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Variation of Population Release Kinetics in Polydisperse Multiparticulate Systems (Microcapsules, Microspheres, Droplets, Cells) with Heterogeneity of One, Two or Three Parameters in the Population of Individuals

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Abstract—Release kinetics of active substances from ensembles of microparticles such as microcapsules, cells, droplets and liposomes constituted of individual entities releasing their contents at constant rates may follow zero order, first order, sigmoid or biphasic equations. The release equation observed depends upon the statistical distribution of release-determining parameters among the population. Typical cases are presented in terms of the distribution of two parameters, payload (m_∞) and time for complete payload release (t_∞) which also define the release rate constant (k). Heterogeneity of the two parameters generally leads to first order ensemble behaviour, whereas heterogeneity of one parameter only may lead to different ensemble release equations, viz. zero order (m_∞ heterogeneous) or first order (t_∞ heterogeneous). Biphasic distribution can lead to an apparent 'burst' effect, with apparent change of kinetics. The presence of a third heterogeneous parameter, lag time, yields a sigmoid ensemble release curve. These conclusions are demonstrated by simulations or experimentally, and are also valid for linearized curves of microparticles following matrix kinetics.

It was recently shown experimentally that microcapsules containing various materials such as theophylline, sodium chloride, sodium citrate and potassium dichromate, encapsulated in ethyl cellulose or Eudragit RS, demonstrated zero order release from single microcapsules while showing first order release from ensembles (Hoffman et al 1986a). The theoretical basis of this phenomenon was also presented (Gross et al 1986). It was established that ensemble kinetics could follow first-order, matrix-diffusion (square root time) or dissolution (cube root mass) kinetics according to the nature of the statistical distribution of parameters such as payload (m_∞) and time for complete release of payload (t_∞) among the population of zero order release individuals.

In natural polydisperse microparticulate populations, including microcapsules, droplets, liposomes and cells, a first order behavioural pattern has proved to be the most common (Nixon & Walker 1971; Madan & Shanbhag 1978; Donbrow & Benita 1982; Thies 1982; Benita & Donbrow 1982a,b; Benita et al 1985a), probably as a result of the prevalence of distributions approximating to gamma or log normal density (Gross et al 1986). Nevertheless, matrix kinetics (Alpar & Walters 1981; Jun & Lai 1983; El Samaligy & Rohdewald 1983), dissolution kinetics (Benita & Donbrow 1982c) and other types (Nixon & Walker 1971; Madan et al 1976; Yalabik-Kas 1983) have been reported. Measurements were made using ensembles of generally undefined distribution character, heterogeneity not being considered a factor.

Theoretically, single 'coated' microcapsules subject to wall membrane-control of release would be expected to manifest constant rate over the major part of their release and, in fact commonly do so (Hoffman et al 1986a,b). Exponential release from individuals would be unexpected, implying a changing concentration gradient throughout the process, though we have recently discovered such an example in porous microspheres (Benita et al 1988). In any case, this should only lead to first order ensemble release in the special case of relatively homogeneous exponential release rate distribution in the population (Gross et al 1986).

In the present work, another experimental case is presented of a sigmoid ensemble curve resulting from the presence of a third heterogeneous parameter, the lag time, in the polydisperse zero order release from individual microcapsules. Other possible cases of overall population behaviour are also defined by means of simulations ranging from zero to biphasic. It is shown that homogeneity of one major parameter only, viz. payload or time for complete payload release, can lead to totally different population release profiles, according to which parameter is homogenized. The case of matrix release is also included to demonstrate that the conclusions are also valid for non zero-order release individuals and it is shown that linearized plots of polydisperse matrix-release observing particles also yield first order linearized population release plots. Implications thus range through a wide variety of disperse systems embracing aerosol, liposome and emulsion behaviour, macromolecular reactions and biological cell processes, as well as solid particle systems.

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Materials and Methods

Microcapsules were prepared by means of a phase separation non-solvent addition technique described fully elsewhere

(Donbrow et al 1984a,b; Benita et al 1985a,b) giving well-formed single core individuals. The coating polymers were polymethylmethacrylates (Eudgragit RS and (more permeable) RL, Roehm Pharma, Darmstadt, West Germany) dissolved in chloroform or tetrahydrofurane, the non-solvent was cyclohexane and an antiaggregating agent, polyisobutylene, was present in the solution. The core materials were sodium citrate and theophylline. Release rate profiles were measured conductimetrically for the salt and spectrophotometrically for theophylline in both ensemble and individual release (Donbrow et al 1984b; Hoffman et al 1986a,b).

