 1999; Bremmell et al., 2001). If there is only one solute diffusing inside the gel, the diffusion coefficient (D_G) is independent of the position (x) and the concentration (C_G) of diffusant (Westrin and Axelsson, 1991). The diffusion flux J in x-directed is given by Fick's first law (Martin, 1993):

$$J = -D_G \frac{\partial C_G}{\partial x} \tag{1}$$

where C_G is the amount of solute per unit volume of gel. In gels, the nanoparticles can only diffuse in the liquid void phase and must detour around the impermeable obstacles of the polymers chains. This effectively increases the path length and thus decreases the coefficient of diffusion. The diffusion coefficient in this case is generally defined as an effective diffusion coefficient (D_e) by

$$J = -D_e \frac{\partial C_L}{\partial x} \tag{2}$$

where C_L is the amount of solute per unit volume of the liquid void phase within the gel. The relationship between C_G and C_L is usually defined as

$$C_G = \varepsilon C_L \tag{3}$$

where ε is the void fraction accessible to the diffusing solute. Thereby the diffusion coefficient and the effective diffusion coefficient are related by the equation:

$$D_e = \varepsilon D_G \tag{4}$$

where ε is defined as

$$\varepsilon = 1 - \phi_p \tag{5}$$

for the low molecular weight solutes and ϕ_p is the polymer volume fraction of the gel.

There are two main reasons why the effective diffusion coefficient in a gel (D_e) is lower than the corresponding diffusion coefficient in water (D_o). First, the polymer reduces the available diffusion volume to a fraction of the total—the exclusion effect. The second is the obstruction effect—impermeable segments of the polymer molecules increasing the path length for a diffusant by τ—the tortuosity factor. Both are incorporated in Eq. (6):

$$\frac{De}{Do} = \frac{\varepsilon}{\tau} \tag{6}$$

It is difficult to determine ε and τ values by experiment. The polymer volume fraction ϕ_p has been successfully employed to estimate the effect of polymers in decreasing diffusion coefficients (Mackie and Meares, 1955a, 1955b) (Eq. (7)), viz

$$\frac{D_G}{D_o} = \frac{(1-\phi_p)^2}{(1+\phi_p)^2} \tag{7}$$

By substituting D_G for D_e from Eqs. (4) and (5), Eq. (7) can be written as

$$\frac{D_e}{D_o} = \frac{(1-\phi_p)^3}{(1+\phi_p)^2} \tag{8}$$

and thus the effective diffusion coefficient can be predicted. The diffusion coefficient at infinite dilution, D, of a sphere of radius r moving in a continuum of viscosity η can be obtained from the Stokes–Einstein equation derived on the assumption that there is no slip at the surface of the sphere:

$$D = \frac{kT}{6\pi\eta r} \tag{9}$$

where k is Boltzmann's constant. Therefore, from Eq. (9), Eq. (8) can be rewritten as

$$\eta_e = \eta_{aq} \frac{(1+\phi_p)^2}{(1-\phi_p)^3} \tag{10}$$

to obtain the effective viscosity in a gel.

Amino latex nanospheres (ALNs) (108 ± 7 (±S.D.) and 495 ± 23 nm) and carboxyl latex nanospheres (CLNs) (48 ± 7, 91 ± 9.8 and 483 ± 10 nm) (Polysciences) were used. AR glycerol obtained from BDH was used after centrifugation to remove any dust particles. The aqueous suspensions contained 0.2% (w/v) of either 50 nm positively or negatively charged latex nanospheres and 0.02% of the 108 and 495 nm positively and negatively charged latex nanospheres in glycerol solutions (0–25%, v/v). All samples were filtered through 0.22 μm filters, except the samples containing 495 and 483 nm nanospheres which were filtered through a 0.9 μm membrane filter prior to measurement of diffusion coefficients by PCS, at a wavelength of 633 nm at 25 °C. The viscosities of glycerol aqueous solutions were determined by using an Anton Paar microviscometer (Anton Paar AMVn, No. 670098). Refractive indices were measured using a refractometer (Bellingham & Stanley Ltd., London) at room temperature.

