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# Ultrasonic preparation of pharmaceutical emulsions. Droplet size measurements by quasi-elastic light scattering

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## Summary

Quasi-elastic light scattering (QLS) has been applied to obtain information of droplet size distributions in model o/w emulsion systems, emulsified by ultrasound at varying sound intensities and treatment times. Results show that the mean droplet diameters and polydispersity of the emulsions decrease with an increase in treatment time or in sound intensity. The mean droplet diameter decreases towards a minimum size of about 0.2 $\mu$m.

The experiments show that QLS measurement with an He–Ne laser and a Malvern K7025 multibit correlator is applicable for evaluating droplet size distributions in emulsions with droplet sizes in the submicron range. The method supplements the Coulter method that can register droplets larger than about 0.6 $\mu$m.

## Introduction

Our previous study (Eberth and Merry, 1983) of droplet size distributions in a pharmaceutically relevant emulsion system showed that although conventional analytical methods (Coulter Counter and light microscopy) are adequate for describing the system when emulsified by a laboratory emulsifying machine, the methods give distorted and insufficient information of the system when emulsified by ultrasound due to a large fraction of droplets with diameters smaller than 1 $\mu$m.

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In this work the same emulsion system prepared by ultrasound (20 kHz) at varying sound intensities and treatment times has been investigated by quasi-elastic light scattering (QLS).

According to Groves (1980) the method of QLS is applicable for spherical particles with diameters in the size range 10 nm–1 $\mu$m and is therefore a potentially useful method for droplet size analysis in this study.

## Materials and methods

*Materials and method of emulsification*

The model pharmaceutical o/w emulsion used in the experiments contained 20 g pristane (2,6,10,14-tetramethylpentadecane) (Aldrich-Europe), 2 g Tween 85 (Koch-Light Laboratories) and 178 g distilled water.

Ultrasonic treatment (20 kHz) was given by a Branson Sonifier Cell Disrupter model B-30 (Branson Sonic Power, U.S.A.) at 20 kHz in pulses lasting 0.5 s in 1-s periods for 1, 2, 10 and 40 min, corresponding to constant treatment times of 0.5, 1, 5 and 20 min, respectively. Sound intensities of 130 W, 175 W, 190 W and 200 W, respectively, were applied. Further details of emulsion preparation have been described earlier (Eberth and Merry, 1983).

*QLS analysis*

For QLS experiments a Malvern Photon Correlation Spectrometer (system 4300) with a Hughes 10 mW He–Ne Laser (632.8 nm), a 128 channel Malvern Multibit correlator (K7025) and a Malvern Data Processor (type MDP 7025) were applied.

The autocorrelation functions computed from the light scattering measurements of polydisperse systems in this study are interpreted by the method of cumulants (e.g. Koppel, 1972; Pusey et al., 1974; Roe and Barry, 1983). The method is valid for particles that are spherical, non-interacting and small compared to 1/K, where

$$K = (4\pi/\lambda) \cdot n \cdot \sin\left(\frac{\theta}{2}\right)$$

for which $\lambda$ is the wavelength of the incident light in vacuo, n is the refractive index of the solution and $\theta$ the applied scattering angle. If the measured particles are spherical as, for example, emulsion droplets, the requirement of droplet diameters being smaller than 1/K is considered less critical than for non-spherical particles; Pusey and Vaughan (1975) state that the simple QLS theory is also applicable for rigid non-interacting spheres ranging from approximately 0.1–2 $\mu$m.

The normalized autocorrelation function $|g^{(1)}(\tau)|$ can for polydisperse systems be described as a sum of exponentials

$$|g^{(1)}(\tau)| = \int_0^\infty G(\Gamma)\, e^{-\Gamma\tau} d\Gamma \qquad (1)$$

where $\tau$ is the delay time and $G(\Gamma)$ is the normalized distribution function of decay rates ($\Gamma$) from which translational diffusion coefficients (D) for systems of spherical particles can be computed by the equation

$$\Gamma = D \cdot K^2 \tag{2}$$

and corresponding particle diameters (2 r) can be computed by means of the Stokes-Einstein equation:

$$r = \frac{k_B \cdot T}{6\pi\eta D} \tag{3}$$

where $k_B$ is the Boltzmann constant, T is the absolute temperature and $\eta$ is the solvent viscosity; r denotes the hydrodynamic radius.

