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# Entrapment of bioactive compounds within native albumin beads: IV. Characterization of drug release from polydisperse systems

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## Summary

A heuristic approach is used to identify the mathematical model best describing the release of a drug from a single particle in a polydisperse system. The method uses only experimental measures of particle size distribution and total release from the dispersion as a function of time. The routine is based on the observation that in the first 40% of total drug release the volume-surface diameter of the distribution, $d_{vs}$, can be used as a single diameter representing the entire population to estimate model dependant release parameters. This property was tested in four different single particle release models having distributions of varying standard deviation; narrow, intermediate, and wide. In its application to drug imbedded in a microsphere, the particle size distribution of the system was measured and the volume-surface diameter determined. Release from the population was measured under sink conditions. The first 40% was fit (SAS) using $d_{vs}$ and assuming different mechanisms to be operating; release parameters characteristic of the assumed single particle mechanism were thus generated. Since only one of the assumed mechanisms should be operating, when the parameter estimates for each are used over a larger time frame (beyond 40%) in conjunction with the effects expected for individual particles of known size via measured distribution, the best single particle model should be that one giving the best overall fit. For norgestrel in a serum albumin microsphere, the single particle model best describing release was matrix diffusion of drug from a particle surrounded by a hydrodynamic layer.

## Introduction

Solid microspheres produced by mild chemical crosslinking of serum albumin were first introduced by Lee et al. (1981) as a parenteral delivery system that could provide a sustained release of drug having the potential for organ or tissue targeting. The method of manufacture is simple. It involves dissolving or dispersing solid drug in an aqueous solution of serum albumin and adding the crosslinking agent glutaraldehyde. The reaction between the dialdehyde and the ϵ-amino groups of lysine residues on albumin begins spontaneously but the rate can be controlled so that the aqueous dispersion can be emulsified in a stirred oil before oligomerization occurs to a significant extent (Sheu et al., 1986). The reaction

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then is allowed to reach completion (10 min) while maintaining a dispersion. The product resulting consists of solid particles than can be collected and washed. The size of the microsphere produced is determined by the size of the aqeous droplet in the initially formed emulsion and can be very small (3 $\mu$m or less) or as large as may be desired. After drying powder-like beads result with drug entrapped. The microspheres are water dispersible, biodegradable, and biocompatible. An in vitro controllable release can be engineered into the system by manipulating several formulation and process variables (Sheu and Sokoloski, 1986). Those variables affecting the size of the emulsion droplet are particularly significant. These are: the dimensions of the reaction container and stirrer, the rate of stirring, the density and viscosity of the internal aqueous and external oil phases, and the interfacial tension between phases. Other controllable variables affecting release are drug loading and the extent of crosslinking. Release can also be modulated by entrapping preformed beads containing drug inside larger beads.

Since an emulsion technique is used the microspheres obtained consist of a distribution of sizes. It has to be appreciated that the rate of drug release into a medium from a sample consisting of a distribution of different sized microspheres is not only dependent on the release mechanism for a single particle but on how the particles are distributed as well (Dappert and Thies, 1978). This should be true for any multiparticulate system whether it be pure solid drug (e.g. dissolution), microcapsules, a microemulsion, or where drug is embedded in a solid matrix. If the delivery system is to be manipulated to engineer a desired release pattern, then both the single particle mechanism and the distribution of the particles have to be considered. The distribution of particles is easily measured and easily controlled. However, deducing the release mechanism for the single particle is not trivial when the only data available are those of release from a population (Gross et al., 1986). This communication discusses a procedure through which it may be possible to identify a workable mechanism for the single particle from experimental population release data, providing the size distribution is known.

## Methods

Bovine serum albumin microbeads having different sizes, drug loading, and extent of crosslinking were prepared as described in a previous paper (Sheu and Sokoloski, 1986). The microbeads produced contained entrapped l-norgestrel. Holding all other process variables constant and changing the interfacial tension and viscosity of the external phase permitted production of different sized beads. The extent of crosslinking is controlled using different ratios of glutaraldehyde to albumin and the amount of water insoluble drug embedded can be controlled by simply using different amounts of drug initially. Table 1 lists the experimental conditions employed to yield the several bead preparations utilized in the study.

Size distributions in the several microbead preparations were determined in saline solution using an Elzone Particle Size Analyzer (Model 112 LSD/ADC 80XY, Particle Data Inc.) and release studies were conducted under sink conditions as described in another study using 400 ml of a release medium consisting of a 40% polyethylene glycol-300 solution in phosphate buffer (pH 7.5, 0.1 M) held in a 500 ml jacketed beaker at $37 \pm 0.1°C$ (Sheu and Sokoloski, 1986). 2 ml of filtered (0.45 $\mu$m) medium were withdrawn at appropriate time intervals and the concentration of l-norgestrel was determined spectrophotometrically by comparing absorbance at a $\lambda_{max}$ of 246 nm to standard samples. 2 ml of fresh medium were returned to the beaker to maintain a constant volume. The Statistic Analysis System (SAS) and an in-house computer (IBM VM/SP 4361) were used to fit release data to various equations describing several potential mechanisms of release.

