International Journal of Pharmaceutics, 58 (1990) 1–12
Elsevier

IJP 01957

Invited Review

Drug release from microdisperse systems: a critical review

C. Washington

Department of Pharmacy, University of Nottingham, Nottingham (U.K.)

(Received 26 May 1989)
(Accepted 15 July 1989)

Key words: Diffusion; Microparticle; Nanoparticle; Drug release; Dissolution

Summary

The review article describes the current state of the art in the study of drug release from colloidal systems. Emphasis is placed on the practical aspects of obtaining kinetic release data from micron or submicron-sized carriers, which poses a range of experimental difficulties not encountered in the study of formulations with a larger particle size. Potential sources of experimental error are discussed, and their effect on the interpretation of the data is examined. Mathematical models of drug release from such systems are also reviewed, and provide information which may be used to study formulation behaviour at a microscopic level.

Introduction

During the last decade there has been a considerable increase in interest in the use of disperse systems as drug carriers. These include liposomes, microparticles, nanoparticles and emulsions. Emulsions in particular have long been used as topical delivery systems, but this article will be primarily concerned with formulations intended for injection, which are rapidly dispersed around the body. Interest in these systems is due to their potential to transport drugs to selected sites and thus increase therapeutic benefit, while minimizing side effects and altering the pharmacokinetics and pharmacodynamics of the drug; they correspond in some measure to the 'magic bullets' postulated by Ehrlich. Due to the small diameter of the capillaries, the particle size of these carriers is of the order of a micron, preferably less. Much of the theory of drug release from delivery systems has been investigated in connection with controlled release devices, which are usually larger and intended for different routes of administration. The behaviour of these systems is well investigated, and their larger size makes them easier to study experimentally. It is convenient to think of injectable systems separately, since their small particle size can cause unique problems in their experimental study.

A central physical characteristic of these drug-carrier systems is the drug release profile, which in its most fundamental form is the fraction of drug released from the disperse system as a function of time after the system has been administered. In this sense, 'administered' means that the carrier is given unrestricted opportunity to release its drug load to the surroundings. This release can be driven by a number of processes, of which the

Correspondence: C. Washington, Department of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

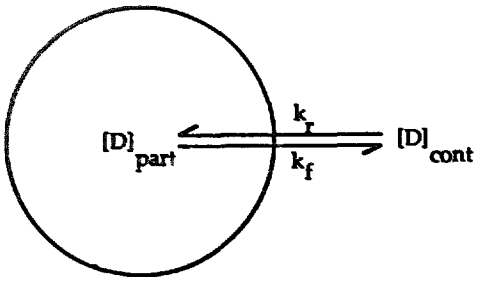

Fig. 1. Diffusion equilibrium of drug between particle and continuous phase.

following appear at present to be the most important:

1. The drug may diffuse out of the carrier by diffusion in the solid matrix. This process is negligibly slow for macroscopic delivery systems, but can be rapid for submicron carriers. Diffusion in solids is characterised by diffusion coefficients of 10^{-18} to 10^{-20} $m^2 \cdot s^{-1}$ or less, resulting in release times of the order of hours or minutes for a particle with a diameter in the hundred nanometer range. The carrier retains its structural integrity in this situation. This situation can be thought of as a perturbation of a partition equilibrium; before dilution the carrier is dispersed in a small volume of continuous phase and the drug is partitioned between the carrier phase and the continuous phase. The system has presumably been designed in such a way that the drug is partitioned largely in the carrier under these conditions.

On dilution the drug will diffuse out of the carrier until the partition equilibrium is re-established. This equilibrium is shown in Fig. 1. Note that the rates of the forward and reverse processes may be functions of concentration and time, and need not be first order. If the degree of dilution is large, $[D]_{cont}$ is small, and the drug will then partition largely into the aqueous phase. At infinite dilution $[D]_{cont}$ will be zero and so the reverse rate will be zero. The drug will leave the carrier completely and accumulate in the continuous phase (although at zero concentration). The rate at which this occurs will be $k_f \cdot [D]_{cont}$, this function being the release profile which we defined more loosely above. If release is first-order, k_f will be constant, but more normally this will not be the case. The (theoretical) situation of infinite dilution is known as a perfect sink. Although perfect sink conditions are never attainable in practise, they are the only situation in which the true release profile as defined above can be measured. The kinetics of release are then determined only by the drug-carrier interaction, and are not influenced by drug in the sink medium. In non-sink (real) situations, at equilibrium the drug is partitioned between carrier and sink, the carrier does not release its total drug load, and the release profile measured may bear little resemblance to the perfect sink profile. As will be seen, this is a major constraint on the design of release profile experiments. The mathematical analysis of drug release from sustained release devices is normally only possible under sink conditions, since the diffusion equations become difficult to solve if a finite time-dependent drug concentration is present in the continuous phase.

2. The solvent may penetrate the microparticle and dissolve the drug, which then diffuses out in solution. The solvent may gain entry by percolation through pores, or hydration of the particle. In the first case this may also be accompanied by gelling, resulting in a viscous layer through which the drug diffuses. This is potentially the most complex mechanism due to the numerous variables involved (particle porosity, rate of hydration, etc). It has been widely studied in connection with controlled release devices of larger dimensions. Since diffusion is driving the release, again sink conditions are required to obtain valid experimental data. The process is often referred to as case II, non-Fickian or anomalous diffusion, and can lead to release with near zero-order kinetics in some cases (Ritger and Peppas, 1987). The theoretical behaviour of these systems has been studied by Lee (1985).