In the applied method of cumulants $e^{-\Gamma\tau}$ is expanded about $e^{-\bar{\Gamma}\tau}$ where $\bar{\Gamma}$ is the mean decay rate

$$\bar{\Gamma} = \int_0^\infty \Gamma G(\Gamma) d\Gamma \tag{4}$$

and the moments $\mu_2$, $\mu_3$, etc., around this mean are:

$$\mu_2 = \int_0^\infty (\Gamma - \bar{\Gamma})^2 G(\Gamma) d\Gamma \tag{5}$$

$$\mu_3 = \int_0^\infty (\Gamma - \bar{\Gamma})^3 G(\Gamma) d\Gamma \tag{6}$$

It has been shown (Koppel, 1972; Pusey et al., 1974) that

$$\ln C^{1/2} |g^{(1)}(\tau)| = 1/2 \ln C - \bar{\Gamma}\tau + \frac{1}{2!}\frac{\mu_2}{\bar{\Gamma}^2}(\bar{\Gamma}\tau)^2 - \frac{1}{3!}\frac{\mu_3}{\bar{\Gamma}^3}(\bar{\Gamma}\tau)^3 + \frac{1}{4!}\frac{\mu_4 - 3\mu_2^2}{\bar{\Gamma}^4}(\bar{\Gamma}\tau)^4 + \ldots \tag{7}$$

C denotes a function of certain parameters characteristic of the instrumental equipment. The Malvern Data Processor computes a value for the average decay rate, from which the mean droplet diameter is computed, by fitting a linear function to the logarithm of the normalized autocorrelation function ($\ln|g^{(1)}(\tau)|$). The polydispersity of the measured system is expressed by the polydispersity factor $\mu_2/\bar{\Gamma}^2$, computed by the Malvern Data Processor as a quadratic fit term. In this work a linear fit was found to be insufficient in the description of some of our systems, due to a significant deviation from linearity (Fig. 1). A polynomial regression program has therefore been developed by which the polynomial degree can be varied and the number of autocorrelation function data included in calculations can be systemati-

cally reduced, corresponding to a reduction in applied maximum delay time ($\tau_{max}$). Mean droplet diameters can be obtained from these calculations by extrapolation, analogous to the method of Brown et al. (1975) (see Appendix).

In the experiments described in the following, emulsions were diluted (about 1 : 5000) with filtered (Millipore 0.2 $\mu$m) distilled water and were measured at scattering angle 90° at thermostated temperature (room temperature). Preliminary experiments confirmed that pore size 0.2 $\mu$m was sufficient to minimize errors due to particle contamination.

*Coulter Counter analysis*

Measurements by the Coulter Counter Model TAII are performed as described in the first part of this study (Eberth and Merry, 1983) (with application of a 30 $\mu$m aperture, corresponding to a lower detection limit of about 0.6 $\mu$m). As only a fraction of the dispersed droplets in ultrasonically emulsified emulsions are registered by the Coulter Counter, to be able to compare QLS and Coulter Counter analysis, volume weighted mean diameters have been estimated from Coulter Counter measurements by assuming that the non-registered droplets have droplet diameters between 0 and 0.6 $\mu$m. By this assumption the mean volume weighted droplet diameters $\bar{d}$ will be found in the interval between $\bar{d}_{min}$ and $\bar{d}_{max}$, where

$$\bar{d}_{min} = \bar{d}_{reg} \cdot v_{reg} + 0(1 - v_{reg})$$

and

$$\bar{d}_{max} = \bar{d}_{reg} \cdot v_{reg} + 0.6(1 - v_{reg})$$

$\bar{d}_{reg}$ and $v_{reg}$ being the volume weighted mean diameter and the volume fraction of dispersed droplets registered by the Coulter Counter, respectively.

## Results and Discussion

The logarithms of the normalized autocorrelation functions of QLS measurements of emulsions prepared at varying ultrasonic intensities (Fig. 1A) and treatment times (Fig. 1B) show a deviation from linearity which is most significant for emulsions treated by ultrasound for short treatment times and/or at low intensities. This implies that these systems appear to be more polydisperse (Eqn. 7).

The mean droplet diameters and polydispersity factors, calculated by the Malvern Data Processor (linear fit procedure) decrease with an increase in treatment time and/or ultrasonic intensity (Table 1A). After an initial decrease the two parameters tend towards a lower limit corresponding to a mean droplet size of about 0.2 $\mu$m and a polydispersity factor of 0.1–0.2. Recalculations of the mean droplet diameters by the method of extrapolation (see Appendix) give values (Table 1B) that are up to 30% lower than the values calculated by the linear fit procedure, but the general tendencies in droplet size variations are the same.

