J. Pharm. Pharmacol. 1984, 36: 73–76
Received September 14, 1983

Particle size analysis of microcapsules

NATALIE J. MORRIS AND B. WARBURTON*

The School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, U.K.

To standardize the preparation of three-walled w/o/w microcapsules it was necessary to assess their particle size distribution, since they occur as both unicored and multicored types. The log-normal law, reported to be obeyed by many particulate systems, including microcapsules, was not applicable to the size data. A curve-fitting computer program using least squares minimization was used to assess the size distribution data. The models tested were the unimodal and bimodal log-normal distributions, the bimodal form being the most appropriate. Using the equations to the curves of best fit, the modal size and standard deviation of each population were estimated, and the relative percentages of unicored and multicored microcapsules could be deduced from an analysis of the bimodal curves in which they were represented as the sum of two constituent unimodal distributions.

There are various ways of producing microcapsules including coacervation, spray-drying and interfacial polymerization (Gutcho 1979). We have been working with a method (Warburton 1981) which produces three-walled w/o/w microcapsules with aqueous cores. To characterize the microcapsules, the effects of changes in manufacturing procedure were examined. One of the physical properties of interest was the size distribution since it affects the release pattern of microcapsules.

Size distribution data are most commonly presented as log-probability plots of diameter versus the cumulative volume percent oversize, which give straight line plots if the distribution is log-normal (Coulter Handbook 1966; Smith & Jordan 1964). The log-normal distribution can be summarized using the geometric mean and the geometric standard deviation. However, the size distributions of these three-walled w/o/w microcapsules did not give straight lines when plotted on log-probability paper, nor could the size data be represented by the Rosin-Rammler law (Herdan 1960).

The distribution may be compared more easily if expressed as an appropriate mathematical model abstracting the major essentials and representing them in as simple a form as possible. To fit the size data to such a model involves curve-fitting using a least squares minimization procedure. The optimum fit can be defined as that which makes the sum of the squares of the residuals a minimum (Lanczos 1967).

We report that curve fitting can be used to model size-frequency plots with distribution equations. In this, size distributions that are not log-normal may be defined.

* Correspondence.

METHODS

Preparation of microcapsules

Materials. Acacia (Macarthys, Essex); crystal violet, di-n-butyl phthalate (BDH Chemicals Ltd, Poole); ethyl acetate (Hopkins and Williams, Essex); ethyl cellulose type T10 (Hercules, Inc., Wilmington, USA); water, double distilled from an all-glass still.

Method

The three-walled w/o/w microcapsules were formed by a multiple emulsion technique (Warburton 1981). Although the method of manufacture has been described in some detail by Morris & Warburton (1982), the conditions under which the present microcapsules were made are defined in order to discuss their particle size characteristics.

The first step involved the preparation of a water-in-oil (w/o) emulsion by dispersion of one part of an aqueous acacia solution (5% w/v) in one part of a 4% w/v solution of ethyl cellulose in ethyl acetate. A Silverson model 407 laboratory mixer-emulsifier was used at 8600 rev min^{-1} (the mixer was fitted with an axial flow head, internal radius 12·79 mm with a shear space of 0·115 mm for a depth of 11·94 mm).

For the second step, one part of the w/o emulsion was dispersed in one further part of 5% w/v acacia solution to give a multiple emulsion w/o/w. Microcapsules were produced when the solvent, ethyl acetate, was removed from the multiple emulsion droplets by dialysis. When a suspension of the

microcapsules was allowed to air-dry, they could be obtained as a powder.

In separate experiments, the ethyl cellulose was also plasticized with 10 and 11·5% w/w dibutyl phthalate. It was intended that the content of plasticizer should be 10% w/w throughout. However, the first batch contained an equivalent of 11·5% w/w. This is because it was not originally realized that the standard method of expressing plasticizer content is w/w. The microcapsules with 10% w/w di-n-butyl phthalate contained crystal violet.