Part of the studies utilized simulated release data that were generated in the following way. The fraction of drug released ($m'$) from a single spherical particle was assumed to follow Eqn 1, 2, 3, or 4 which represent respectively a sphere dissolution mechanism, Eqn 1 (Martin et al., 1983); a mechanism where drug is dispersed in an insoluble matrix without a surrounding hydrodynamic layer, Eqn 2 (Higuchi, 1963); drug dispersed with a hydrodynamic layer, Eqn 3 (Roseman and Cardarelli, 1980); and Eqn 4 a mechanism where

drug is dissolved in the matrix (Jost, 1968).

$$m' = 1 - \left(1 - \frac{kt}{r_0}\right)^3 \quad (1)$$

$$3 - (2m') - 3(1 - m')^{2/3} + \frac{(A_1)(m')}{r_0} = \frac{At}{r_0^2} \quad (2)$$

$$3 - (2m') - 3(1 - m')^{2/3} + \frac{(A_1)(m')}{r_0} = \frac{A't}{r_0^2} \quad (3)$$

$$m' = 1 - \frac{6}{\pi^2} \cdot \sum_{\nu=1}^{\infty} \frac{1}{\nu^2} \cdot \exp\frac{-\nu^2 Bt}{r_0^2} \quad (4)$$

$k$ is a dissolution rate constant defined by Eqn 5, $A$ or $A'$ is a constant given by Eqn 6, and $B$ is the exponential diffusion constant defined by Eqn 7.

In Eqn 3 constant $A_1$, taking into account a hydrodynamic resistance layer, is defined by Eqn 8:

$$k = \frac{2DC_s}{h \times \rho} \quad (5)$$

$$A = \frac{6DC_s}{\tau \rho L} \quad (6)$$

$$B = \pi^2 D \quad (7)$$

$$A_1 = \frac{2D_s \kappa h_a}{D_a} \quad (8)$$

In Eqns 1–8, $D$ is the diffusion coefficient, $C_s$ is the solubility of the drug in the microsphere's matrix or release medium, $t$ is the time, $r_0$ is the radius of the microbead, $\tau$ is the tortuosity, $\rho$ is the density of the drug in the matrix, $L$ is the total amount of drug/volume of bead, $h$ is the thickness of the hydrodynamic layer, $\kappa$ is the matrix-medium partition coefficient of the drug,

TABLE 1

*Experimental conditions used in the manufacture of crosslinked serum albumin microspheres containing norgestrel and the results of release studies and particle size analysis* [a]

| Study | Glutaral. concn. (% vol.) | Drug loading (mg/ml) | External phase oleic acid/light mineral oil (g/g) | Volume-surface diameter (μm) | Fitted constants | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | $A$ | $A'$ ($A_1$) | $k$ | $B$ |
| Particle size | | | | | | | | |
| A | 1.0 | 50 | 20.0/0.0 | 17.1 | 0.1229 | 0.3867(2.27) | 0.0869 | 0.2886 |
| B | 1.0 | 50 | 2.0/18.0 | 26.1 | 0.2037 | 0.7308(3.51) | 0.1110 | 0.4764 |
| C | 1.0 | 50 | 0.5/19.5 | 50.2 | 0.4411 | 1.2933(5.89) | 0.1088 | 0.9716 |
| D | 1.0 | 50 | 0.1/19.9 | 97.2 | 0.6032 | 1.1602(5.14) | 0.0809 | 1.3890 |
| E | 1.0 | 50 | 0.0/20.0 | 147.4 | 0.8828 | 1.5364(6.92) | 0.0713 | 2.0452 |
| Drug loading | | | | | | | | |
| A | 1.0 | 20 | 0.0/20.0 [b] | 9.7 | 0.0504 | 0.1630(1.26) | 0.0669 | 0.1198 |
| B | 1.0 | 50 | 0.0/20.0 [b] | 11.5 | 0.0414 | 0.1467(1.54) | 0.0503 | 0.0978 |
| C | 1.0 | 100 | 0.0/20.0 [b] | 13.1 | 0.0552 | 0.1838(1.86) | 0.0518 | 0.1260 |
| Extent of crosslinking | | | | | | | | |
| A | 1.0 | 50 | 0.0/20.0 [b] | 8.1 | 0.0370 | 0.1173(1.05) | 0.0574 | 0.0879 |
| B | 2.0 | 50 | 0.0/20.0 [b] | 9.9 | 0.0287 | 0.0905(1.23) | 0.0374 | 0.0660 |
| C | 3.0 | 50 | 0.0/20.0 [b] | 10.8 | 0.0269 | 0.0816(1.39) | 0.0297 | 0.0600 |
| D | 4.0 | 50 | 0.0/20.0 [b] | 10.3 | 0.0247 | 0.0745(1.32) | 0.0285 | 0.0550 |

[a] The concentration of bovine serum albumin used in all studies was 200 mg/ml phosphate buffer, pH 7.4.
[b] Contains 20% w/w of a 11% Tween 80/89% Span 80 mixture.

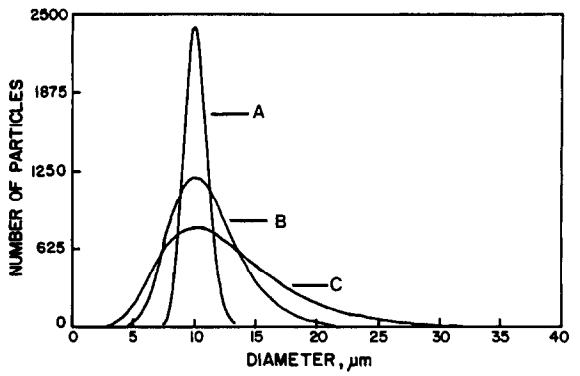


Fig. 1. Computer-generated log-normal distributions about a geometric mean of 10 $\mu$m at three different standard deviations. The standard deviations used are: A 0.04139; B, 0.1139; C, 0.1761.

and $\nu$ is an integer; $\nu = 1$–15 was used in the simulated data.