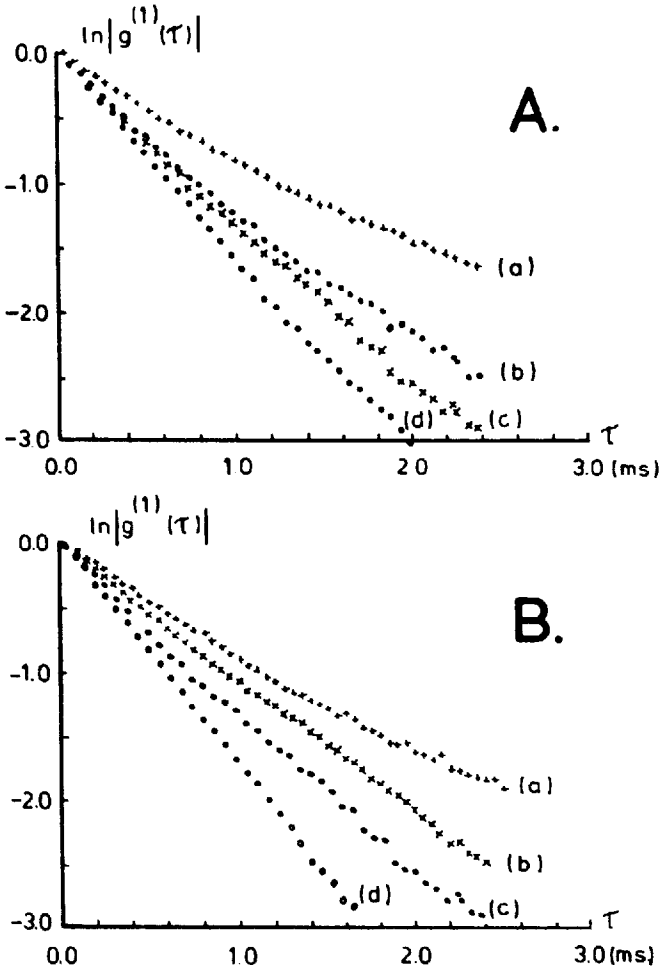


Fig. 1. QLS analysis depicted as the logarithm of the normalized autocorrelation function in o/w emulsions (10% w/w pristane, 1% w/w TWEEN 85 and 89% w/w water) prepared by ultrasound (20 kHz) for: (A) 5 min at intensity levels (a) 130 W, (b) 175 W, (c) 190 W and (d) 200 W; and (B) at intensity level 190 W for (a) 0.5 min, (b) 1 min, (c) 5 min and (d) 20 min.

These results are in agreement with the theory of Li and Fogler (1978a and b) that droplet sizes decrease by dispersion towards a lower limit, when emulsified by ultrasound, but as also mentioned in our previous paper (Eberth and Merry, 1983), monodispersity is not obtained with the applied emulsion system and method of emulsification.

The higher moments ($\mu_2$, $\mu_3$, etc., Eqn. 7) corresponding to further details of the decay rate distribution shape (standard deviation, skewness, etc.) in accordance with the method of cumulants, were not determined due to large random errors and due to a strong dependency on the degree of the selected polynomial fitting function.

Although the tendencies in droplet size variations are the same for both Coulter Counter (Table 2) and QLS analysis (Table 1), the volume-weighted mean diameters obtained from Coulter Counter analysis are larger than the mean diameters obtained from QLS analysis. In studies of polystyrene particles (Brown et al., 1975) it has

TABLE 1

QLS ANALYSIS OF THE DISPERSED DROPLETS IN O/W EMULSIONS (10% w/w PRISTANE, 1% w/w TWEEN 85 AND 89% w/w WATER) PREPARED BY SIMPLE MIXING FOLLOWED BY ULTRASOUND (20 kHz) BY A STANDARDIZED SONIFICATION PROCEDURE AT VARYING SOUND INTENSITIES AND TREATMENT TIMES

(A) Measurements performed at constant delay times and results calculated by a linear fit procedure (Malvern Data Processor). Mean droplet diameters (in $\mu$m) and polydispersity factors (in parentheses).