3. The carrier may be degraded or dissolved by its surroundings, the drug being sufficiently immobile to diffuse from the carrier over the same timescale. In this case the accumulation of drug in the continuous phase follows the degradation of the carrier. As long as this is much faster than the diffusion-controlled release from the formulation, there is no need to perform a perfect sink experiment to study this process. In practice, however, it is better to work under good sink conditions in

order to avoid errors such as those caused by readsorption of drug to the carrier surface or the possibility of saturating the sink if the drug is poorly soluble.

In practice, the release profile of a practical system may be a combination of these limiting mechanisms. The information contained in the release profile has a number of uses. At its simplest, it can be used as quality control data to ensure the continued reliability of a formulation. However, it would be unfortunate if this were the limit of its application, since the release profile contains fundamental information describing the structure and behavior of the formulation on a microscopic scale and the drug-carrier interaction. Ultimately it may be possible to correlate release with the microstructure of the carrier and enable a predictive approach to be made to the design of formulations with desired properties. It will be seen that some progress along this route has been made by a combination of experimental study and theoretical modelling of release profiles.

Experimental Techniques

As has been shown, measurement of release profiles requires good sink conditions, implying that release must occur into a large volume of sink medium. This poses a problem since the drug must be assayed in the sink medium, and as the sink volume is increased the concentration of drug being measured decreases. A compromise usually has to be found. If it is only desired to find an approximate release half-life, the experimental conditions are less critical than if the detailed form of the release profile is being obtained to study, e.g. the disperse phase structure. The situation is even more critical if the release of hydrophobic drugs from lipid carriers such as emulsions is being considered, since the solubility of the drug in the sink phase may be extremely low and very large dilutions may be needed to prevent the so-called 'sink' from being saturated with the drug. In extreme cases the concept of drug release may cease to be useful, for example the amphotericin B emulsion formulations which we have recently investigated (Forster et al., 1988).

It has been recommended as a rule of thumb that the drug concentration in the sink phase in dissolution experiments be kept below 10% of saturation. This is a useful starting point for experimental design, but can be misleading, since it suggests that sink saturation is the only source of experimental error. If the drug adsorbs to or interacts strongly with the disperse phase, the release profile may be distorted at very low solute levels. A high concentration of drug in the sink will increase the reverse association of drug with carrier, even if the sink is not approaching saturation.

If the drug is poorly soluble in water, it may be permissible to add nonaqueous solvents or solubilizing agents to the sink (e.g. Benoit et al., 1984). In this case it is essential to study the release rate as a function of the concentration of solubilizer in the sink, since the results may be of little value if the effects of the sink additives predominate. Studies of this type may also be of value in determining the release mechanism. If the drug is released by diffusion through a polymer matrix, the sink solvent composition may not influence drug release, but if the solvent penetrates the matrix, its composition is more likely to influence the release rate. Leelarasamee et al. (1986) observed that addition of solubilizing agents below their CMC to the sink medium increased the rate of release of hydrocortisone from poly(dl-lactic acid) microcapsules. There are several possible explanations for this effect, including improved wetting of the polymer and increased penetration of solvent.

Measurement of the release profile is complicated if the drug is unstable in solution, e.g. 1-(2 chloroethyl)-3-cyclohexylnitrosourea (lomustine) (Bissery et al., 1984). Loss of drug during an experiment was clearly demonstrated by Henry-Michelland et al. (1987). The total recovery of drug into the sink should always be checked in order to discount losses such as this, adsorption of drug to the apparatus, particles, filters or membranes or other loss routes. Plastic dialysis cells should be carefully tested for drug adsorption, particularly if small amounts of surface-active or hydrophobic drug are involved. If the release profile does not reach 100% at 'infinite' times (and many published studies do not), then the possibil-

ity of experimental errors due to drug loss should be investigated. A carefully designed protocol will allow the amount of released drug to be integrated and compared to that present initially in the carrier.

A number of experimental methods for the determination of release profiles from disperse systems have been used in the past. All have their advantages and disadvantages. They fall into a number of broad classes.

1. Membrane diffusion techniques (e.g. Hashida et al., 1980; Sasaki et al., 1984; Benita et al., 1986; Miyazaki et al., 1986). In this approach the carrier disperse phase, suspended in a small volume of continuous phase, is separated from a large bulk of sink phase by a dialysis membrane which is permeable to the drug. The drug diffuses out of the sample and through the membrane to the sink, wherein it is periodically assayed. Although experimentally straightforward, this technique can be highly misleading. None of the sample is diluted into a sink; the concentration gradient of drug which drives diffusion across the membrane is the partition controlled concentration in the carrier's surrounding phase. The sample and sink are well stirred, and so the accumulation of the drug in the sink is controlled by the consecutive rate processes of (non-sink) partitioning and diffusion of the drug across the membrane.

