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Note

Drug release from microparticulates; deconvolution of measurement errors

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Summary

This paper examines some of the potential errors which can occur in the measurement of rapid drug release from disperse delivery systems. The effects of finite instrument response times on the drug release profiles in a continuous flow drug release apparatus are studied, and examples are provided to demonstrate the significance of these effects in a typical experiment. Correction for this effect is shown to be of particular importance if the release profiles are being used to study diffusion processes within the delivery device.

The behaviour of a colloidal drug carrier formulation is often characterized in vitro by measurement of the drug release profile. Data of this type can be used to estimate the likely behaviour of the formulation in vivo and to study diffusion processes within the system (see, e.g., Ritger and Peppas, 1987). Several experimental protocols have been used in the past to measure drug release (Washington, 1990), but the most useful are those which measure release under sink conditions. In these experiments the delivery system is allowed to release its drug into a large volume of buffer, so that the resulting solution is 'infinitely dilute'. Under these conditions problems of receptor-phase saturation are avoided, and more importantly all the reverse processes of drug-carrier recombination have zero rate. The resulting kinetics reflect only the processes involving loss of drug from the carrier, such as diffusion, carrier degradation, and dissolution.

Perfect sink conditions are a theoretical construct and cannot be achieved in practise. The released drug could not be assayed in an infinitely dilute solution. However, many experimental protocols use large-dilution sink procedures, the most popular being the flow filtration cell (see, e.g., Koosha et al., 1988). In this experiment the drug carrier system is diluted into a stirred cell equipped with a filter which retains the carrier but allows the released drug solution to be removed for assay, while being replaced with a similar volume of fresh dissolution medium. It should be stressed that the analysis presented here applies only to this system and not to the classical dissolution experiment in which drug is allowed to accumulate in a large reservoir to which all assay samples are returned.

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The drug concentration-time profile from the filtration cell is usually taken to be proportional to the drug release rate from the carrier. This approximation is adequate for studying release profiles from macroscopic sustained-release devices, or particles with diameters of tens of microns, where the release profile occurs over several hours. However, there is much interest in intravenously injectable particulates of diameters in the region of 0.1–0.5 μm; due to their small size these materials release their drug load much more rapidly than larger carriers (Guy et al., 1982). Release of 90% of the drug within 1–2 h is typical from many of the polymeric nanoparticulates studied in our laboratories. Under these conditions, a significant error is introduced into the release profile due to the response time of the ultrafiltration cell. This is due to the time required at a given flow rate to replace all the liquid in the cell, and causes, for example, an infinitely fast drug release profile to be 'smeared out' into a pulse with a rapid rise time and slow decay as the cell is flushed out.

In order to minimise this effect it is reasonable to attempt to replace the solvent volume in the cell rapidly by using a small cell and high flow rate. Unfortunately, this is not always possible, since, to retain the smallest particles in the cell, fine filters or ultrafilters with slow flow rates must be used. The experimenter is forced to compromise between efficient filtration and adequate flow rate. It should be noted that many published studies do not allow the magnitude of these problems to be assessed by the reader (or even the referee), since no mention of cell flow rates and volumes is made.

An alternative approach is to remove mathematically the error from the experimental data by deconvolution. This is a well-known technique which is covered in most textbooks of time series analysis (e.g. Kuc, 1984). Briefly, the experimenter obtains the release profile of the drug from the carrier, and in a similar experiment under identical conditions obtains the profile from a bolus injection of the drug in solution (the so-called impulse response or instrument function of the apparatus).

The procedure for extracting the undistorted drug release profile is straightforward. Both the experimental drug concentration-time profile (the 'data') and the instrument response function are converted to the frequency domain by Fourier transformation. The data is then divided by the instrument function, since division in the frequency domain is equivalent to deconvolution in the time domain. Finally, the result, which is the frequency-domain representation of the deconvoluted release profile, is inverse transformed to yield its corresponding time series, i.e. the deconvoluted drug release profile.

We have written software which performs this deconvolution and applied it to the release data of prednisolone from poly(d,l-lactide) microspheres in order to assess the likely magnitude of the errors involved under typical experimental conditions.

Microspheres of poly(d,l-lactide) containing 21.5 w/w% prednisolone were prepared as described previously (Koosha et al., 1988). Their volume mean diameter was measured to be 5.46 μm (10–90% range 3–7 μm) by laser diffraction (Malvern Instruments 2600D). The continuous flow ultrafiltration cell was similar to that described previously. The cell volume (Amicon 8200) was 200 ml and was pressurised to 10 lb/inch^2 providing a flow rate of 2 ml min^{-1} with the ultrafilter used (Amicon M2, molecular weight cut-off 1000). The release medium was 0.01 M phosphate buffer (pH 7.4) and released prednisolone was assayed at 242 nm by ultraviolet absorbance. The instrument function of the apparatus was measured by the injection of a bolus of prednisolone in water (10 ml, 0.5 mg/ml), and the drug release was determined by injection of 10 mg of microspheres suspended in 2 ml buffer.

The data and instrument functions were digitized by measurement of amplitude at 64 uniformly spaced time intervals. Deconvolution was performed using software written in Basic on a Macintosh SE.