| Emulsification time | Sound intensity | | | |
|---|---|---|---|---|
| | 130 W | 175 W | 190 W | 200 W |
| 0.5 min | – | – | 0.47 | – |
| | – | – | (0.46) | – |
| 1 min | – | 0.44 | 0.37 | 0.31 |
| | – | (0.40) | (0.28) | (0.22) |
| 5 min | 0.47 | 0.27 | 0.26 | 0.25 |
| | (0.39) | (0.18) | (0.15) | (0.15) |
| 20 min | – | – | 0.23 | 0.24 |
| | – | – | (0.11) | (0.15) |

(B) Mean droplet diameters calculated by extrapolation to delay time 0 (see Appendix)

| *(a) Sound intensity: 190 W* | | | | |
|---|---|---|---|---|
| Treatment time (min) | 1/2 | 1 | 5 | 20 |
| mean diameter ($\mu$m) | 0.32 | 0.29 | 0.23 | 0.20 |
| *(b) Treatment time: 5 min* | | | | |
| Sound intensity (W) | 130 | 175 | 190 | 200 |
| mean diameter ($\mu$m) | 0.32 | 0.24 | 0.23 | 0.22 |

been confirmed that the mean particle sizes obtained from QLS analysis are the z-average particle sizes. According to the definitions of the two parameters, the z-average diameter is larger than the volume-weighted mean diameter in a polydisperse system.

This discrepancy in mean diameters registered by the Coulter Counter and by QLS measurements is possibly due to errors in both methods of analysis. In QLS analysis very small parts of the total sample volume are measured where the probability of a larger droplet occurring is reduced. This implies that QLS measurements mostly give information of the smaller droplets of emulsion systems. The larger droplets of the measured emulsion systems are subject to a Stokes sedimentation that can become significant in comparison with Brownian diffusion rates and may be registered in the time dependence of the autocorrelation function (this will bias calculations of droplet sizes as these are based on the assumption that droplet movements are pure Brownian). The occurrence of a big droplet may also have the

TABLE 2

COULTER COUNTER ANALYSIS OF THE DISPERSED DROPLETS IN O/W EMULSIONS (10% w/w PRISTANE, 1% w/w TWEEN 85 AND 89% w/w WATER) PREPARED BY ULTRASOUND (20 kHz) AT (a) VARYING SOUND INTENSITIES (TREATMENT TIME: 5 MIN) AND (b) VARYING TREATMENT TIMES (SOUND INTENSITY: 190 W).

$\bar{d}_{reg}$ and $v_{reg}$ are the volume-weighted mean diameter and volume fraction of dispersed droplets registered by the Coulter Counter, respectively. $\bar{d}$ denotes the estimated volume weighted mean diameter of the droplets in the sample.

(a)

| Sound intensity (W) | 130 | 175 | 190 | 200 |
|---|---|---|---|---|
| $v_{reg}$ (in %) | 60 | 18 | 11 | 8 |
| $\bar{d}_{reg}$ ($\mu$m) | 2.7 | 2.4 | 1.7 | 1.9 |
| $\bar{d}$ ($\mu$m) | 1.6–1.9 | 0.4–0.9 | 0.2–0.7 | 0.2–0.7 |

(b)

| Treatment time (min) | 0.5 | 1 | 5 | 20 |
|---|---|---|---|---|
| $v_{reg}$ (in %) | 65 | 44 | 11 | 6 |
| $\bar{d}_{reg}$ ($\mu$m) | 3.6 | 3.3 | 1.7 | 3.3 |
| $\bar{d}$ ($\mu$m) | 2.3–2.6 | 1.5–1.8 | 0.2–0.7 | 0.2–0.8 |

effect that the measurement concerned is discarded because of the possibility of confusion with a dust particle.

The droplet diameters do not fulfill the requirement of being smaller than 1/K (in this case about 50 nm) but this is as mentioned before considerered less critical in these measurements, as the droplets are nearly spherical.

## Conclusions

From the results in this and our previous paper (Eberth and Merry, 1983), it can be concluded that by ultrasonic preparation of emulsions, droplet size distributions are obtained that are broad at the onset of emulsification and become more narrowly distributed as the treatment time and/or the sound intensity increases. The mean droplet diameter decreases to a minimum droplet size, which for the investigated system is about 0.2 $\mu$m. This is close to the generally defined lower limit for emulsion droplets.

