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Photon correlation spectroscopy of pharmaceutical systems (sodium dodecyl sulphate, sodium deoxycholate and chlorpromazine hydrochloride micelles and polystyrene latices)

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Summary

Photon correlation spectroscopy (P.C.S.) was used to measure diffusion coefficients and to derive radii of pharmaceutically interesting systems (sodium dodecyl sulphate, sodium deoxycholate and chlorpromazine hydrochloride micelles and polystyrene latices). The equipment used an argon ion laser and a Malvern K7025 multibit correlator; the first data channel was omitted from any analysis because of electronic contributions and a measured rather than a calculated background was employed to normalize data—the percentage difference between the two backgrounds measured data accuracy. We analyzed our results with linear and quadratic fits, emphasizing the importance of a graph plot routine. At 25°C in 0.15 M NaCl an $\overline{R}_h$ (hydrodynamic radius of a sphere) of 22.4 Å for 2% w/v sodium dodecyl sulphate agreed with published data, 10% w/v sodium deoxycholate gave a radius of 17 Å and 2% w/v chlorpromazine hydrochloride yielded 16.8 Å.

Introduction

Photon correlation spectroscopy (P.C.S.) is a relatively new technique with many pharmaceutical applications (Fairbrother, 1979). Several systems are available commercially (e.g. Ford and Langley, 1979; McConnell, 1981) and, despite the potential value to pharmacy, few papers have appeared in the pharmaceutical press.

Until relatively recently (Oliver, 1981) little information has been presented on

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P.C.S. problems and what there is tends to be written for physicists and is difficult for pharmaceutical or biological scientists to appreciate. We encountered several general problems, particularly with data analysis, and one purpose of this paper, besides presenting original measurements, is to highlight these problems and their solution.

The theoretical principles of P.C.S. have been reviewed (Jamieson and Marat, 1973; Chu, 1974; Pusey and Vaughan, 1975) and applications include measurements on e.g. micro-organisms (Nossal and Chen, 1973), polymers (Jolly and Eisenberg, 1976) and micelles (Mazer et al., 1976). The method determines the dynamics of molecules or particles in solution or suspension as photons of a laser beam scatter when they encounter particles in Brownian motion and the scattered light intensity fluctuates. Such fluctuations proceed with a time characteristic of the movement and so the translational diffusion coefficient can be calculated.

We present here information about the light-scattering apparatus, experimental technique, data analysis and reproducibility for a variety of systems including bile salt, sodium dodecyl sulphate and chlorpromazine hydrochloride micelles, and polystyrene latices.

Materials and methods

To check correct operation of the equipment we used polystyrene latex (Dow Chemicals, MI, U.S.A.), diameter 0.234 μm, as a standard, well characterized, monodisperse system. One drop of concentrate was dispersed in 50 ml fresh double-distilled water from an all-glass still. Sodium dodecyl sulphate, SDS, (B.D.H., Biochemical Grade, Poole, U.K.) was recrystallized 3 times from 95% ethanol. Sodium deoxycholate (NaDC) (Calbiochem, A Grade, San Diego, U.S.A.) was 99% (checked by T.L.C.—Güveli and Barry, 1980). Chlorpromazine hydrochloride was used as received from May and Baker, Dagenham, U.K.. Sodium chloride (B.D.H. Analar Grade) was roasted in air; SDS, NaDC, chlorpromazine hydrochloride and sodium chloride were dried in vacuo at 110°C for 3–4 h.

Micellar solutions of SDS, NaDC and chlorpromazine hydrochloride were prepared in 0.15 M NaCl. NaDC solutions were adjusted to pH 10 with 1 M sodium hydroxide (B.D.H. Reagent Grade) to ensure complete ionization of the monomer ($pK_a \simeq 6.0$). The pH of the chlorpromazine hydrochloride solution was 4.5 giving essentially complete ionization $pK_a \simeq 9.5$).

Scattering cells were soaked in chromic acid for 24 h, rinsed with distilled water and sprayed with hot acetone vapour, before drying in a laminar flow cabinet. Solutions were passed through membrane filters—0.45, 0.22 μm ("Nuflow", Oxoid, U.K.) or 0.1 μm (Sartorius, F.R.G.)—in the cabinet.