Determination of microcapsule size

Size distributions were obtained using the Coulter Counter, model B for capsules prepared with ethyl cellulose plasticized with dibutyl phthalate and containing crystal violet, and an optical microscope for capsules containing ethyl cellulose plasticized with dibutyl phthalate but no dye. For the Coulter Counter, microcapsules were dispersed in Isoton II (Coulter Electronics Ltd) which consists of buffered 0·9% w/v sodium chloride solution. It is possible to set a limiting lower diameter on the Counter by adjusting the sensitivity, and the Counter then records the number of microcapsules with diameters above this limiting diameter. As the diameters measured are equivalent volume diameters (the diameter of a sphere with the same volume as the particle) and the microcapsules are spherical, the volume diameters of the Counter are the same as the diameters of hydrated microcapsules in 0·9% NaCl. The raw data were converted from a number distribution to a volume distribution.

When the optical microscope was used (Olympus BH), fields were photographed and a total of 586 microcapsules sized. The number of counts per field varied from 9–51 giving a mean of 32·5 microcapsules per field and a standard deviation of 12.04. The counts were multiplied by the cube of the projected diameters to obtain a volume distribution.

Size distribution models

If the Gaussian distribution is drawn on the same axes as those for size-frequency plots, the familiar bell-shaped curve results. The equation for the normal distribution is:

$$y = H \exp^{-[(x-\bar{d})^2]/(2\delta^2)} \quad (1)$$

When related to size distributions, y represents the frequency of occurrence of particles with diameter x whilst $\bar{d}$, δ and H are constants for any one distribution, with $\bar{d}$ and δ representing the modal diameter and the standard deviation respectively.

A Gaussian distribution law implies the presence of particles with negative diameters and so is rarely used for particulate purposes.

To change from normal to log-normal distributions, logarithms are taken of the diameters x and $\bar{d}$, the modal diameter, and of the standard deviation, δ. H is a scaling factor marking the position of the mode on the y axis. The resulting unimodal equation is:

$$y = H.\exp^{-[(\log x - \log \bar{d})^2]/(2 \log^2 \delta)} \quad (2)$$

The expression inside the exponential is of $\log^2$ over $\log^2$, so either natural logarithms of those to base 10 may be employed. The equation for bimodal distribution is found by summing the equations for two unimodal distributions.

$$y = H_1.\exp^{-[(\log x - \log \bar{d}_1)^2]/(2 \log^2 \delta_1)} + H_2 \exp^{-[(\log x - \log \bar{d}_2)^2]/(2. \log^2 \delta_2)}. \quad (3)$$

RESULTS AND DISCUSSION

Fig. 1 shows that as a result of the second emulsification in the manufacture of w/o/w microcapsules, multiple emulsion droplets were formed which contained a varied number of internal w/o droplets from the first emulsification. Both unicored and multicored types were present. Although as a mixture, these two types of microcapsule did not obey the log-normal law, it was thought that they might do so

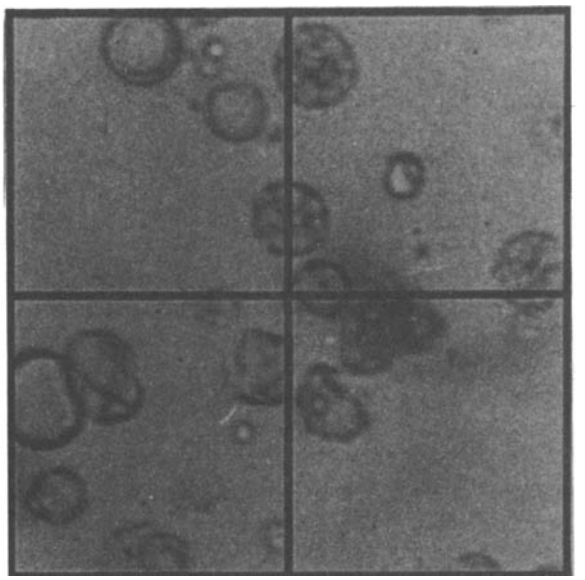

FIG. 1. Optical micrograph of microcapsules.

individually. Davis et al (1976) reported that the size distributions of their multiple emulsion systems were bimodal, thereby lending support to our findings of bimodality, since our microcapsules were formed from multiple emulsions.