A population of $10^5$ particles was assumed and it was further assumed that the particles were either normally distributed or log-normally distributed. A constant geometric mean diameter of 10 $\mu$m was used at three standard deviations; for the normally distributed particles $\sigma = 1$, 2, or 3 was used and for the log-normal case, the corresponding standard deviations used were 0.0414, 0.1139, and 0.1761. The hypothetical log-normal distributions are illustrated in Fig. 1 representing a narrow, intermediate, and broad distribution. The three normal distributions used represent similar relative spreads in sizes.

Release from the several distributions of $10^5$ particles was calculated assuming that all single particles in the distribution had a release that followed either Eqn 1, 2, 3, or 4 with values of $k$, $A$, $A'$, $A_1$, or $B$ constant. Table 2 lists the constants used; the values were chosen arbitrarily simply to provide convenient times for drug release. Total fraction of drug released at a particular time for each assumed distribution was obtained by simple summing of individual particle releases and is similar to the method used by Cartensen and Musa (1972). 100, 200 and 300 values for $r_0$ were used at each of the three standard deviations; narrow to broad, respectively. The procedure essentially involved the division of the distribution curves (Fig. 1) into 100, 200, or 300 segments where an average radius $r_0$ is used to represent the size of the particles in each segment. The number of particles in each segment was calculated and the fraction of drug ($f$) in each segment of size $r_0$ was calculated by dividing the volume ($\frac{4}{3}\pi r_0^3$) of beads in the segment by the total volume. The drug was assumed to be evenly distributed in and among the beads. Thus, as an example, the total fraction of drug released at time $t$ where the single particle mechanism is described by Eqn 1 would be obtained by summing individual releases as given in Eqn 9 where 100/200/300

TABLE 2

*Constants used to generate population release data where the mechanism is dissolution (Eqn 1), drug dispersed (Eqn 2 or 3), and diffusion (Eqn 4) and the statistical diameters calculated for six particle size distributions used*

| $\sigma$ | Normal distribution | | | Log-normal distribution | | |
|---|---|---|---|---|---|---|
| | 1.0 | 2.0 | 3.0 | 0.0414 | 0.1139 | 0.1761 |
| $k$ | 0.02 | | | 0.02 | | |
| $A$ | 0.05 | | | 0.05 | | |
| $A'$ | 0.05 | | | 0.05 | | |
| $A_1$ | 1.00 | | | 1.00 | | |
| $B$ | 0.20 | | | 0.20 | | |
| $d_{ln}$ | 10.00 | 10.00 | 10.00 | 10.04 | 10.34 | 10.8 |
| $d_{sn}$ | 10.05 | 10.19 | 10.43 | 10.09 | 10.69 | 11.7 |
| $d_{vn}$ | 10.10 | 10.38 | 10.81 | 10.13 | 11.05 | 12.6 |
| $d_{vs}$ | 10.19 | 10.75 | 11.61 | 10.22 | 11.80 | 14.7 |
| $d_{wm}$ | 10.29 | 11.09 | 12.26 | 10.31 | 12.57 | 16.9 |

$r_0$ values over the population range of $\mu \pm 3\sigma$ are used.

$$m'_{\text{total}} = \sum^{r_0} \left[1 - \left(1 - \frac{kt}{r_0}\right)\right] f \qquad (9)$$

## Results and Discussion

It appeared that the identification of an equation representing a particular single particle release mechanism was possible if a particle size analysis was available and the drug release profile for the population was known. The reason for this is as follows. Particle sizes and their distribution are easily measured. An instrument such as the Elzone Particle Size Analyzer utilizes 128 channels and thus gives the frequency of occurrence of 128 size levels or values for $r_0$. If it is assumed that drug embedded in the population is uniform throughout, then the fraction of the total drug that will be found in particles having a radius of $r_0$ would be equal to the volume fraction $f$ of those particles. The volume fraction can easily be calculated as described under Methods. The task then would be to find which of the possible single particle equations (Eqns 1–4), when summed all all sizes in the distribution, best described the experimentally measured drug release-time profile for the population.

Fitting data that use Eqns 1–4 taking into account 128 values for $r_0$ for each time $t$ was not convenient because of the time needed to reach convergence, especially for an equation such as Eqn 4. However, if a single statistical diameter can be identified that adequately represents the kinetic behavior of the entire population, the fitting of data to each of the four possible equations would be greatly facilitated. In the search for such a diameter it seemed that using simulated release data for drug from a system of known single particle kinetic dependence and a known distribution would best establish the applicability and properties of statistical diameters tested. It was possible to generate hypothetical population re-