The scattering cell containing filtered solution (Fig. 1) was placed in the goniometer water bath (25 ± 0.1°C). A 2 W Spectra Physics argon ion laser (Model 164) provided the necessary power of 100–300 mW, at 488 nm. The primary lens focussed the beam into the centre of the cell and the light was collected by a trap to prevent total internal reflection.

The photomultiplier assembly collected the scattered light and transmitted a signal to the Malvern K 7025, 128-channel, multibit correlator. The correlation data were passed to a Commodore 32K Pet, interfaced with a printer (Printer M 879), where the data were analyzed, graphed and printed.

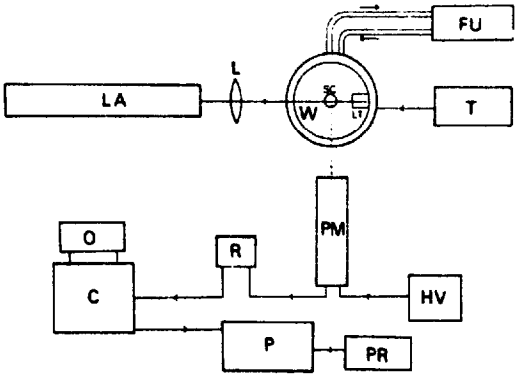

Fig. 1. Photon correlation spectroscopy apparatus. Key: LA, laser, Spectra Physics Model 164 argon ion; L, lens; W, water bath; SC, scattering cell; LT, light trap; FU, filtration unit (for water bath); T, Malvern temperature controller; PM, photomultiplier assembly; HV, high voltage supply to PM; R, ratemeter; C, Malvern K 7025 correlator; O, oscilloscope; P, Commodore 32 K Pet; PR, printer.

Sample time (or delay time) selection used an oscilloscope and an estimate of the required sample time was made from the scattering intensity. Large particles, needing low laser power and a small photomultiplier aperture, required long sample times. For 0.2 μm polystyrene latex an initial estimate would be 100 μs but for a micellar system it may be only 1 μs. Next we chose a long sample time for which most of the channels were equivalent to the background scatter. This portion of the correlation function should be rigorously flat; any curvature or downward trend indicates long time decaying components needing refiltering. Usually 'dust' contamination sharply increases the count rate and the oscilloscope trace scrolls. When the solution was 'clean' we selected a sample time to include more channels for data analysis.

We measured the refractive indices with an Abbe 60 refractometer at $25 \pm 0.1°C$ and the solvent viscosity was assumed to be 0.9046 cp (0.15 M NaCl at 25°C—Weast, 1978).

The correlation data produce a single exponential curve, representing a monodisperse system, or a sum of exponentials, $G(\Gamma)$ given by a variety of sizes. For a monodisperse system, assuming no particle interaction and that the particles are small compared with the wavelength of light:

$$c^{1/2}|g^{(1)}(\tau)| = c^{1/2} \exp(-\Gamma(\tau)) \tag{1}$$

Plotting log corrected counts ($\ln c^{1/2}|g^{(1)}(\tau)|$) against sample time ($\tau$) gives a straight line with slope Γ. Now

$$\Gamma = DK^2 \tag{2}$$

where the translational diffusion coefficient is D and K is the scattering vector:

$$K = (4\pi/\lambda)n \sin(\theta/2) \tag{3}$$

where λ is the wavelength of light in vacuo, n is the solution refractive index and θ is the scattering angle (90°).