Results and Discussion

The most typical release behaviour is that shown in Fig. 1 where the upper experimental cumulative curve fits closely a first order equation (P=1). The population was found experimentally to consist of zero-order individuals and summation of the amounts released by the individuals gave a curve identical with that measured on the ensemble. Here, the microcapsule cores were of sodium citrate and the wall polymer was Eudragit RS. Most microcapsules studied by us using a variety of core and wall materials and techniques exhibited this pattern of behaviour, the single microcapsules releasing at constant rates as expected theoretically (Hoffman et al 1986a) and the population kinetics being first order. The two parameters m_∞ and t_∞ varied greatly in the population as a whole, the first bearing out Kondo's (1978) statement on microcapsule size variation (though the core materials were relatively narrow cuts prepared by sieving), whereas the slope variation has not previously been known. There appears to be some dependence of slope on payload probably arising from wall thickness dependence on payload but there are a number of exceptions.

A more complex situation arises where a third heterogeneous parameter is present. This is illustrated by the experimental system shown in Fig. 2 (upper diagram) for

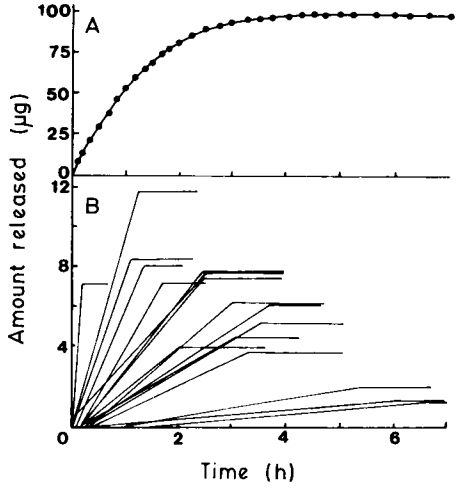

FIG. 1. Experimental release profiles of sodium citrate microcapsules (individuals, B; ensembles, A, with full curve showing first order simulation). [Microcapsules, 30:70% w/w Eudragit RS: sodium citrate by phase separation (Donbrow et al 1984a,b; Benita et al 1985a,b).]

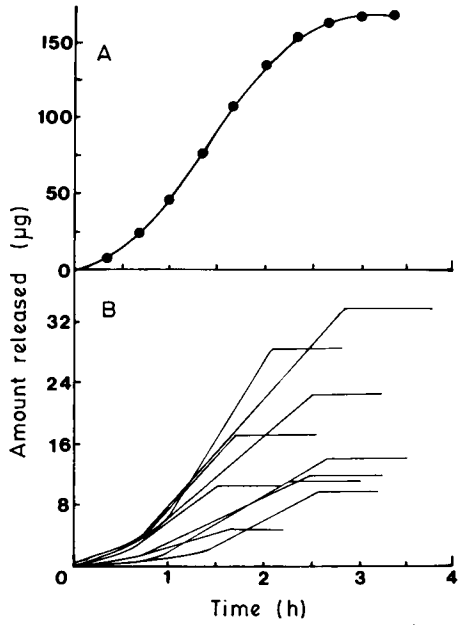

FIG. 2. Experimental release profiles of theophylline microcapsules (individuals, B; ensembles, A) showing lag time heterogeneity. [Microcapsules: Eudragit RL: theophylline. By phase separation, two solvent method (loc. cit. Fig. 1).]

release of theophylline. The ensemble release appears to be S-shaped, invoking involvement of a uniform initial time-dependent overall process such as wetting, swelling, solvent-penetration or degradation preceeding release. In reality, the source of the sigmoid form lies in the heterogeneous distribution of the third parameter, the lag time, among the individuals (Fig. 2 lower) as well as the payload and rate constant. Lag time distribution may or may not show correlations with one of the other parameters. It might, for example, be dependent on the wall thickness, which, in turn, could be a factor in determining the slope value, k_i. In the experimental example, there is a tendency for the faster-releasing capsules to have shorter lag-times than the slower-releasing ones, as well as higher payloads, suggesting that the 'fast' have thinner walls, though, again, individual behaviour is not clear-cut. These microcapsules were prepared using a slightly porous polymethacrylate (Eudragit Retard RL) as coating polymer.

It is interesting to look at some cases in which one or other of the determinant parameters of the individuals is homogeneous, to see their influence on the overall behaviour, and also to look at some other possible situations such as matrix diffusion and biphasic parameter distribution, and these will be demonstrated by simulation.