A simple kinetic analysis of this experiment (Washington, 1989) demonstrates that the release rate of drug is completely obscured by partitioning in the sample. The model is shown in Fig. 2. It can be shown that, if the drug A is largely partitioned into the carrier, as would be the case in a practical formulation, the concentration $[A]_t$ of the drug in the colloid disperse phase is given by:

$$[A]_t = [A]_0 \cdot \exp\left(\frac{-k_2 V_B t}{K_p V_A}\right),$$

where K_p is the partition coefficient of drug between continuous and disperse phases. It can be seen that the release is controlled by the partition coefficient and is independent of the release rate constant k_1. This latter is of course the release rate which we are intending to measure. This analysis is not restricted to first-order processes. The experiment often misleads naive experimenters who add free drug to the inside of the dialysis bag and observe that it equilibrates with the sink in a short time, and conclude that the membrane diffusion is sufficiently fast not to distort the release kinetics of the disperse system. Unfortunately the diffusion rates are much higher in this case since all the drug is available in the internal continuous phase to drive the membrane diffusion. The correlation of release rate with drug partition coefficient in this experiment is illustrated well by Sasaki et al. (1984) for the release of a series of mitomycin prodrugs from an emulsion vehicle.

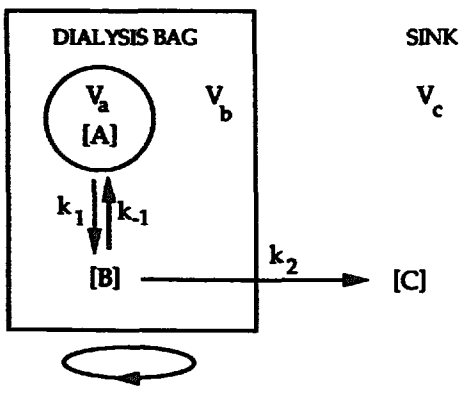

Fig. 2. Kinetics of non-sink membrane dialysis.

In the case where release is due to dissolution or disintegration of the carrier, the experiment is less prone to error but still unsatisfactory. The accumulation of drug in the sink is the result of consecutive release followed by membrane diffusion. If release occurs over a long period, e.g. several days, the results can reflect the release profile, but should properly be deconvoluted from the membrane diffusion kinetics, as will be described shortly.

2. Sample and separate techniques (Tsai et al., 1986; Farah et al., 1987; Henry-Michelland et al., 1987). This heading covers a wide range of methods of varying usefulness. The carrier is diluted into a sink, and this is sampled at intervals. The continuous phase of the sample is then separated from the disperse phase, usually by filtration or centrifugation, and the released drug is assayed. This type of technique is satisfactory if the disperse and continuous phases can be separated

cleanly and sufficiently rapidly not to influence the release profile. This can prove difficult, particularly if the disperse phase consists of very small particles (e.g. below 1 μm). In this case the particles become more difficult to filter off, or the time to sediment them by centrifuging increases, while the release profile can be very fast. As the particle size becomes smaller the separation problems increase while the release becomes faster still.

An interesting example of this method was used by Widder et al. (1979) to study drug release from magnetite-loaded albumin microspheres. The authors exploited the magnetic properties of the carrier to sediment the microspheres from the sample prior to assay.

3. In situ methods (e.g. Wakiyama et al., 1981). In this case the carrier is diluted into a large volume of sink, but the released drug is assayed in the sink without separating the residual carrier-bound drug. In order to do this a method of assay is required which is sensitive only to drug in solution. Potentially useful methods include polarography and UV/visible spectroscopy. Polarography requires a suitable redox potential, while spectroscopic methods require a chromophore in the drug. The major problem with spectroscopy is that the scattering of the disperse phase can become very large compared to the absorbance of the drug in solution. Since scattering increases as $1/\lambda^4$, it becomes an increasing problem at shorter UV wavelengths. Consequently strong chromophores at long wavelengths are needed, and the data generally requires background subtraction or multicomponent analysis.

Molecules bound to or incorporated into carrier systems will generally have different spectroscopic properties to those in solution. Illum et al. (1986) have made use of the bathochromic shift which occurred when the model drug rose bengal was adsorbed to poly(butyl-2-cyanoacrylate) nanoparticles to measure the release kinetics. This method is particularly convenient for cyanoacrylate nanoparticles, which are sufficiently small to show low scattering, but which are difficult to filter or centrifuge due to their small (~ 100 nm) size.

Release of liposomal contents has been measured using the well-known technique of fluorescence self-quenching in carboxyfluorescein or calcein (Szoka et al., 1979, Lelkes, 1984). This technique does not appear to have been used widely for other drugs or delivery systems, probably since the spectroscopic properties of most drugs are not closely investigated at a formulation stage, and drug loadings are often too low in colloidal formulations for self-quenching effects to be observed. Many drugs, however, have chromophores which can quench a suitable fluorophore by long range Forster energy transfer; we have used this property to study the location of amphotericin B in emulsion and liposomal formulations (Washington et al., 1988) and it may be possible to extend this approach to the measurement of release profiles.