For a mixture of sizes, the scattered light contains a variety of components. The data can be characterized in different ways (Chu et al., 1979): (1) cummulants; (2) Pearson frequency curves; (3) Laplace transform; and (4) histogram. We used the method of cumulants (Koppel, 1972; Brown et al., 1975), fitting a quadratic function to plots of $\ln c^{1/2}|g^{(1)}(\tau)|$ vs (τ).

$$\ln c^{1/2}|g^{(1)}(\tau)| = \tfrac{1}{2} \ln c - \bar{\Gamma}(\tau) + \frac{1}{2!}\left(\frac{\mu_2}{\bar{\Gamma}^2}\right)(\bar{\Gamma}(\tau))^2 - \frac{1}{3!}\left(\frac{\mu_3}{\bar{\Gamma}^3}\right)(\bar{\Gamma}(\tau))^3$$

$$+ \frac{1}{4!}\left(\frac{\mu_4 - 3\mu_2^2}{\bar{\Gamma}^4}\right)(\bar{\Gamma}(\tau))^4 + \cdots \tag{4}$$

The particle size is related to the diffusion coefficient by the Stokes-Einstein equation:

$$D = \frac{kT}{6\pi\eta\bar{R}_h} \tag{5}$$

where k is Boltzmann's constant, T is the absolute temperature, η is the solvent viscosity and $\bar{R}_h$ is the hydrodynamic radius of a sphere.

Results and discussion

The channel contents were normalized using a background determination which can be obtained from the correlator monitor channels (calculated background) or from the mean of the last 10 channels (measured background).

The calculated background works reasonably well for large particles, such as polystyrene latices, since total scattering intensity is large and delay times are long. With small particles such as micelles, complications (including stray light, dust scattering and counter dead times) make a calculated background suspect. The measured background can also mislead if there are any long-time decaying components in the correlation function. Then, even with delay channels (64 sample times), the background may not be reached for the longest delay time available.

For an ideal system containing monodispersed particles, which is clean and measured under perfect experimental conditions, the calculated and measured backgrounds should be equal. We found that the calculated background was nearly always lower. Equal background determinations are difficult to achieve but the percentage difference between the backgrounds quantifies data accuracy. A value of

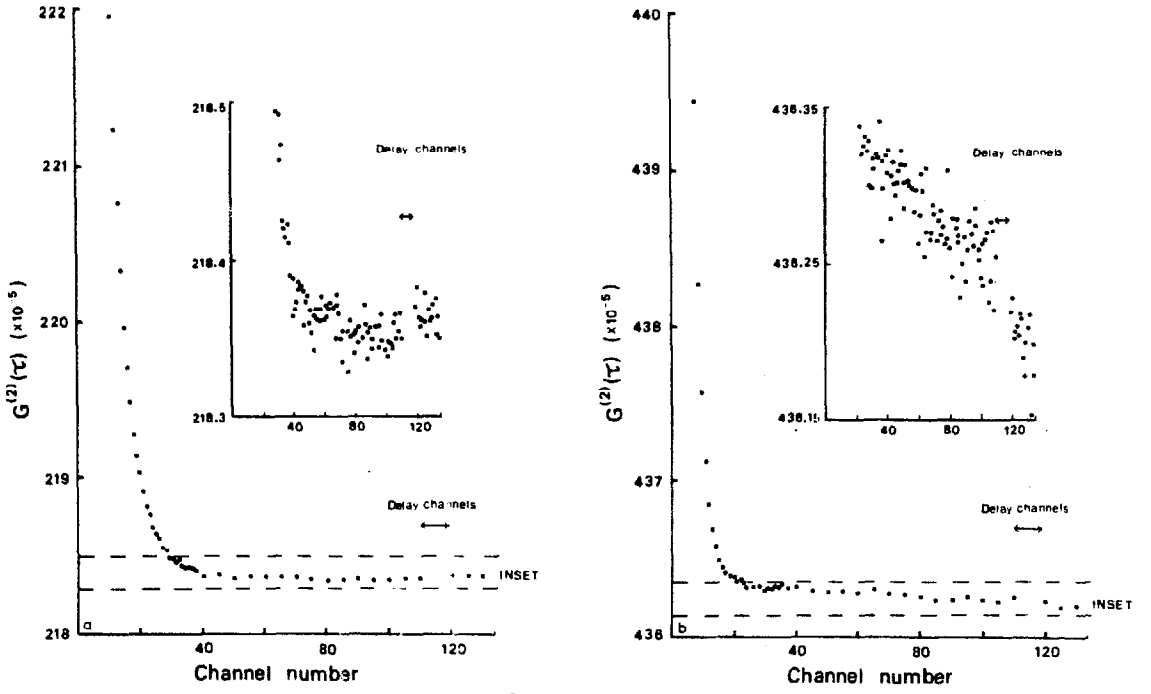

Fig. 2. Second-order correlation function, $G^{(2)}(\tau)$, for 2% w/v sodium dodecyl sulphate in: (a) 0.6 M NaCl; and (b) 0.15 M NaCl. Insets show the area bounded by the dashed lines with ordinate expanded ten-fold and abscissa scale halved.