As the droplet sizes in emulsions affect the absorption and elimination of emulsion droplets and incorporated drugs (e.g. Laval-Jeantet et al., 1982; Kubis, 1980) the use of ultrasound in production of pharmaceutical emulsions should not be uncritical; the droplet size data of the emulsified product ought to be determined and considered in relation to the application of the drug.

By combining Coulter Counter measurements and/or light microscopy measurements (covering the size range of droplet diameters larger than about 1 $\mu$m) with

QLS measurements a more detailed picture of droplet size distributions that can occur in ultrasonically prepared pharmaceutical emulsions is obtained.

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## Appendix

For emulsions with broad particle size distributions computation of mean droplet diameters from QLS measurements has been done in several ways in this work, varying the number of data points of the autocorrelation functions (corresponding to a variation of maximum delay times between 1.2 ms and 6 ms) and the polynomial degree of polynomials fitted to the normalized autocorrelation functions, according to the method of Brown et al. (1975).

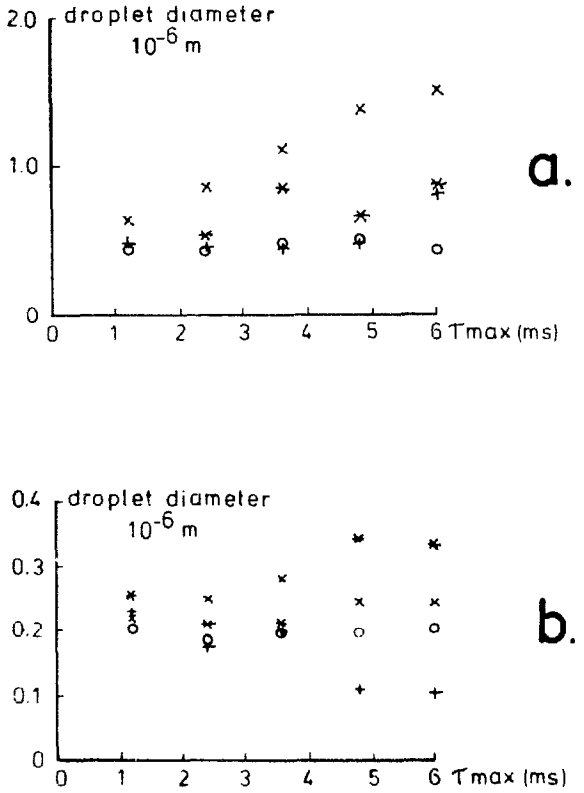


Fig. 2. QLS analysis of the mean droplet diameter in o/w emulsions (10% w/w pristane, 1% TWEEN 85 and 89% w/w water) prepared by simple mixing followed by ultrasound (20 kHz) at intensity level 190 W for: (a) 0.5 min and (b) 20 min, respectively. Values calculated by variation of polynomial degree and total delay time. ×, *, 0 and + indicate 1st–4th degree fits (cf. Appendix).

Fig. 2a illustrates the computations applied to an emulsion prepared by ultrasound at intensity 190 W for 0.5 min. It is seen that there is a decrease in the computed mean diameters with a decrease in the applied maximum delay time and with an increase in the applied polynomial degree. Fig. 2a also shows that if the polynomial degree is sufficiently large there is no dependency on the choice of delay time, and that if the applied maximum delay time is sufficiently small there is no dependency on the choice of polynomial degree. This implies that it may be possible to eliminate a dependency between calculated mean diameter and polynomial degree or applied maximum delay time by either increasing the polynomial degree until a decrease in mean size is no longer detectable or by calculating mean diameters at varying delay times and extrapolating to delay time zero ($\tau_{max} \rightarrow 0$).

Another emulsion prepared by ultrasound at intensity 190 W for 20 min was analyzed by the same method. Fig. 2b shows that for this emulsion system, which has a smaller mean droplet size and a narrower droplet size distribution, the calculated mean droplet diameters are independent of the choice of polynomial degree and maximum delay time.

As a consequence of these experiments, mean droplet sizes of the emulsions investigated in this study were calculated by a linear fit procedure (Malvern Data Processor) and were recalculated by extrapolation ($\tau_{max} \rightarrow 0$) if a dependency on the applied delay time was observed or suspected.

It should be realized that the method described above does not give the true z-average of the particle diameters in a polydisperse sample, as the method increases the weighting factors of the smaller particles. The method may minimize systematic errors but as a drawback there is a corresponding increase in random errors. The application should therefore be carefully considered in each particular case in relation to the physical meaning of the measurements.

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