For studies with the HPMC (Sigma) gels, a 2.0% (w/v) gel stock was prepared in cold double distilled deionized water and the polymer was allowed to swell in water for 24 h until a clear state was reached. Various gels containing 0.02% (w/v) of 108 nm positively or 91 nm negatively charged nanospheres were prepared. The bulk viscosities of the gels were measured using a Carri Med CSL 500 Rheometer with 4 cm, 2° cone. The samples were filtered and the diffusion coefficients were measured under the conditions mentioned above. All the experiments were carried out in triplicate.

The diffusion coefficients of latex nanospheres with diameter from 48 to 500 nm are illustrated in Fig. 1. It was not surprising that in water and Newtonian glycerol aqueous solution *D* values obey Stokes–Einstein behaviour over a range of system viscosities. This was also confirmed by the linear relationship between the measured diffusion coefficient *D* and the reciprocal viscosity found in the inset in Fig. 1, as predicted by the Stokes–Einstein equation. Fig. 2 shows the theoretically estimated values (D_{theo}) of the diffusion coefficients versus those actually measured (D_{exp}). Although the nanospheres used are not monosized, their size distribution was in a very narrow range (small ±S.D.). From the standard deviation values of nanosphere diameter, the percentage of the maximum error limit for D_{theo} was calculated and used to evaluate the D_{exp} values. The solid line corresponds to Eq. (9) and the dashed line shows the acceptable deviation limit (10%) from the solid line. There was a good correspondence between the measured values and their theoretical estimates for 91 and 483 nm CLN and 495 nm ALN. As can be seen, all measured diffusion coefficients (D_{exp}) of 91 nm CLN fell within the 5% error limit while that of 495 nm ALN and 483 nm CLN fell within the 10% error limit. However, most of the D_{exp} values of 48 nm CLN and 108 nm ALN were found in the 10% and 30% error range which implied

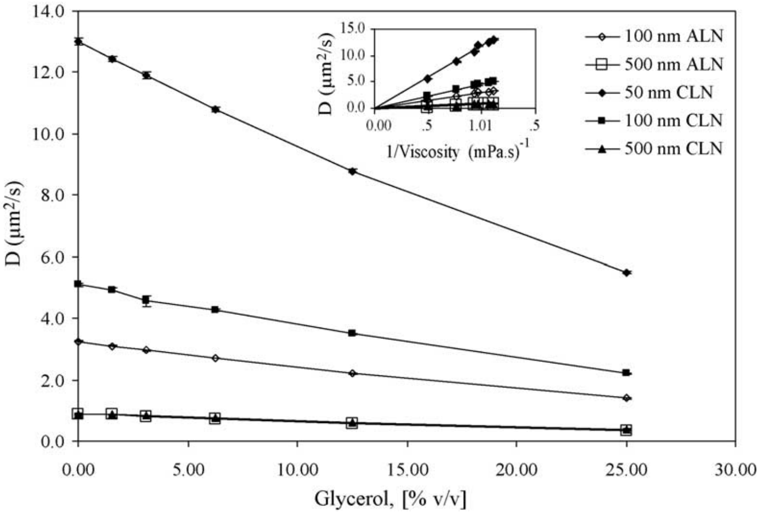

Fig. 1. Diffusion coefficients of positively (ALN) and negatively charged nanospheres (CLN) (0.2% (w/v) of 48 nm CMS and 0.02% (w/v) of 108 and 495 nm ALN and 91 and 483 nm CLN), in various concentrations of aqueous glycerol solutions. Inset illustrates the expected linear relationship between the diffusion coefficient *D* and the reciprocal viscosity.