$< 0.05\%$ indicates good data and the diffusion coefficient will be essentially the same for both backgrounds if they agree to $< 0.02\%$.

Using a 32 K Commodore Pet we analyzed the correlation data with a modified version of the Malvern Applications Program (7025 Spect. I. VI, Malvern Instruments, U.K.). The Malvern program only prints values for the diffusion coefficient, diameter and polydispersity, using a quadratic least-squares fitting routine. The analyses employ calculated backgrounds which, for our experiments, nearly always produced misnormalization. Therefore we incorporated the measured background and used it for data normalization. We also added a graph plotting routine, which indicated any spurious contributions to the correlation function, e.g. long-time tails from dust scattering. The graph plot had a discrimination of one character in 76 giving a reasonable visual representation of $\ln c^{1/2}|g^{(1)}(\tau)|$ vs (τ). Long-time tails are not readily apparent on the oscilloscope so the graph plot has proved essential; Figs. 2 and 3 demonstrate its value. Figs. 2a and b show the raw data counts vs channel number, each channel representing one sample time period—5 μs for Fig. 2a and 4 μs for Fig. 2b. The insets expand the ordinate to show more detail as the correlation function decays to the background. Fig. 2a shows that the true background had been achieved because the last data channels reached a constant value, but Fig. 2b illustrates a slow decay. Fig. 3 shows the log plot for the data represented in Fig. 2b, revealing the long-time tail. Any curve fitting procedure would include some of the tail and mislead. The original Malvern program would print just a diffusion coefficient calculated from the slope of the fitted points, which are poorly related to

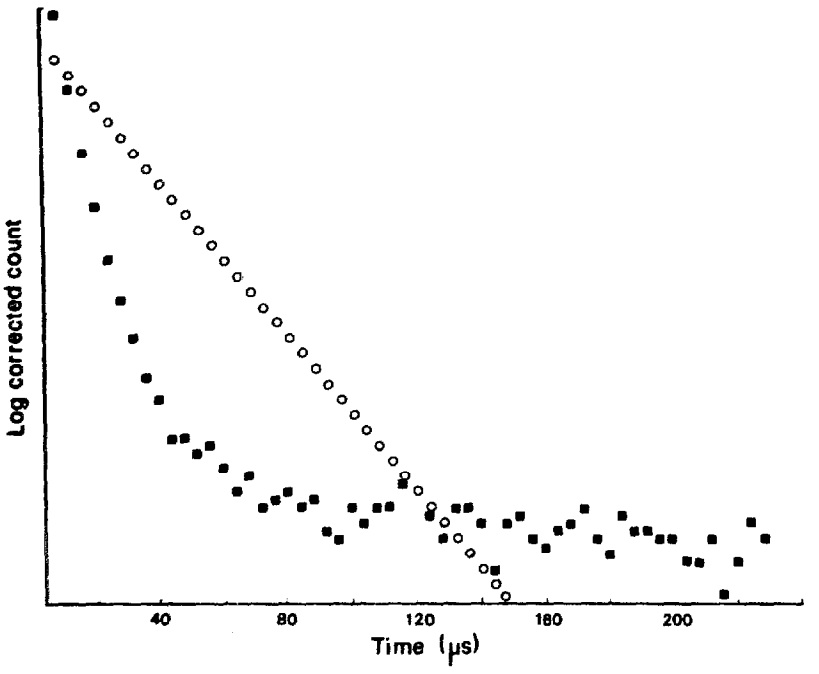

Fig. 3. ln $c^{1/2}|g^{(1)}(\tau)|$ vs sample time for 2% sodium dodecyl sulphate in 0.15 M NaCl from the data shown in Fig. 2b. ■, experimental points; ○, points fitted by linear weighted least-squares analysis.

the experimental values because of the long-time tail. Fig. 2a is the ideal shape for a correlation function, with a background difference of 0.007%. Fig. 3 deviates from ideality, with a background difference of 0.208%.