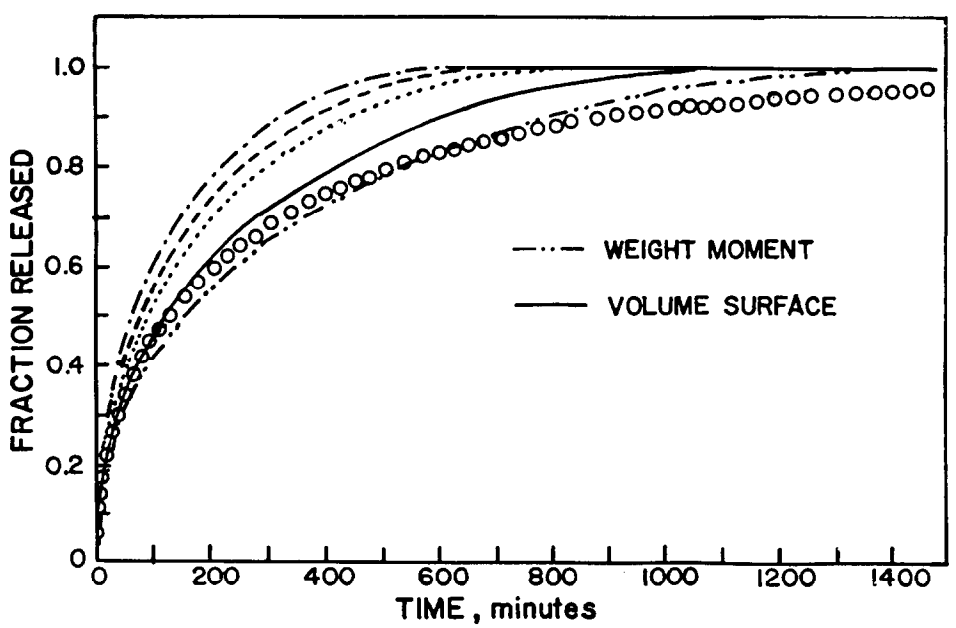


Fig. 2. A plot of fraction of drug released vs time from a log-normal distribution of particles with a geometric diameter of 10 $\mu$m and a standard deviation of 0.1139; open circles give the theoretical release assuming a mechanism given by Eqn 2. The lines represent the release calculated using five statistical mean diameters: $d_{\text{ln}}$ (·–·–·), $d_{\text{sn}}$ (– – – – –), $d_{\text{vn}}$ (· · · · · ·), $d_{\text{vs}}$ (———), $d_{\text{wm}}$ (–· · –· · –) (see text for definition of statistical diameters).

leased data for systems having $10^5$ particles with a defined single particle release (Eqns 1–4) and a defined particle size distribution (normal or log-normal). Typical results are shown as the symbols in Fig. 2 for a presumed Eqn 2 release (drug dispersed in an insoluble matrix) for a log-normal distribution having an intermediate standard deviation.

For a particular size distribution where $n$ is the number of particles of diameter $d$, five measures of mean diameter are possible (Martin et al., 1983).

$$\text{Length-number, } d_{ln} = \frac{\sum nd}{\sum n}$$

$$\text{Surface-number, } d_{sn} = \left(\frac{\sum nd^2}{\sum n}\right)^{1/2}$$

$$\text{Volume-number, } d_{vn} = \left(\frac{\sum nd^3}{\sum n}\right)^{1/3}$$

$$\text{Volume-surface, } d_{vs} = \frac{\sum nd^3}{\sum nd^2}$$

$$\text{Weight-moment, } d_{wm} = \frac{\sum nd^4}{\sum nd^3}$$

Table 2 lists these statistical diameters for the various normal and log-normal distributions assumed. Using these several mean radii as a single value for $r_0$ in Eqns 1–4 with the defined rate constants it was possible to generate $m'$ vs $t$ data for each distribution and mechanism. The five lines in Fig. 2 represent the results obtained using each of the five statistical diameters in Eqn 2 for a log-normal distribution of particles of intermediate standard deviation. The trends seen in Fig. 2 are typical of the results found for each assumed mechanism and distribution. At the smaller standard deviation all five lines lie close to the expected release. At the higher standard deviation, the trends seen in Fig. 3 are more prominent.

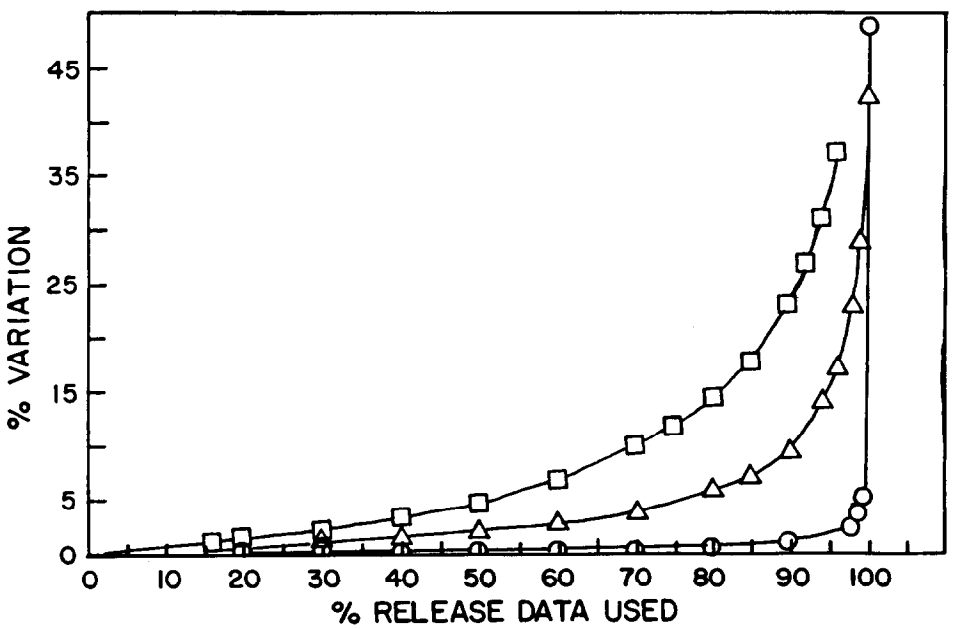


Fig. 3. Relationship between the error expected in estimating the constant $A$ in Eqn 2 at various percentages of initial data used. The true value of $A$ was assumed to be 0.05. An expected release was calculated assuming $10^5$ particles that were log-normally distributed with $\sigma = 0.04139$ (circles), 0.1139 (triangles), and 0.1761 (squares). SAS fitting was then applied using a single $r_0$ term, $d_{vs}$, in Eqn 2 to estimate $A$ at various initial percentages of release data.