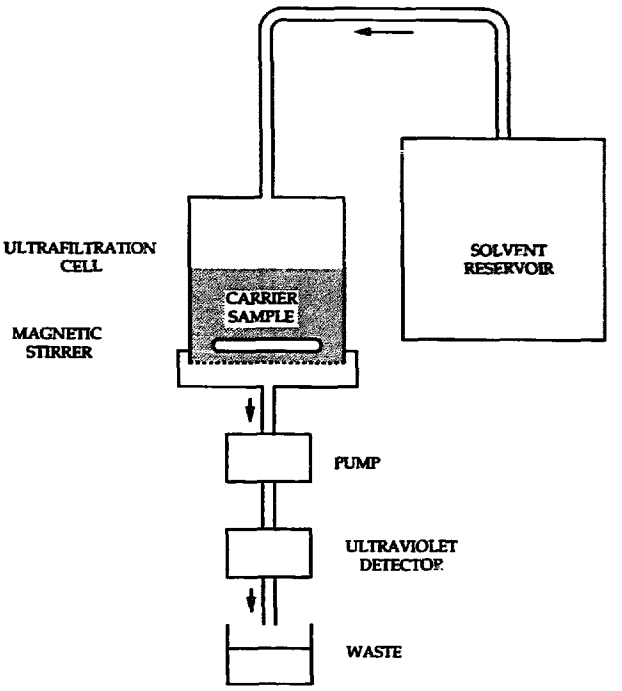

Fig. 3. Continuous flow drug-release apparatus.

4. Continuous flow methods (e.g. Burgess et al., 1987; Koosha et al., 1988). This is currently the most popular method. The carrier is added to a small amount of sink contained in a filtration cell (Fig. 3). A large area filter is used, which usually covers the cell base. The sink phase is removed through the filter for continuous analysis (usually by UV spectroscopy or fluorescence) and discarded, and fresh sink is added to the suspension

to keep the volume constant. The cell is stirred to keep the disperse phase in suspension, otherwise it would clog the filter. In practice, variations in flow rate due to filter clogging when the sample is injected can be a problem.

If the sink phase was removed and replaced infinitely rapidly, then at any time the concentration of drug would be proportional to the instantaneous release rate of the system. This contrasts to the other techniques described here, in which the drug accumulates in a fixed sink and so its concentration is the integral of the release rate. This can give the latter method a practical advantage, particularly for the measurement of the later part of the release profile, since it is often more accurate to measure a small concentration of drug than the same amount as a small change in a high concentration, which would be observed in the cumulative experiments.

Unfortunately it is impossible to remove and replace sink phase infinitely rapidly, particularly when membrane filters or ultrafilters are used, which have a low flow rate. These are usually run under increased pressure to increase the flow rate. This finite response time of the experiment will distort the release profile. An estimate of the magnitude of the error can be made by measuring the time taken for the total volume of sink phase in the cell and cell-detector tubing to be replaced. This is simply the cell volume divided by the flow rate. If this characteristic 'flushing time' of the cell is long compared to the expected release half-life, there is little hope of obtaining useful data. Consequently this type of experiment is usually a compromise between a fast flow rate (rapid time response) and a high drug concentration (which requires a low flow rate). As will be seen, release profiles often show rapid initial 'bursts', the speed of which, compared to the experimental time resolution, makes their study difficult. In such cases, or when the drug release time is comparable to the experimental response time, the true release profile can be extracted by deconvolution (Washington and Koosha, 1989). The theory is covered in standard textbooks of time series analysis (e.g. Kuc, 1984) and several methods are available. The experimenter must first obtain the "instrument response function" or response to a delta input function. This is obtained by measuring the release profile observed when a bolus of drug in solution is injected into the apparatus. This would be a delta function if the instrument response was infinitely fast, but in practice will be smeared out by the finite volume replacement time of the apparatus. Since deconvolution is equivalent to division in the frequency domain, the Fourier transform of the particle release profile is divided by the transform of the instrument function, and the result transformed back to the time domain. The resulting function is the deconvoluted release profile. This is free of the distorting effects of the experimental configuration and can be used to study the drug-carrier system more accurately. Convolution effects such as this can be extremely important in determining the detailed shape of the release function (Washington and Koosha, 1989).

Mathematical Models of Drug Release

A large number of mathematical treatments of drug release from carriers have appeared in the literature. Many of these are concerned mainly with large ($> 10\ \mu$) particles intended for sustained release rather than intravenous administration. The field has been reviewed several times, notably by Peppas (1984). It is useful to distinguish three different approaches:

Ab initio methods

Ab initio methods attempt to predict the release profile of a system from fundamental considerations such as particle diameters, diffusion coefficients and structural features of the system, without reference to experimental data. As such they often represent highly simplified situations, since real systems are often too complex to be modelled in this way. The starting point is usually Fick's laws for the system of interest.