The program also includes a choice of curve-fitting procedures to calculate D. A weighted least-squares fit for linear data calculates D from the slope (Eqns. 1 and 2) and a cumulant expansion to two terms of ln $c^{1/2}|g^{(1)}(\tau)|$(Eqn. 4) gives D from the linear term. The polydispersity of non-linear data can be calculated from a combination of the linear and quadratic terms in the cumulant expansion.

Our polydispersity value is the same as the quality parameter (Q) which Pusey et al. (1974) used to test the single exponentiality of the correlation function.

$$Q = \frac{\bar{\mu}_2}{\bar{\Gamma}^2} \tag{6}$$

where $\bar{\mu}_2$ is the moment about the mean of G (Γ), the relative width of the distribution, and $\bar{\Gamma}$ is the mean decay rate. $\bar{\Gamma}$ and $\bar{\mu}_2$ are represented by the linear and quadratic terms of the cumulant analysis.

Another measure of the polydispersity is the variance of the distribution, G (Γ), (Mazer et al., 1976)

$$V = 100 \times \frac{\left(\overline{\Gamma^2} - (\bar{\Gamma})^2\right)^{1/2}}{\bar{\Gamma}} \% \tag{7}$$

where V is the variance and $(\overline{\Gamma^2} - (\bar{\Gamma})^2)$ is equivalent to $\bar{\mu}_2$, the relative width of the distribution. V and Q are related by:

$$V = 100\, Q^{1/2} \tag{8}$$

Theoretically, Q is zero for a single exponential, a monodisperse system, although this is rarely achieved. We take a general limit of < 0.1 ($V < 32\%$) to indicate an essentially monodisperse system (Brown et al., 1975).

The third cumulant can be related to the skewness of the distribution (Mazer, 1973). Using the 3 parameters, mean diffusion coefficient, variance and skewness we can derive a bar graph of the size distribution using the Pearsonian system of frequency curves (Mazer, 1973; Cohen et al., 1976).

We tested the validity of our data analysis by measuring the diffusion coefficient, D, and diameter of 2% w/v SDS in 0.15 M NaCl at different sample times (Table 1 and Fig. 4). For a valid fit D should be independent of sample time, within experimental error. The error bars in Fig. 4 represent the standard error of the slope for both linear and quadratic fits.

Fig. 4 also demonstrates the method of Brown et al. (1975) to determine D. At short delay times the linear term only of Eqn. 4 is significant so it is possible to estimate D by extrapolating the line through the data points of the linear fit to zero sample time.

TABLE 1

EFFECT OF SAMPLE TIME ON DIFFUSION COEFFICIENT, DIAMETER AND POLYDISPERSITY FOR THE LINEAR AND QUADRATIC FITTING PROCEDURES USING 2% w/v SDS IN 0.15 M NaCl [a]

Sample time (μs)	Linear fit			Quadratic fit		
	Background difference [b] (%)	Diffusion coefficient ($\times 10^7$ cm$^2 \cdot$s^{-1})	Diameter (Å)	Diffusion coefficient ($\times 10^7$ cm$^2 \cdot$s^{-1})	Diameter (Å)	Polydispersity Q
0.4	0.163	9.93 ± 0.07	48.5 ± 0.4	11.1 ± 0.1	43.3 ± 0.2	0.183
0.6	0.304	9.35 ± 0.07	51.6 ± 0.4	10.7 ± 0.1	44.7 ± 0.1	0.202
0.8	0.136	9.46 ± 0.06	51.0 ± 0.4	10.8 ± 0.1	44.3 ± 0.2	0.200
1.0	0.081	9.66 ± 0.10	49.9 ± 0.5	10.6 ± 0.1	45.2 ± 0.3	0.155
1.5	0.050	9.38 ± 0.08	51.4 ± 0.4	10.8 ± 0.1	44 4 ± 0.3	0.191
2.0	0.188	8.38 ± 0.08	57.5 ± 0.6	10.6 ± 0.1	45.4 ± 0.2	0.233
3.0	0.050	8.43 ± 0.09	57.1 ± 0.7	10.6 ± 0.1	45.1 ± 0.3	0.227
4.0	0.060	8.00 ± 0.19	60.2 ± 1.5	10.6 ± 0.1	45 5 ± 0.3	0.240