The data for the crystal violet microcapsules, plasticized with 10% w/w dibutyl phthalate and sized using the Coulter Counter did not yield a straight line when plotted on log-probability axes (Fig. 2),

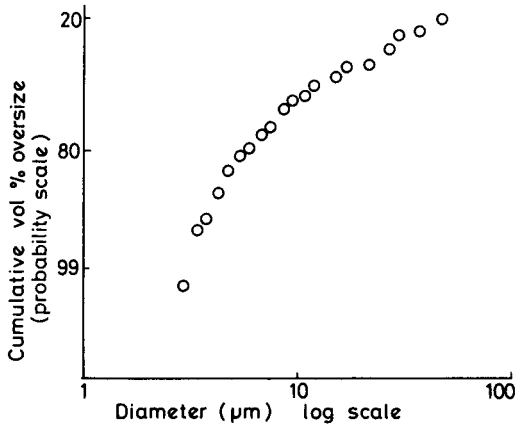

FIG. 2. Log-probability plot for crystal violet microcapsules with 10% w/w dibutyl phthalate.

confirming that the distribution did not obey the simple unimodal log-normal law. The size-frequency plot for these data (Fig. 3) appeared to be a skewed distribution with two peaks. The 'empty' microcapsules plasticized with 11·5% w/w dibutyl phthalate counted under the optical microscope also exhibited skewed bimodality. Again it was found that the size data could be represented by a bimodal log-normal distribution (Fig. 4). When the counts for the unicored and muticored microcapsules were separately fitted to unimodal log-normal distributions it appeared that the bimodality in the total count could

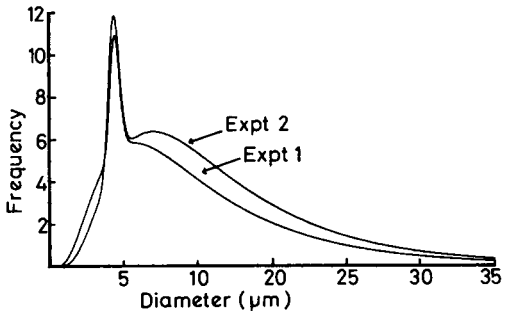

FIG. 3. Size-frequency plot for crystal violet microcapsules with 10% w/w dibutyl phthalate.

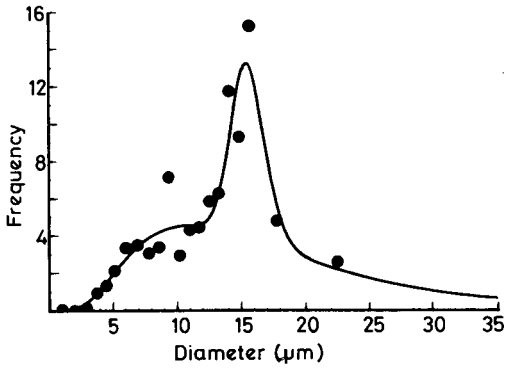

FIG. 4. Bimodal log-normal distribution for crystal violet microcapsules with 10% w/w dibutyl phthalate, experiments 1 and 2.