Guy et al. (1982) solved the diffusion equations for transport through a spherical particle into a perfect sink. They considered two limiting cases, in which the releasing particle was a uniform sphere with no energy barrier to release at the surface, or in which the diffusion through a surface barrier was rate-limiting. The first model corre-

sponds to a solid particle which is a uniform solid solution of drug, whereas the second is similar to a microcapsule or liposome. In the case of the solid particle with no phase boundary they found:

$$\frac{M_t}{M_0} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-n^2\pi^2\tau)$$

where

$$\tau = \frac{Dt}{r_0^2}$$

D is the diffusion coefficient of drug in the microsphere, t is time and r_0 is the particle radius. M_t is the amount of drug released from the sphere at time t, and M_0 the initial drug loading. Approximate forms have been described for this expression at short times by approximation or series truncation:

$$\frac{M_t}{M_0} = 6\sqrt{\frac{\tau}{\pi}}$$

(Guy et al., 1982). Baker and Lonsdale (1974) provided a similar expression with an extra term:

$$\frac{M_t}{M_0} = 6\sqrt{\frac{\tau}{\pi}} - 3\tau.$$

These expressions have been re-cast from the original description into the reduced variable notation used by Guy.

Approximate methods are essential in the case in which the interfacial transport is rate limiting (e.g. a microcapsule), in order to simplify the mathematics. At short times, release does not significantly decrease the drug concentration inside the microcapsule and the release is approximately zero-order:

$$M_t = Ac_0r\kappa\tau;\ \kappa = \frac{k_1 l}{D}$$

where A is the surface area of the sphere, c_0 the initial concentration in the sphere, k_1 the interfacial rate constant, l the thickness of the interface and D the diffusion coefficient of drug in the interface. At long times the release is a single exponential:

$$\frac{M_t}{M_0} = 1 - \exp(-3\kappa\tau).$$

Often the drug will not be present as a true solid solution, but as a dispersion of drug in a matrix. This situation normally arises when formulators wish to obtain a higher drug loading than could be achieved in a solid solution, and is most easily detected in a real formulation by thermal analysis. Higuchi (1961) studied systems of this type, with macroscopic controlled release devices in mind, but the results have been extensively applied to microparticulates (Baker and Lonsdale 1974). The results will be valid as long as the solid drug particles are small compared to the dimensions of the device. The result:

$$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_0}\right)^{2/3}\right] - \frac{M_t}{M_0} = 3\frac{C_s Dt}{r_0^2 A}$$

suggests that release is neither zero- nor first-order. Here C_s is the drug solubility in the dissolution medium, D the diffusion coefficient of drug in the hydrated matrix, r_0 the radius of the particle and A the drug loading per unit volume. In this case D may vary with parameters such as drug load, since it is environment-sensitive. Since the above expression for a spherical matrix is quite complex, many authors have used the expressions for flux Q from a planar slab matrix:

$$Q = \sqrt{Dc_m(2c_t - c_s)t}$$

where c_m is the solubility of drug in the matrix, c_t is the initial drug concentration and c_s is the drug solubility in the sink phase. This expression was modified by Higuchi (1963) to account for the stochastic features of the dispersion, which we might expect to be particularly important when

the carrier is small:

$$Q = \sqrt{D\frac{\epsilon}{\Gamma}c_m(2c_i - c_s)c_s t}$$

ϵ is the porosity of the matrix and Γ describes the tortuosity of the capillaries through which the drug diffuses. Expressions of this form are usually condensed to:

$$M_t = k\sqrt{t};$$

this represents the well-known square root law. Since it was derived from the flux from an infinitely deep plane matrix, it does not allow the drug reservoir to be significantly depleted, and so it could only be expected to be valid for the release of small fractions of the drug load. These derivations also assume that the drug dissolves easily; if dissolution at the surface of the drug crystal becomes rate-limiting, the situation becomes much more complex. Analytic solutions for several systems of this type have been described by Harland et al. (1987, 1988) who should be consulted for a mathematical discussion. Under certain conditions it may be possible to achieve zero-order release after long times with these devices. It should be noted that all the preceding discussions assume that the drug is uniformly distributed in the disperse phase. When colloidal systems are considered, it is more likely that the drug distribution varies significantly from uniformity. The surface may be enriched by adsorption of the drug, or it may be depleted through washing processes during preparation, although this latter may return to equilibrium rapidly. An indication of the effects of this nonuniform radial drug distribution can be seen in the work of Lee (1980, 1986), who has modelled release from systems in which the initial drug concentration was non-uniform. The object of the work was to obtain specified release profiles from macroscopic matrix devices, but the results are equally applicable to microscopic systems. The models are described for both diffusion-controlled and case II release.

These models do not take into account the presence of a permanent thermodynamic energy minimum at the surface during release, as would be present if the drug was preferentially adsorbed at the surface. When the degree of complication reaches this level, the mathematical models become highly complex and simulation techniques become useful.

Numerical simulation techniques

Numerical models of drug release are of most value in the study of systems which are too complex to be modelled analytically. Most models consider the releasing device to be made up of a number of concentric thin layers. The evolution of the concentrations in the layers is calculated by assuming that diffusion takes place from one layer to the next, driven by the difference in concentration between them. This is equivalent to numerically integrating the diffusion equations in the system, but generally allows more complex situations to be studied for which the diffusion equations could not be solved. Factors such as device attrition, diffusion of solvent into the device, and even nonhomogeneity of device, can be taken into account. Non-spherical and multilayer devices can also be studied.

Armand et al. (1987) used this technique to study release from swelling Eudragit matrix formulations, in which the primary release mechanism is the diffusion of solvent into the polymer, followed by dissolution of drug and its diffusion out of the device. Both experiment and calculation demonstrate that drug release follows a square root law for small release fractions after a lag phase.