[a] Count rate $\simeq 4 \times 10^5$ Hz, experimental duration = 1000 s, refractive index = 1.337, scattering angle = 90°.

[b] Difference between measured and calculated backgrounds.

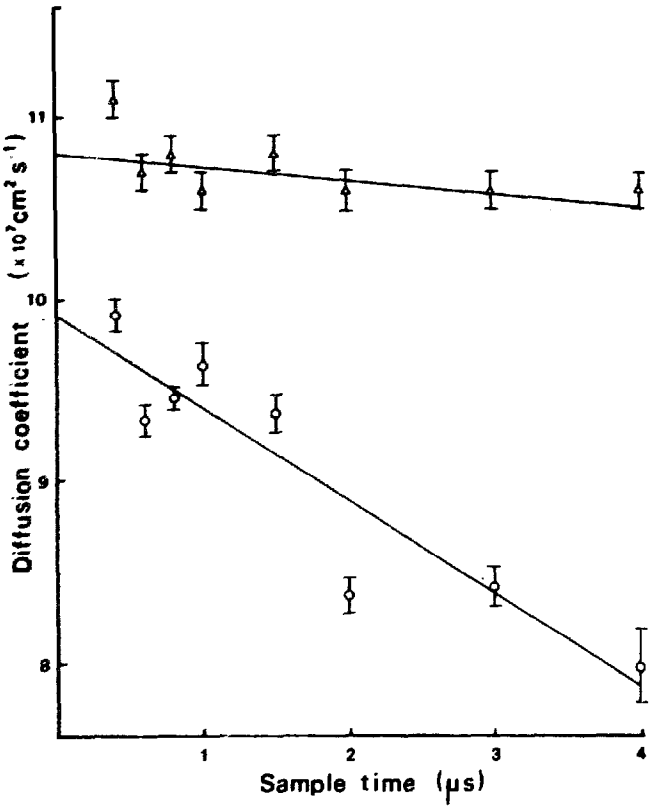

Fig. 4. Variation of diffusion coefficient for 2% w/v sodium dodecyl sulphate in 0.15 M NaCl with sample time using a linear fit (○) and a quadratic fit (△). Full lines calculated by linear regression: linear data, $r = -0.921$; quadratic data, $r = -0.604$.

Linear regression of the quadratic data gives a correlation coefficient of -0.604 ($0.1 < P < 0.2$). We therefore simply took the mean value of the diffusion coefficient, 10.7×10^{-7} cm$^2 \cdot$ s^{-1}, to give a hydrodynamic radius, $\bar{R}_h$, of 22.4 Å. Mazer et al. (1976) give an $\bar{R}_h$ value of 25 Å for this system but later the same group (Missel et al., 1980) suggest that their value should be nearer 23 Å as their previous sample contained an average chain length of 12.8 carbon atoms. Extrapolating the linear data to zero sample time gives an $\bar{R}_h$ value of 23.8 Å which is only 6% greater than the quadratic data fit.

The choice of experimental duration is important; the length must be sufficient to produce statistically accurate data. Table 2 shows the effect of duration on accuracy for chlorpromazine hydrochloride in 0.15 M NaCl, the first time this system has been measured by P.C.S. These data confirm that accuracy is roughly proportional to the square-root of time (Foord et al., 1970), 1% accuracy being achieved after 100 s. The quadratic fitting shows a monodisperse system at this time ($Q < 0.02$), so results can be described adequately by the single exponential fit.