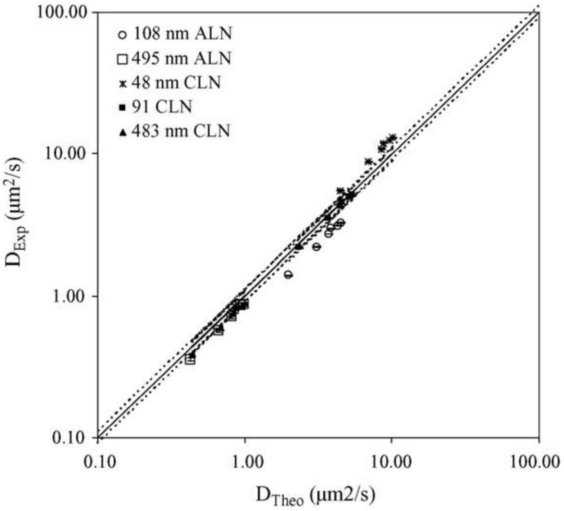

Fig. 2. The parity plot shows the measured diffusion coefficients (D_{exp}) vs. the estimated values (D_{theo}) of positively (ALN) and negatively charged nanospheres (CLN) (0.2% (w/v) of 48 nm CMS and 0.02% (w/v) of 108 and 495 nm ALN and 91 and 483 nm CLN) in various concentration of aqueous glycerol solutions. The solid line has been calculated from Eq. (9) (D_{theo}) and dash lines is ±10% of D_{theo}.

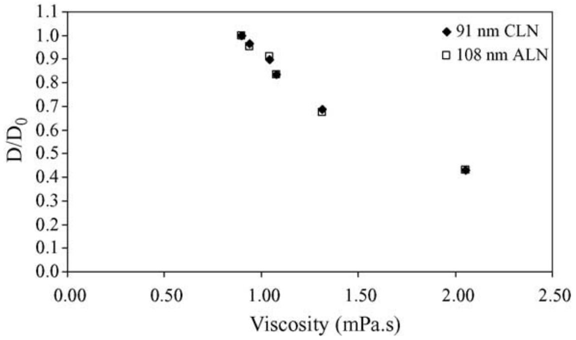

Fig. 3. The relative diffusion coefficients of 0.02% (w/v) dispersion of 108 nm positively and 91 nm negatively nanospheres in various concentrations of glycerol solutions.

an inaccuracy and constraint of the PCS for this application. It might be expected that the relative diffusion coefficient of the 91 nm CLN should be higher than that of the 108 nm ALM, but the results (Fig. 3) suggests that glycerol medium hinders the 91 nm CLM more than the 108 nm ALM. The reason for this is still not clear and further studies are required on this.

An increase in the bulk viscosity of the HPMC gel results in a decrease in relative diffusion coefficient (D/D_0) of the microspheres (Fig. 4). The insert illustrates the deviation of D from the Stokes–Einstein relationship for 108 nm positively and 91 nm negatively nanospheres as a function of the reciprocal viscosity of HPMC gels. There was a slight effect of particle charge on the diffusion coefficient as shown by the lower relative diffusion coefficients of the negatively charged nanospheres (Fig. 4b). However, it is seen from Fig. 4 that the effect of particle size is far more prominent than the effect of the particle charge. Furthermore, it was observed that the polydispersity index (PI) of systems containing the positively charged nanospheres increased dramatically from 0.217 at HPMC concentrations of 0.2% (w/v) to 0.495, 0.768 and 0.928 when the concentration of HPMC was 0.4%, 0.6% and 0.8% (w/v), respectively. A similar trend was not observed in the case of negatively charged nanospheres where the PI was found to be in the range of 0.035–0.470 (over the range 0.2–0.8% (w/v) HPMC). These results might suggest an interaction between the nanospheres and the polymer.

The effective viscosities, the viscosity that nanoparticles in motion “experience” in the HPMC gel at various concentrations were calculated. The values (calculated using Eq. (10)) were found to be 0.899, 0.908, 0.917 and 0.926 mPa s at HPMC concentration of 0.2%, 0.4%, 0.6% and 0.8% (w/v), respectively (Table 1). At low concentrations of HPMC, the effective viscosity (η_e) was close to the viscosity of water (0.8904 mPa s). The η_e value increased slightly with further increase in the concentration of HPMC, as

Table 1
The calculated effective viscosities in HPMC gels

Concentration of HPMC (%, w/v)	Density (g/ml)	Volume fraction (ϕ)	$(1-\phi)/(1+\phi)$	$(1-\phi)^3/(1+\phi)^2$	η_e
0.2	0.9945	0.0020	0.9900	0.9900	0.8994
0.4	1.0031	0.0040	0.9921	0.9803	0.9083
0.6	1.0242	0.0058	0.9884	0.9713	0.9167
0.8	1.0276	0.0077	0.9847	0.9621	0.9255