Liu et al. (1988) used simulation techniques to study the release from a loaded sphere coated with a further layer of polymer, in which solvent penetration was taken into account. Their experimental data were obtained from macroscopic systems (several millimetres in diameter), and good correlation with the calculations was found for the thinner polymer coatings.

Empirical correlations

Empirical methods of describing drug release are driven by experimental observation rather than theoretical considerations. Unfortunately the square-root law has often been (ab)used in this

manner; it is used with little justification in many cases. Demonstrating square-root law release does not allow the structure of the drug delivery system to be elucidated since both matrix release and release from solid solutions can obey this law at short times.

The relationship:

$$\frac{M_t}{M_0} = kt^n$$

has been proposed by Sinclair and Peppas (1984) and Ritger and Peppas (1987). The constant n is termed the diffusional exponent, and it should equal 0.5 for diffusional (Fickian) release from a planar slab. Values greater than 0.5 indicate anomalous diffusion. This is generally indicative of a system which swells in the solvent prior to diffusional release, which can be treated analytically by moving-boundary (Stefan-Neumann) methods (Lee 1980). Analysis of the model and comparison to the exact solutions demonstrate that n is equal to 0.5 only for a flat slab, and is different for different geometries. Fickian release from a sphere is characterised by $n = 0.432$. Since release from spheres is often adequately fitted when $n = 0.5$, it is evident that this approach requires precise data to allow the extraction of a useful value for n. A corollary to this is that many of the experimental techniques in the literature require improvement before they can be used to discriminate between the various mechanisms of drug release. Simply obtaining a reasonable fit to one's data is not adequate. The expression has been extended to allow the description of lag phases, but these are not often observed in colloidal systems due to the rapidity of the diffusion process over such short distances.

One of the more popular empirical relations is to describe release as a biexponential process:

$$\frac{M_t}{M_0} = 1 - [A \exp(-\alpha t) + B \exp(-\beta t)]$$

where α and β are the rate constants of the two lifetime components into which the decay function is being decomposed. The exponentials usually consist of a rapid and a slow function, being assigned to 'burst phase' and 'sustained release' respectively. As we shall see, these emotive phrases often have little real significance.

The decomposition of a monotonically decreasing function into exponential components should be performed with some caution. Lanczos (1957) originally demonstrated the magnitude of the problem by the example that a sum of three exponentials was well fitted by a sum of two exponentials with distorted time constants and amplitudes. Consequently, reliable recovery of exponential components requires data of an extremely high degree of accuracy which is often not attainable. Attempts to decompose experimental release profiles into more than two components with significantly different time constants must be treated with some scepticism. A corollary of this problem is that it is extremely difficult to extract true multiple exponentials, so that when these exist, a double exponential function provides an apparently adequate model. This had led many experimenters into two misconceptions; firstly that these correspond to two distinct physical processes (which may be true in some cases), and secondly that monodisperse homogeneous microspheres display a single exponential release profile. This attractive hypothesis is demonstrated to be incorrect by many of the models described herein, particularly when the full time range of data is being studied. The hazards of multiexponential fitting to the unwary cannot be overstressed.

The use of empirical functions to model release data has been taken to an extreme by Lin (1987) who tried ten separate simple functions as fitting equations for the release of theophylline from microcapsules. Although a best fit equation was found ($1/y = A/x + B$) this approach does not significantly increase our understanding of the physical chemistry of the system.

It is convenient at this point to discuss the 'burst effect' described by many authors, by which is meant a rapid initial release of drug from the disperse carrier. This is often sufficiently rapid to suggest its identification as a distinct physical process. The main problem in discussing the burst effect is the multiplicity of physical processes which can give rise to it. These include:

1. Drug in solution in the aqueous phase. This should not be underestimated; for example con-

sider a drug with a microsphere/water log P of 3 which is partitioned between 50 mg of microspheres in 5 ml water (a typical situation). In this case at equilibrium approximately 10% of the drug is in the aqueous phase.

2. Drug solubilized by free surfactant, which is often present even in the cleanest preparations.

3. Drug bound on the surface of the microsphere. This is a common situation, and has even been used as a drug loading method in cases where other methods fail (Illum et al., 1986). This is similar to the situation in which much drug is present, causing a solid particle to become porous and easily accessible to solvent. This behaviour is illustrated by Bodmeier and McGinty (1987) who produced poly (dl-lactide) microspheres containing quinidine. Low drug loadings showed slow release, but as the drug loading was increased, a rapid burst effect was produced. This could be correlated with the appearance of pores (SEM) and the presence of free drug (DSC melting endotherm).

4. The contribution of the smaller particles in a polydisperse formulation should not be overlooked. Many ab initio theories suggest that the release rate of a particle of radius r is proportional to $1/r^2$. This can cause smaller particles to produce an extremely rapid initial release. We have modelled an example of this by integrating the model of Guy et al. (1982) over a typical lognormal particle size distribution (that measured for Intralipid 20%) to find the effective release profile. This is shown in Fig. 4. The long tail due to deep release from the larger particles, and the initial spike due to surface release and small particle release, combine to provide an extremely strongly curved profile. The rapid initial release would normally, of course, require deconvolution to be extracted from the experimental data. This curve can be well fitted by a biexponential function, erroneously suggesting that two processes (with rate constants differing by approximately a factor of 10) are occurring. The mean error of this fit is approximately 1%, and few experiments produce data sufficiently free from random and systematic error to test the inadequacy of such a model.