Care is necessary in attaching physical significance to the cumulants in Eqn. 4. $\bar{\Gamma}$ can be related to the mean diffusion coefficient and $\bar{\mu}_2/\bar{\Gamma}^2$ gives a measure of polydispersity for a well-behaved system with an approximately Gaussian size distribution about a well-defined mean, $\bar{\Gamma}$. In less well-behaved systems, however,

TABLE 2

ACCURACY OF DIFFUSION COEFFICIENT, DIAMETER AND POLYDISPERSITY MEASUREMENTS FOR 2% w/v CHLORPROMAZINE HYDROCHLORIDE IN 0.15 M NaCl [a]

Experimental duration (s)	Linear fit			Quadratic fit			
	Diffusion coefficient ($\times 10^6$ $cm^2 \cdot s^{-1}$)	Diameter (Å)	Error of mean (%)	Diffusion coefficient ($\times 10^6$ $(cm^2 \cdot s^{-1})$)	Diameter (Å)	Error of mean (%)	Polydispersity Q
1	1.41 ± 0.06	34.2 ± 1.5	4.3	1.66 ± 0.32	30.0 ± 6.6	21.5	– [b]
10	1.41 ± 0.03	34.1 ± 0.6	1.8	1.45 ± 0.07	33.2 ± 1.7	5.1	0.049 ± 0.096
100	1.41 ± 0.01	33.8 ± 0.3	0.7	1.44 ± 0.03	33.6 ± 0.6	1.7	0.026 ± 0.032
1000	1.42 ± 0.01	33.9 ± 0.1	0.2	1.43 ± 0.01	33.6 ± 0.2	0.5	0.016 ± 0.009

[a] n = 10, count rate $\simeq 5 \times 10^5$ Hz, sample time = 1 μs, refractive index = 1.339, scattering angle = 90°.

[b] Values too variable to be meaningful.

where the spread of G (Γ) is greater, or where G (Γ) is multimodal, the physical significance of $\bar{\Gamma}$ is obscure. This histogram method may be more appropriate for systems such as microemulsions (Gulari et al., 1980) which may contain a bimodal distribution of micelles and microemulsion. For the micellar systems investigated here we asume an approximate Gaussian size distribution (Mazer et al., 1976; 1980; Candau and Zana, 1981).

For sodium dodecyl sulphate (Table 1) the mean polydispersity is 0.187 ± 0.035 ($V = 43\%$), comparing unfavourably with published values, viz. Mazer et al. (1976) $V = 28\%$ ($Q = 0.08$), and Rohde and Sackmann (1979) $Q \simeq 0.05$ ($V = 22\%$), for 2% w/v SDS in 0.1 M NaCl. Our high polydispersity indicates 'dust' (this includes any species moving so slowly that its contribution to the correlation function is essentially constant over the measured range of delay times). In some instances the contaminant produces a curved correlation function, indicating a high polydispersity and even giving a long-time tail to the data (Figs. 2b and 3). 'Dust', as well as being an extreme case of polydispersity, can also serve as a local oscillator which interferes with the scattered radiation to produce a heterodyne term in the observed homodyne correlation function.

We assessed the effect of passage through different pore size filters, on the measured diffusion coefficient, diameter, polydispersity and percent background difference (our assessment guide of valid data) for 10% w/v NaDC in 0.15 M NaCl (Table 3). For 0.45 μm filters, solutions showed evidence of scattering from 'dust'—fluctuating count rates, large background differences and long-time tails. Solutions filtered through 0.22 and 0.1 μm membranes gave good plots with no long-time tails, low background differences and stable count rates. The diffusion coefficients and diameters were similar with 0.22 and 0.1 μm filters but the 0.1 μm filtered solution showed considerably reduced polydispersity, indicating improved separation of long-time decaying components. The high polydispersity ($Q = 0.234 \pm 0.028$) for the 0.45 μm filtered solution confirmed the presence of 'dust' even though Q was less than some literature values. An example is $V = 67\%$ ($Q = 0.45$) for the lecithin–sodium taurocholate solution, 1.25 g/dl at 40°C (Mazer et al., 1980). This

TABLE 3

EFFECT OF FILTER SIZE ON THE DIFFUSION COEFFICIENT, DIAMETER, POLYDISPERSITY AND THE BACKGROUND DIFFERENCES FOR 10% w/v NaDC IN 0.15 M NaCl [a]