Fig. 1 shows the release profile obtained (a) when a bolus of prednisolone solution was injected into the cell, and (b) when prednisolone loaded microspheres were injected. The approximate times to clear 90% of the drug from the filtrate were 140 and 960 min, respectively. Note

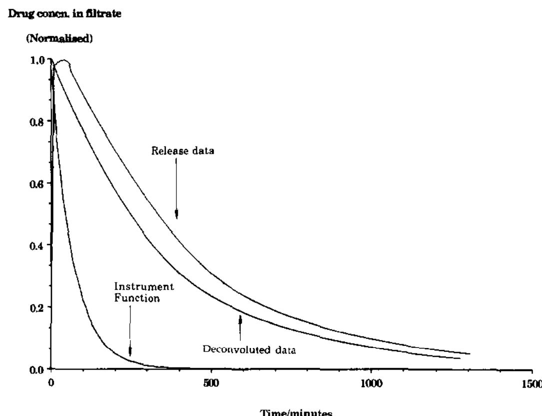

Fig. 1. Experimental instrument function, drug release profile and deconvoluted release profile for prednisolone release from poly(d,l-lactic acid) microspheres.

that both drug release profiles have been normalised to a peak value of 1, since, in order to perform the deconvolution, it is not necessary to know the relative amplitudes of the instrument function or data.

Fig. 1 shows the prednisolone release profile together with the true release profile obtained by deconvoluting the instrument response as described. This reduces the time to clear 90% of the drug from the cell to 930 min.

Using this particular experimental configuration, we obtain an instrument response which is a factor of 7 faster than the release rate of the drug delivery system under study. It may be thought that this is sufficiently rapid for the release profile to be undistorted by the experimental response time. The deconvoluted profile of Fig. 1 demonstrates that this is not the case. Although the general shapes of the release profiles are similar, the release rates are significantly different; for example, the time to half-release (T_{50}) has been decreased from 320 to 250 min. Since deconvolution is essentially an 'unsmoothing' operation, the deconvoluted data has more superimposed noise. More importantly, the shape of the peak has been grossly changed in the initial few minutes of the experiment; the raw data showed a delay and a slow peak, while the true profile reaches a maximum almost immediately. The origin of this error is of course the time needed to fill the tubing connecting various parts of the experiment. The consequences of errors of this sort in the initial period of the experiment are considerable, since most models of diffusion and drug release analyse only the initial stages of release, in order to simplify the mathematics of diffusion.

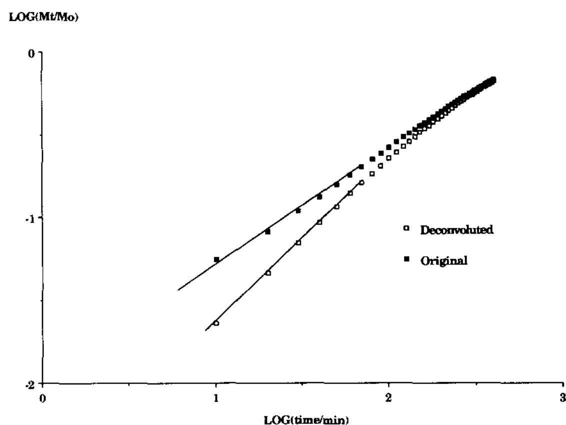

Fig. 2. Critical exponent plots for prednisolone release from poly(d,l-lactic acid) microspheres with and without instrument response deconvolution.

The level of error can be appreciated if we calculate the critical diffusion exponents for prednisolone release before and after deconvolution. These correspond to n in the model equation (Sinclair and Peppas, 1984):

$$M_t/M_0 = Kt^n$$

M_t/M_0 is obtained by integration of the release profiles of Fig. 1, n is obtained as the gradient of the plot in Fig. 2. For the original data, $n = 0.45$, while for the deconvoluted data, $n = 0.62$, a considerable difference. It is also notable that the initial stage of release (up to 100 min) is a significantly better fit to the straight line after deconvolution.

The system studied here releases its drug slowly over several hours due to its comparatively large size of 5 μm. Despite this significant errors are present and could still be produced even if the release profile was slower than that studied here, or alternatively if the apparatus had a faster response time. The effects of convolution on the data are considerable, particularly if a detailed study of the diffusion processes is desired.

NB: For the purposes of evaluating studies where no instrument function is available, it can be approximated as an exponential decay:

$$[\mathrm{I}]_t = [\mathrm{I}]_0 \exp(-ft/V)$$

where $[\mathrm{I}]_t$ is the concentration of the released drug at time t, f is the flow rate through the ultrafiltration cell, and V is the cell volume. This assumes that the cell is well stirred and that its volume is large compared to that of the connecting tubing. We have not used this approximation in these studies, but others may find it useful for evaluating previously published data.

The effects of instrument response time may introduce a significant error into drug release profiles, which is particularly serious if the data are to be used for the study of physicochemical processes such as diffusion within the drug delivery system. We hope that the data presented will convince workers in the field of the need for critical data analysis in this area.

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