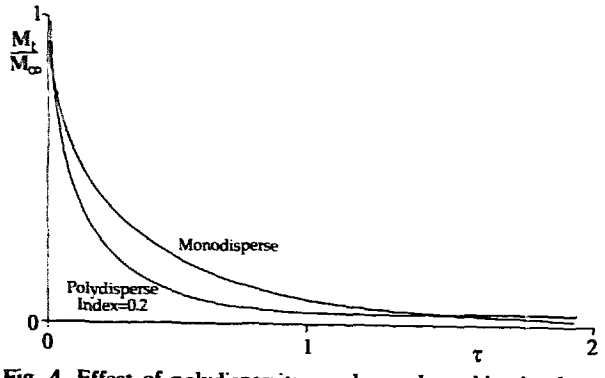

Fig. 4. Effect of polydispersity on drug release kinetics from microspheres.

The relative importance of these contributions to the burst effect varies with the carrier under consideration. Thus microspheres, which are often washable, sievable and can be dried, are less likely to show bursts from small particles or excess surfactant. These can be important contributions to release from emulsions, which cannot be washed and can contain a relatively broad droplet size distribution. Emulsions, however, can be prepared at relatively high disperse phase volume, making the effects of drug partition less important.

Conclusions

The mathematical modelling of release from microdisperse systems is well established, particularly in view of the extensive study of macroscopic systems which can be applied. It has been shown that many systems with fundamentally different physicochemical behaviour and mechanisms of release display similar mathematical behaviour. This suggests that experimental data of considerable accuracy is needed to distinguish between them. The experimental study of release from submicron systems is subject to many potential errors which must be overcome before the models described here can be thoroughly tested. It is hoped that the description in this review of some of these problems will assist other workers in the study of colloidal formulations.

References

Armand, J.Y., Magnard, F., Bouzon, J., Rollet, J., Taverdet, J.L. and Vergnaud, J.M. Modelling of drug release in

gastric liquid from spheric galenic forms with Eudragit matrix. Int. J. Pharm., 40 (1987) 33–41.

Baker, R.W. and Lonsdale, H.K. Controlled release: mechanisms and rates. In Tanquary, A.C. and Lacey, R.E. (Eds.), Controlled Release of Biologically Active Agents, Plenum, New York, 1974, pp. 15–71.

Benita, S., Friedman, D. and Weinstock, M. Pharmacological evaluation of an injectable prolonged release emulsion of physostigmine in rabbits. J. Pharm. Pharmacol., 38 (1986) 653–658.

Benoit, J.P., Benita, S., Puiseux, F. and Thies, C. Stability and release kinetics of drugs incorporated in microspheres. In Davis, S.S., Illum, L., McVie, J.G. and Tonlinson, E. (Eds.), Microspheres and Drug Therapy. Pharmaceutical, Immunological and Medical Aspects, Elsevier, Amsterdam, 1984, pp. 91–102.

Bissery, M.C., Valeriote, F. and Thies, C. In vitro and in vivo evaluation of CCNU-loaded microspheres prepared from poly(($\pm$) lactide) and poly(β-hydroxybutyrate). In Davis, S.S., Illum, L., McVie, J.G. and Tonlinson, E. (Eds.), Microspheres and Drug Therapy. Pharmaceutical, Immunological and Medical Aspects, Elsevier, Amsterdam, 1984, pp. 91–102.

Bodmeier, R. and McGinty, J.W. The preparation and evaluation of drug-containing poly(dl-lactide) microspheres formed by the solvent evaporation method. Pharm. Res., 4 (1987) 465–471.

Burgess, D.J., Davis, S.S. and Tomlinson, E. Potential use of albumin microspheres as a drug delivery system. I. Preparation and in vitro release of steroids. Int. J. Pharm., 39 (1987) 129–136.

Farah, N., Bouzon, J., Rollet, M., Taverdet, J.L. and Vergnaud, J.M. Dry emulsion: a sustained release form: modelling of drug transfer in liquids. Int. J. Pharm., 36 (1987) 81–88.

Forster, D., Washington, C. and Davis, S.S. Toxicity of solubilized and colloidal amphotericin B formulations to human erythrocytes. J. Pharm. Pharmacol., 40 (1988) 325–328.

Guy, R.H., Hadgraft, J., Kellaway, I.W. and Taylor, M.J. Calculations of drug release rates from spherical particles. Int. J. Pharm., 11 (1982) 199–207.

Harland, R.S., Dubernet, C., Benoit, J.P. and Peppas, N.A. Coupled diffusion/dissolution processes may give zero-order release of drugs from microspheres. Proc. Int. Symp. Cont. Rel. Bioact. Mater., 14 (1987) 27–28.

Harland, R.S., Dubernet, C., Benoit, J.P. and Peppas, N.A. A model of dissolution controlled, diffusional drug release from non-swellable polymeric microspheres. J. Controlled Release, 7 (1988) 207–215.