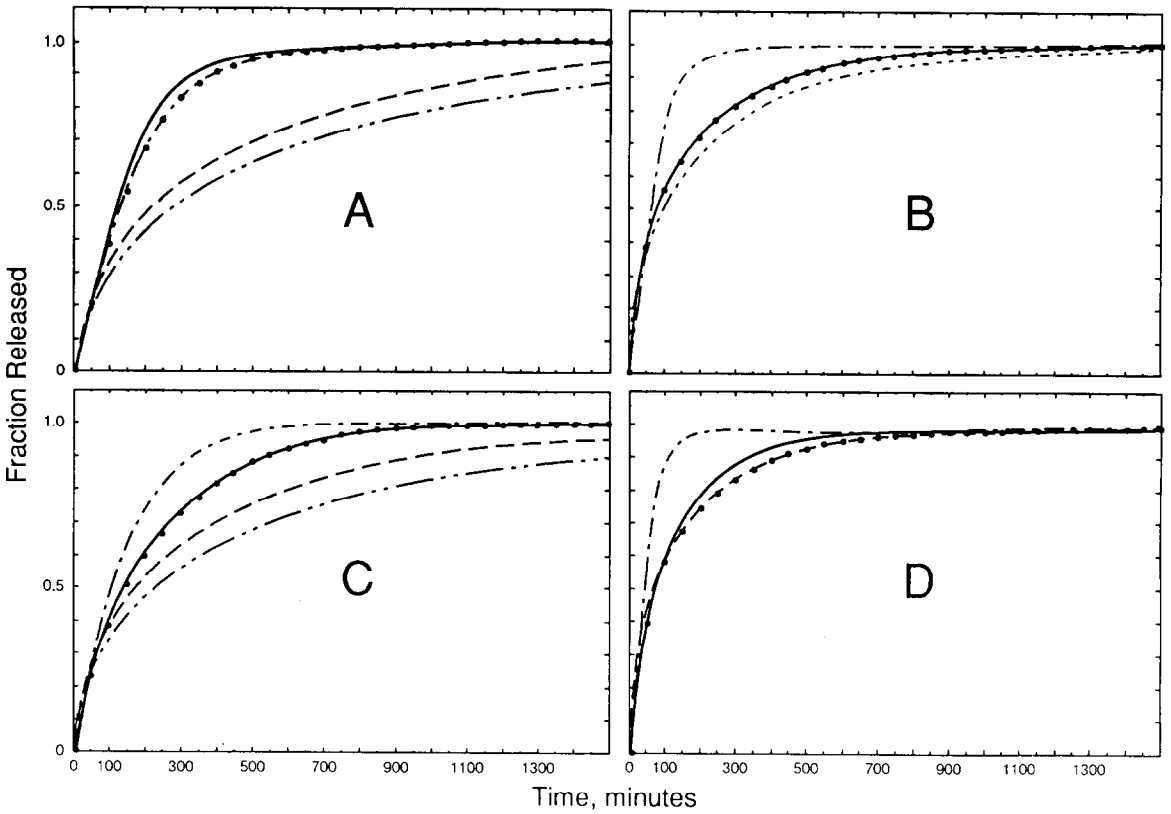


Fig. 4. Relationship between fraction of drug released (symbols) and time for $10^5$ particles log-normally distributed ($\sigma = 0.1139$) as calculated for four potential single particle mechanisms: A, dissolution or erosion (Eqn 1); B, dispersed drug/no hydrodynamic layer (Eqn 2); C, dispersed drug/hydrodynamic layer (Eqn 3); D, dissolved drug (Eqn 4). Constants used are given in Table 2. The lines represent the release calculated from constants $k$, $A$, $A'$, $A_1$, and $B$ estimated from the first 40% of the release data and then applied to the entire time profile: (- - - - -), Eqn 1; (- - - - - -), Eqn 2; (———), Eqn 3; (- - - - -), Eqn 4. In B (- - - - - -) is hidden. In D (- - - - -) is hidden.

Three general conclusions could be made: (1) When the distribution of particles is narrow any one of the five diameters can be used to describe release over long times because the system behaves like a homogeneous system. (2) As the standard deviation increases, regardless of the single particle release, the weight moment mean diameter gives a best overall fit of the data although at early times it tends to underestimate release and at long times it overestimates release. (3) It was evident that there was a very good fit of the initial population release when the volume-surface mean diameter was used as a single diameter estimate. This was true for each mechanism, for each distribution, and for each standard derivation.

In a comparison of the 'true' constants that were used to generate release data (Table 2) with those that are obtained by SAS curve fitting when $d_{vs}$ and different percentages of the initial release data are used, it was found that an error of 5% would be expected at the largest population standard deviation if the first 40% of the data was used. Fig. 3 shows how the error (negative % deviation) in the release constant used in Eqn 2 ($A = 0.05$) varies with the amount of initial release data that is used to estimate the constant. In all subsequent analyses that were undertaken only the first 40% of the 'experimental' release data were used to estimate constants appropriate to a particular mechanism.

Based on the observed properties of $d_{vs}$ it it was felt that it was possible to deduce the single

particle mechanism from population release data in the following stepwise way. First, the initial 40% of the experimental population release data would be SAS fitted using a single $r_0$, the volume-surface mean, obtained from distribution data, in each of the possible single particle release mechanism equations. Fitting equations such as Eqn 1, 2, 3, or 4 to the initial experimental data should provide a relatively good estimate for the hypothetical constants $k$, $A$, $A'$, $A_1$ and $B$, only one of which reflects the true mechanism and which, under boundary conditions imposed, should be a constant and be applicable to all particles in the population over the release-time profile. The next step was to calculate an expected population release by summing releases for all particles over the entire time profile using the estimated constants, the appropriate equations, and 128 values for $r_0$ as determined from a measured particle size distribution of the particles. The goodness of the fit between this calculated release and the real or experimental data identifies the true single particle release mechanism. Goodness of fit was determined by comparing the sum of the squared residuals when each equation was used.