Filter (μm)	Background difference (%)	Diffusion coefficient [b] ($\times 10^6 cm^2 s^{-1}$)	Diameter (Å)	Polydispersity Q
0.45	0.376 ± 0.205	1.26 ± 0.03	38.4 ± 0.9	0.234 ± 0.028
0.22	0.049 ± 0.013	1.37 ± 0.01	34.9 ± 0.2	0.127 ± 0.011
0.1	0.042 ± 0.055	1.42 ± 0.01	33.9 ± 0.4	0.067 ± 0.022

[a] n = 10, count rate $\simeq 4 \times 10^5$ Hz, experimental duration = 100 s, sample time = 1 μs, refractive index = 1.353, scattering angle = 90°.

[b] Obtained from quadratic fitting.

value may be justified but with our systems we are now suspicious of any values greater than Q = 0.2. It is interesting to note in Table 1 that the percent background difference is greater than 0.05 in most instances which is most likely because 'dust' contamination affects the correlation function. We consider that filtration through a 0.1 μm filter would reduce the polydispersity to levels reported by other workers with only a small effect on the measured diffusion coefficient.

Long-time tails have been noticed by other workers using different systems. Number density fluctuations have been considered by some authors (Pusey, 1979; Goodall et al., 1980). If the scatterers are too far separated, their number in the scattering volume may fluctuate and this contributes an additional flat component to the expected correlation function. We noticed these effects for very dilute suspensions of polystyrene latex (about 10 $\mu g \cdot ml^{-1}$) for which the particle size can still be measured but the scattered light intensity varies with time and the percentage background difference is large ($\simeq 0.2\%$). 'Dust' scattering effects can be detected by comparing the correlation function of the sample with that of filtered solvent, which should be flat.

Pusey (1978) demonstrated the long-time tail effect produced by interparticle interaction of polystyrene latex, after removal of counter-ions. Insoluble materials, such as dodecanol in dilute solutions of SDS, produced a long-time tail (Corti and Degiorgio, 1977). For w/o microemulsions, long-time tails were attributed to gel formation (Bellocq et al., 1980).

Several other effects can curve the correlation function and form long-time tails (Degiorgio, 1977; Oliver, 1981). A laser intensity drift of 0.6% produces a misnormalization of 0.01%; in the light-stabilized mode our laser had a fluctuation of $\sim 0.3\%$.

Spurious effects can also be produced from detector afterpulses, dead times, gain fluctuations in the photomultiplier and electronic amplifier and threshold fluctuations in the discriminator. These can be detected by illuminating the photomultiplier tube with a stable source of white light, such as a 12 V bulb powered by an accumulator. If no disturbances are present, the resulting correlation function should be rigorously flat over the whole of the delay time period with a constant normalized value of one; also the calculated and measured backgrounds should be equal. Correlations can exist with a white-light source but these develop at unobtainably short delay times. We found some electronic effects in the first 2 μs of the correlation function so we ignored the first data channel in our analysis as this sample time period contains a distorted number of counts.

Stray light and flare curve the correlation function upwards because of a heterodyne effect. Chu et al. (1979) found that a stray light contribution as small as 0.5% had a marked effect on the apparent width of the distribution, while 2% made it bimodal. Total internal reflection of the laser beam from the glass wall of the water bath can cause stray light, which we eliminated with a light trap in the water bath. This was a hollow blackened aluminium cylinder with a pin hole for entry of the laser beam and a conical end-piece for dissipation within the trap.

Bulk motion and sedimentation may curve the correlation function downwards. To eliminate convection effects we allowed time for temperature equilibration.

Sedimentation would only be a problem for very large particles, i.e. those of a size above the limit of the usefulness of the technique.

Conclusions

Removal of sample contaminants, elimination of stray light and electronic contributions, careful data analysis and automatic graph plotting will yield rapid and accurate measurements of diffusion coefficients and particle size for a variety of pharmaceutical systems. With our data analysis and experimental modifications we are able to accurately measure particle sizes from the micron size range down to a few Ångstroms.

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