Hashida, M., Yoshioka, T., Muranishi, S. and Sezaki, H. Dosage form characteristics of microsphere-in-oil emulsions. 1: Stability and drug release. Chem. Pharm. Bull., 28 (1980) 1009–1015.

Henry-Michelland, S., Alonso, M.J., Andremont, A., Maincen, P., Sauzieres, J. and Couvreur, P. Attachment of antibiotics to nanoparticles: preparation, drug release and antimicrobial activity in vitro. Int. J. Pharm., 35 (1987) 121–127.

Higuchi, T. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci., 50 (1961) 874–875.

Higuchi, T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 52 (1963) 1145–1149.

Illum, L., Khan, M.A., Mak, E. and Davis, S.S. Evaluation of carrier capacity and release characteristics for poly(butyl-2-cyanoacrylate) nanoparticles. Int. J. Pharm., 30 (1986) 17–28.

Koosha, F., Muller, R.H. and Davis, S.S. A continuous flow system for in-vitro evaluation of drug-loaded biodegradable colloidal carriers. J. Pharm. Pharmacol., 40 (1988) 131P.

Kuc, R. Introduction to digital signal processing. McGraw Hill, New York, 1984.

Lanczos, C. Applied Analysis, Prentice-Hall, Englewood Cliffs, 1957, pp. 272–280.

Lee, P.I. Diffusion release of a solute from a polymeric matrix: Approximate analytic solutions. J. Membrane Sci., 7 (1980) 225–275.

Lee, P.I. Kinetics of drug release from hydrogel matrices. J. Controlled Release, 2 (1985) 277–288.

Lee, P.I. Initial concentration distribution as a mechanism for regulating drug release from diffusion controlled and surface erosion controlled matrix systems. J. Controlled Release, 4 (1986) 1–7.

Leelarasamee, N., Howard, S.A., Malanga, C.J., Luzzi, L.A., Hogan, T.F., Kandzari, S.J. and Ma, J.H.K. Kinetics of drug release from polylactic acid-hydrocortisone microcapsules. J. Microencapsulation, 3 (1986) 171–179.

Lelkes, P.I. Methodological aspects of dealing with stability measurements of liposomes in vitro using carboxyfluorescein assay. In Gregoriadis, G. (Ed.), Liposome technology, Vol. 3, CRC Press, Florida, 1984, pp. 225–246.

Lin, S.Y. In vitro release behaviour of theophylline from PIB-induced ethylcellulose microcapsules interpreted by simple mathematical functions. J. Microencapsulation, 4 (1987) 213–216.

Liu, H., Magron, P., Bouzon, J. and Vergnaud, J.M. Spherical dosage form with a core and shell. Experiments and modelling. Int. J. Pharm., 45 (1988) 217–227.

Miyazaki, S., Hashiguchi, N., Hou, W.M., Yokouchi, C. and Takada, M. Preparation and evaluation in vitro and in vivo of fibrinogen microspheres containing adriamycin. Chem. Pharm. Bull., 34 (1986) 3384–3393.

Peppas, N.A. Mathematical modelling of diffusion processes in drug delivery polymeric systems. In: Langer, R.S. and Wise, D. (Eds.), Medical Applications of Controlled Release Technology, Vol. 2, CRC Press, Boca Raton, Florida 1984, pp. 169–187.

Ritger, P.L. and Peppas, N.A. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. J. Controlled Release, 2 (1987) 37–42.

Sasaki, H., Takakura, Y., Hashida, M., Kimura, T. and Sezaki, H. Antitumour activity of lipophilic prodrugs of mitomycin C entrapped in liposome or O/W emulsion. J. Pharm. Dyn., 7 (1984) 120–130.

Sinclair, G.W. and Peppas, N.A. Analysis of non-Fickian transport in polymers using simplified exponential expressions. J. Membrane Sci., 17 (1984) 329–331.

Szoka, F.C., Jacobson, K. and Paphajopoulos, D. The use of aqueous space markers to determine the mechanism of interaction between phospholipid vesicles and cells. Biochim. Biophys. Acta, 551 (1979) 195–203.

Tsai, D.C., Howard, S.A., Hogan, T.F., Malanga, C.J., Kandzari, S.J. and Ma, J.K.H. Preparation and in vitro evaluation of polylactic acid-mitomycin C microcapsules. J. Microencapsulation, 3 (1986) 181–193.

Wakiyama, N., Juni, K. and Nakano, M. Preparation and evaluation in vitro of polylactic acid microspheres containing local anesthetics. Chem. Pharm. Bull., 29 (1981) 3363–3368.

Washington, C. Evaluation of non-sink dialysis methods for the measurement of drug release from colloids: effects of drug partition. Submitted to Int. J. Pharm., (1989).

Washington, C. and Koosha, F. Drug release from microparticulates; deconvolution of measurement errors. Submitted to J. Pharm. Pharmacol., (1989).

Washington, C., Taylor, S.J. and Davis, S.S. The structure of colloidal formulations of amphotericin B. Int. J. Pharm., 46 (1988) 25–30.

Widder, K., Flouret, G. and Senyai, A. Magnetic Microspheres: synthesis of a novel parenteral drug carrier. J. Pharm. Sci., 68 (1979) 79–82.