The approach was first examined using simulated release data. Using Eqn 1, 2, 3, or 4 as the true single particle release, an expected release for each possible mechanism was calculated using the constants given in Table 2. The circles in Fig. 4 show the release for a dissolution mechanism ($A$, Eqn 1), a drug dispersed mechanism without a hydrodynamic layer ($B$, Eqn 2), one with a hydrodynamic layer ($C$, Eqn 3) and a diffusion mechanism ($D$, Eqn 4) for $10^5$ log-normally distributed particles at $\sigma = 0.1139$ (intermediate spread). The first 40% of each data set was taken and fitted, in turn, to Eqn 1, 2, 3, or 4 using a single $r_0$, the volume-surface diameter for the distribution, to generate values of $k$, $A$, $A_1$ and $A'$, and $B$. These constants then were used in combination with 100, 200 or 300 $r_0$ terms obtained from the distribution and summed over all $r_0$ to calculate a release that would be expected if the rate limiting step were dissolution, drug dispersed no hydrodynamic layer, drug dispersed with a hydrodynamic resistance layer, or the drug dissolved case. The results obtained are given in Fig. 4.

Fig. 4 graphically depicts the general limitations of the approach with respect to deducing the single particle mechanism from population release. In Fig. 4A the true mechanism is dissolution. It would be differentiated from a drug dissolved or a drug dispersed-without hydrodynamic layer-mechanism. However, there is the possibility that a mechanism involving a dispersed drug with a hydrodynamic resistance layer could be erroneously deduced. However, it should be possible to differentiate a dissolution mechanism from this case by visually observing if the microspheres vanished with time.

Fig. 4B and D are cases where the true mechanism is drug dispersed/no hydrodynamic layer and drug dissolved, respectively. It is seen that only the dissolution possibility might be eliminated in either situation. It should be possible to rule out a drug dispersed mechanism with or without a resistance layer from an exponential mechanism based on whether or not the solute is dissolved in the matrix. Eqns 2 and 3 involve the same type of drug delivery system and the difference merely involves how significant the aqueous resistance layer is.

Fig. 4C is the case where the true single particle mechanism is of the Eqn 3 type. It is evident that when it occurs it can be distinguished from the other three potential mechanisms considered.

The method was then used in real systems. The systems consisted of serum albumin microspheres containing norgestrel that had different average particle sizes (17–150 $\mu$m) all made at a constant ratio of albumin to glutaraldehyde, different drug loadings, and different ratios of albumin to crosslinking agent to affect crosslinking density. The release of drug was studied under sink conditions for each preparation using a sample whose size distribution was experimentally measured. For each of the 128 segments measured by the Elzone Particle Size Analyzer, the mean size and the number of particles was known. Fig. 5 shows a typical particle size analysis. The mean size for each segment was used as $r_0$ and the volume fraction ($f$) of the size was calculated. From these data an expected release was calculated based on the four different mechanisms (Eqns 1–4) using the volume-surface diameter and the first 40% of

the experimental release data to obtain estimates for $k$, $A$, $A_1$ and $A'$, and $B$. These estimates are given in Table 1 together with the volume-surface diameter that was calculated for the distribution. Fig. 6 gives the results obtained using a sample having a volume-surface diameter of 50.2 $\mu$m (Table 1). It is typical of the results found at the other sizes produced. In the manufacture of these different sizes only the external phase of the formulation was changed; all other formulation and process variables were constant. In Fig. 6, the lines represent the release expected when different mechanisms are assumed. It is clear that the single particle mechanism that best describes the actual population release is one where drug is dispersed in the matrix with a hydrodynamic layer imposed. This result is not surprising. The constants $k$, $A$, $A'$ and $A_1$ in Eqns 1–3 contain a drug solubility term while constant $B$ of Eqn 4 does not. Our results would lend credence to the drug dispersed mechanism since it has been observed that the rate of release of water insoluble drugs is much slower than that of water soluble drugs thus indicating a dependence of rate on solubility (Lee et al., 1981).

It is interesting to note that the constants calculated from the first 40% of the experimental data indicate that release rate seem to depend on the size of the average particle size; the larger the particle the larger the constant. For some, and as yet unexplained reason the effective diffusivity or possibly the size of the hydrodynamic layer changes with average size at a constant stirring rate.

The method described to deduce a single particle mechanism from population data is dependent on several factors; it is dependent on the accuracy of both release and size analysis data and it depends on being able to characterize mathematically all potential release mechanisms and to include them among possible choices. In this paper four cases of release were considered (Eqns 1–4) that were judged to be viable possibilities. Of