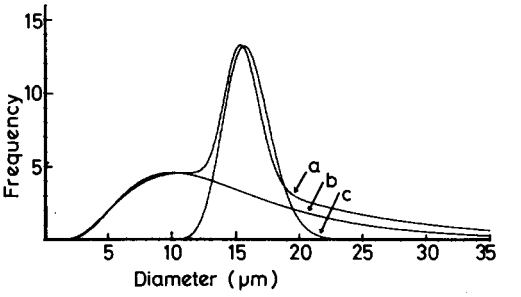

FIG. 5. Size data for microcapsules with 11·5% w/w dibutyl phthalate fitted to a bimodal log-normal distribution.

be related in terms of the size distributions for these two types of microcapsule. Fig. 5 shows that the first modal diameter was due to a population of unicored microcapsules and the second modal diameter to multicored microcapsules, which were present in the ratio 74 : 26 by volume respectively.

The estimated modal diameters and standard deviations for the three curves in Fig. 5 are shown in Table 1.

Size distributions from the microscope did not agree with those from the Coulter counter because the environmental conditions of the two methods of

Table 1. Estimates of the modal diameters and standard deviations for microcapsule size data fitted to log-normal distributions. The microcapsules were plasticized with 11·5% w/w dibutyl phthalate.

	Microcapsules		
	Unicored	Multicored	Total
Modal diameter 1 (μm)	10·03	—	10·89
Standard deviation 1 (μm)	1·70	—	1·82
Modal diameter 2 (μm)	—	15·68	15·42
Standard deviation 2 (μm)	—	1·12	1·09

particle sizing were different. In the Coulter experiments, the charge centres in the acacia molecules were shielded by the sodium and chloride ions allowing the acacia molecules, and hence the microcapsules, to be small and relaxed. In the optical experiments the acacia molecules were in 40% v/v aqueous glycerol which has a lower dielectric constant than the 0·9% w/v sodium chloride solution and therefore allowed the acacia molecules, and hence the microcapsule, to expand. The amount of size change would have depended on both the rheological surface compliance of the acacia film and the change in force between the charge centres in the acacia molecules.

This explanation does not altogether account for the difference in size between the microcapsules shown here, because the different formulations play a part. The microcapsules with 10% w/w plasticizer, examined using the Coulter Counter, have crystal violet present. This is a positively charged molecule, which will shield the negative charges on the acacia molecules, which themselves become tightly coiled and a solution of tightly coiled molecules has a lower viscosity than the corresponding solution with extended molecules. When such a solution is emulsified under identical conditions as that with extended molecules, smaller droplets are formed than with the more viscous solution. In other words, smaller droplet sizes would result when crystal violet is present. This has been confirmed by comparison of size data from the Coulter Counter for microcapsules with the same amount of plasticizer, one without and the other with crystal violet.

It has therefore been demonstrated that populations of both unicored and multicored three-walled microcapsules may be resolved into two separate size distributions each obeying the log normal size distribution.

Hence a simple set of six parameters H_1, $\bar{d}_1$, δ_1 and H_2, $\bar{d}_2$, δ_2 will characterize the total population and can be used to correlate the effects of change in the manufacturing process.

Acknowledgements

The authors would like to thank the following from the School of Pharmacy for their help with the present work. Dr D. G. Peacock and Mr S. W. Moore of the computer Unit, and Dr A. A. Deshmukh for general comments. N. J. Morris wishes to thank S.E.R.C. for financial support.

REFERENCES

Coulter Counter Handbook (1966) Coulter Electronics Ltd., Luton, Beds.

Davis, S. S., Purewal, T. S., Burbage. A. S. (1976) J. Pharm. Pharmacol. 28: 60P

Gutcho, M. H. (1979) Microcapsules and other capsules. Advances since 1975. Noyes Data Corporation, Park Ridge, N.J.

Herdan, G. (1960) Small Particle Statistics, Butterworth, London, pp 86–88

Lanczos, C. (1967) Applied Analysis. Pitman, London pp 344–346

Morris, N. J., Warburton, B. (1982) J. Pharm. Pharmacol. 34: 24P

Smith, J. E., Jordan, M. L. (1964) J. Colloid Sci. 19: 549–559

Warburton, B. (1981) G.B. Patent 2,009,698