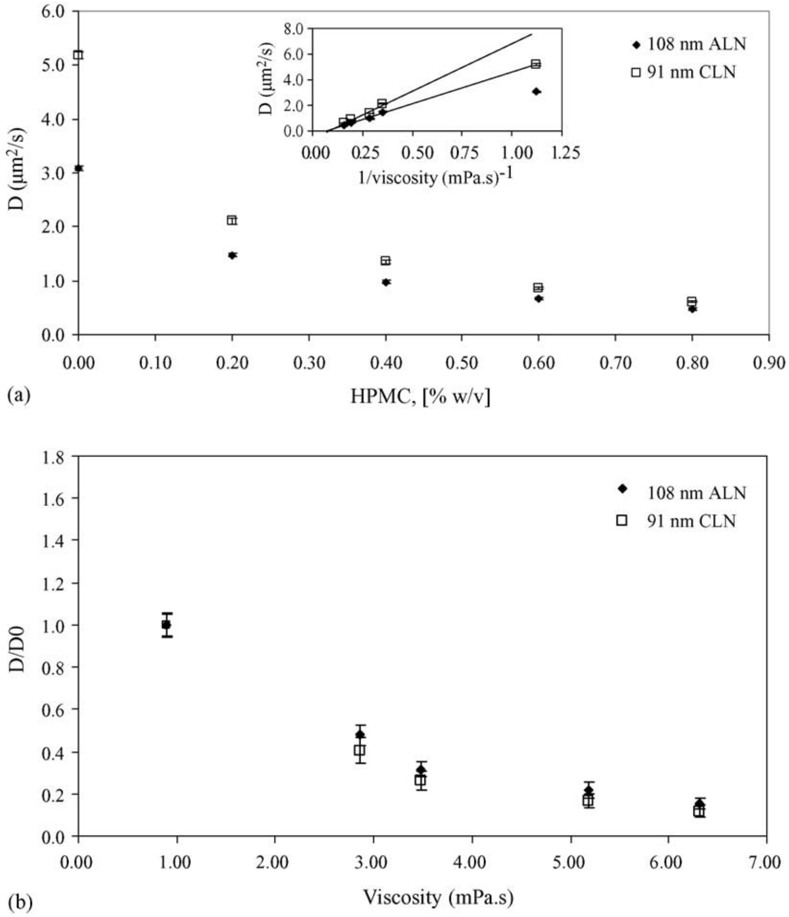

Fig. 4. (a) Diffusion coefficient of 108 nm positively (ALN) and 91 nm negatively charged nanospheres (CLN) (0.02% w/v), in various concentrations of HPMC gel. The insert shows the correlation between the diffusion coefficient of 0.02% (w/v) 108 nm positively and 91 nm negatively nanospheres and the reciprocal viscosity of the HPMC gels. (b) Correlation between the relative diffusion coefficients of 0.02% (w/v) dispersion of 108 nm positively and 91 nm negatively nanospheres in various concentrations of HPMC gels.

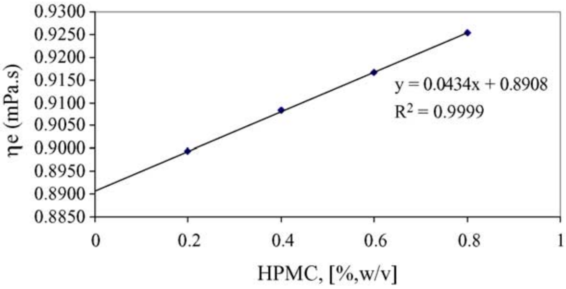

Fig. 5. Correlation between the effective viscosities of the HPMC gels and the concentrations of HPMC gels, extrapolated to zero percent HPMC indicating the value of pure water.

might be anticipated with increased water of hydration or portions of the polymer obtruding into the channels, increasing the effective viscosity (Table 1). This is also in accordance with the relationship in Eq. (10). As can be seen in Fig. 5, the values of microscopic viscosity determined by extrapolation to zero percentage HPMC is 0.8908 which is the viscosity of water at 25 °C.

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