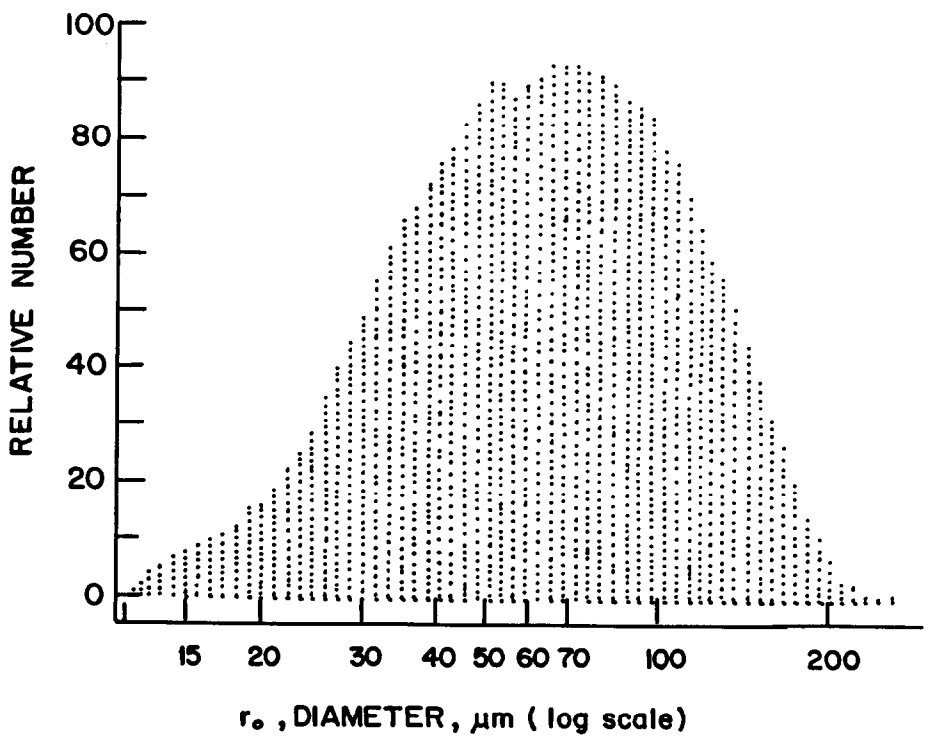


Fig. 5. The typical relationship found between relative frequency and size of serum albumin microspheres, as determined in a particle size analyzer. The size is presented on a log scale.

course if the true mechanism had been swelling, enzymatic erosion of the matrix, or some mixed mechanism, the method should have failed; these mechanisms would have had to be included in the analysis of best fit. When the method does not clearly identify a mechanism, the reason may be that the proper equation was not a part of the analytical process. When the method was used to deduce the mechanism of release from particles containing different amounts of drug loaded or when they were made using different ratios of glutaraldehyde to albumin a clear identification of a working equation was not found; the experimental data fell between that expected for a dissolution mechanism and a drug dispersed mechanism with a hydrodynamic diffusion layer imposed. Typical of these results is Fig. 7 for a study where drug loading was varied (*B* in Table 1). The only difference in the manufacture of these spheres and those used in the studies involving different sizes, where a mechanism clearly was identified, was that 20% w/w of surfactant (Table 1) was added to the external phase before the aqueous dispersion was added. It should have been removed in the washing procedure. Beside the possibility of not including all possible mechanisms in the analysis, there is also the potential problem associated with the determination of the size distribution. If

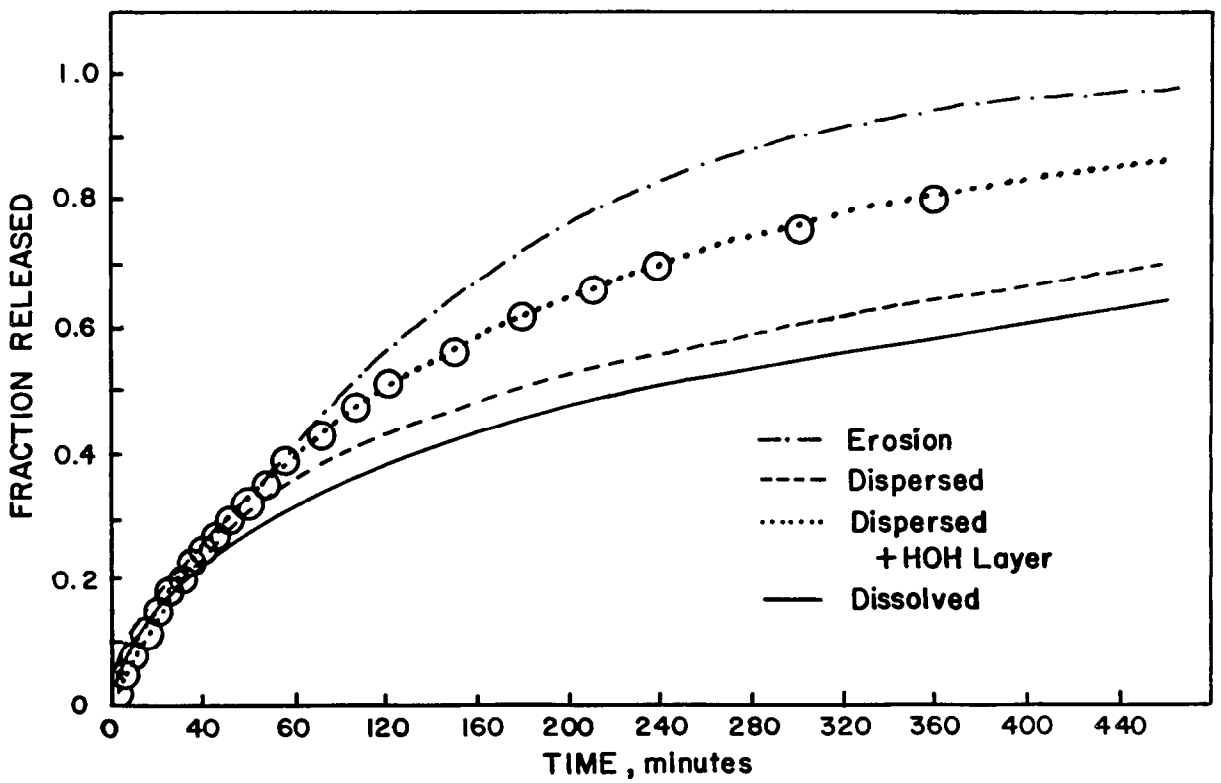


Fig. 6. The relationship between the fraction of norgestrel released (circles, experimental) and time from distributions of microspheres having a volume-surface diameter of 50.2 $\mu$m. The lines represent the calculated fraction released-time relationship for different assumed mechanisms: (·–·–·), Eqn 1; (- - - - -), Eqn. 2; (·····), Eqn. 3; (———), Eqn 4. The first 40% of the experimental data were fitted using $d_{vs}$ as a single diameter in each of the equations (Eqns 1–4) to generate the release constants listed in Table 1. These were then used in combination with the measured particle size distribution to generate the release expected over the entire time profile assuming, in turn, each potential mechanism.

in the measurement small or large particles were excluded, the goodness of fit of even the 'true' mechanism would suffer. In the loading and cross-linking effect studies the average particles size was much smaller than that in the studies involving different sizes. If the particle size analyzer failed to count the very small or large particles in the sample, the 'calculated' release would be low. It is this explanation that is most attractive since we feel that the drug dispersed mechanism should be operative in these systems. Qualitatively the observations made relative to the loading and extent of crosslinking are consistent (Table 1); loading, in the percentages studied (5–10% of the total bead weight), is not expected to affect release and the greater the extent of cross linking the slower the release.

## Conclusions

If the particle size distribution and mechanism of release of a drug from a single particle are known or can be surmised with confidence, then the release to be expected from the population can be calculated. In the case of a known single particle mechanism, a good estimate of the overall population release rate can be obtained quickly using the weight-moment diameter of the population as a single value for size. A better estimate of rate constant can be obtained using initial experimental release data and the volume-surface diameter of the population as a single size. Using this rate constant and the measured size distribution should give a very good prediction of overall release rate. Data fitting to help identify an un-

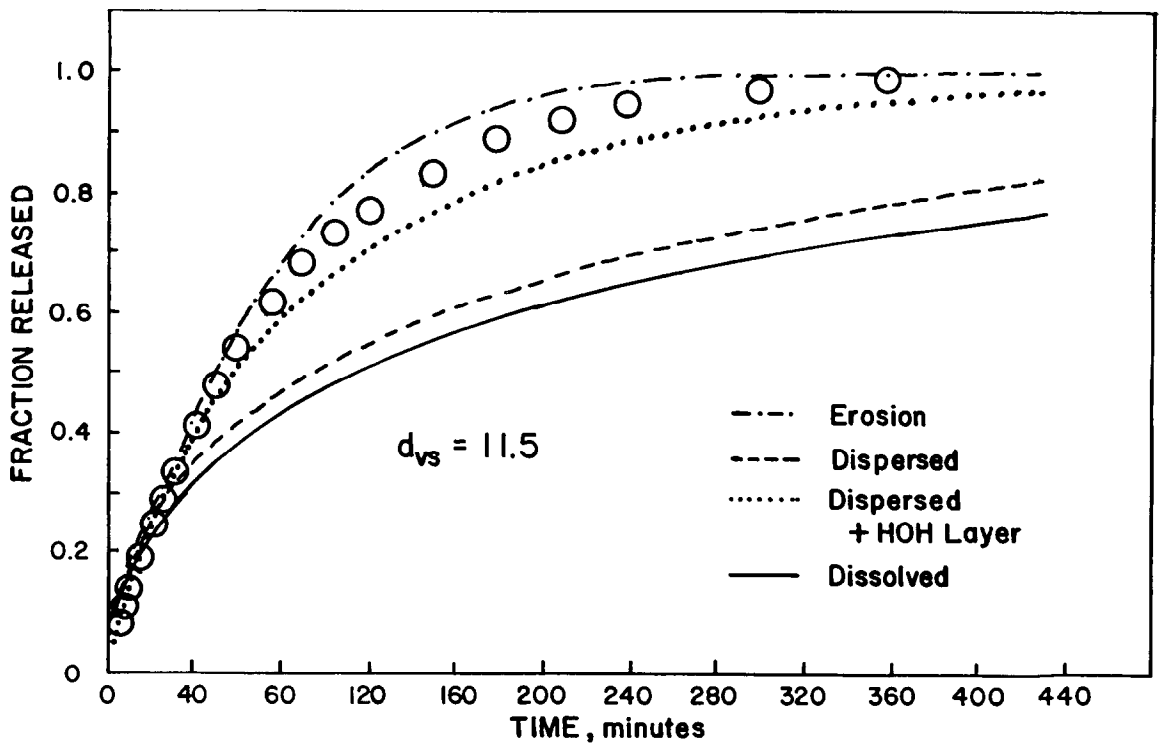


Fig. 7. The relationship between fraction of norgestrel released (circles, experimental) and time for distributions of microspheres representing drug loading of 50 mg/ml. The lines represent the calculated fraction released-time relationship for different assumed mechanisms; (– · – · –), Eqn 1; (– – – – –), Eqn 2; (· · · · · ·), Eqn 3; and (———), Eqn 4. The first 40% of the experimental data were fitted using $d_{vs}$ as the single diameter in each of the equations (Eqns 1–4) to generate the release constants listed in Table 1. These were then used in combination with the measured particle size distribution to generate the release expected over the entire time profile assuming, in turn, each potential mechanism.

known single particle release equation using particle size analysis and population release data is facilitated when the initial experimental release and the population's volume-surface diameter is used to estimate release constants assuming different potential single particle mechanisms to be operating.

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