Simulation

The discordancy between individuals and ensembles is illustrated in Fig. 3 for particles with a hypothetical distribution of payloads and release rate constants. The individual particles release their payloads at a rate proportional to the square root of time (lower curve), in accordance with a diffusional mechanism of release (Madan et al 1976), as expected for single microspheres behaving as insoluble matrices containing microdispersions of the active material

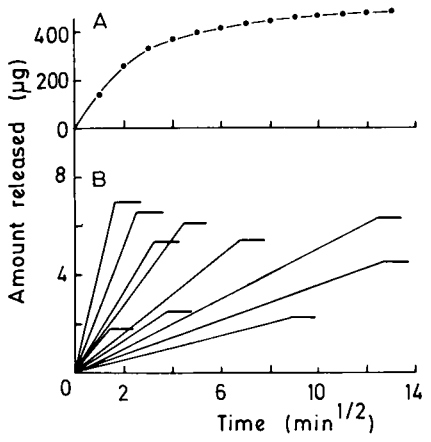

FIG. 3. Predicted release from microparticles liberating payloads at rates proportional to square root of time. Lower graph B: individual release curves. Upper graph A: ensemble release (same individuals).

but have been linearized using a $t^{1/2}$ scale. Summation of the quantities released by the single particles on the same time scale yields a cumulative curve totally unrelated to the determining square root time equation (Fig. 3, upper curve). The same conclusion emerges whatever basic kinetic profile is exhibited by the single units and however the time scale is linearized, provided the individuals have two or more determinant parameters heterogeneously distributed. Thus the experimental example of a first order cumulative curve from zero order release in individuals shown earlier (Fig. 1) is not unique to zero-order kinetics of the latter.

Identity of form for ensemble and individual curves represents a special case in which the time for total payload release, t_∞, is homogeneous in the population, though the payload, m_∞, may still be heterogeneous. In this rare situation $m_i = k_i t$ for release from single individuals (i) (Fig. 4, lower diagram), where m_i = amount released in time t, k_i = individual release rate constants. The instantaneous cumulative payload release is given by

$$M(t) = \Sigma\,(m_i)_t = \Sigma\, k_i t = t\Sigma k_i = Kt,$$

where K is sum of rate constants.

$$M(t) = \Sigma \frac{(m_\infty)_i t}{t_\infty} = \frac{t}{t_\infty}\Sigma(m_\infty)_i = \frac{t}{t_\infty} m_\infty$$

where $m_\infty = \Sigma\,(m_\infty)_i$ and $K = m_\infty / t_\infty$.

On the other hand, identity of the cumulative and individual kinetics is not obtained if the value of k is homogeneous in the population while m_∞ remains heterogeneous (Fig. 5), since exhaustion of the varying payloads introduces a discontinuity. Polydispersity being the norm in most natural growth or degradation processes, the overall kinetic equation is not coincident with that of the individuals except in cases of total parameter monodispersity or homogeneity of t_∞. Since these are exceptional, positive inferences drawn regarding underlying mechanisms are probably unreliable in the majority of cases reported. Again, where the cumulative curve shows an apparent initial rapid release at the beginning of the process followed by a slower release, sometimes of different kinetic form, theoretical deductions are frequently made. It may be inferred that some of the active substance is dissolved in the external wall material, or adsorbed on the surface, or that there is a change in mechanism (Donbrow & Benita 1982; Vidmar et al 1984), the initial process being sometimes termed a 'burst' effect. However, such behaviour may well stem from bimodal heterogeneity derived from a combination of two populations having rapid and slow payload release (Fig. 6). Alternatively, such an apparently linear phase may represent initial Fig. 4 behaviour, curvature setting in only when payload exhaustion becomes significant.

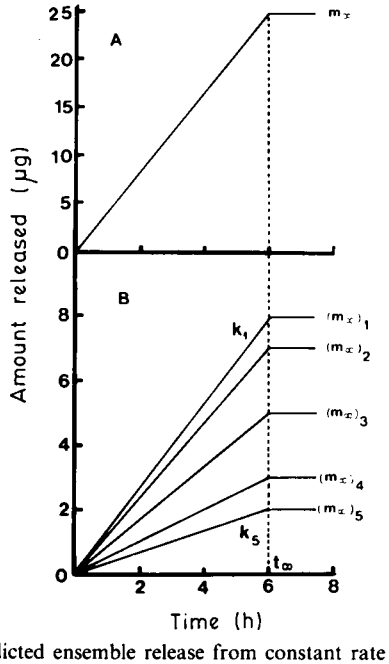

FIG. 4. Predicted ensemble release from constant rate individuals homogeneous in total payload release time (t_∞) but heterogeneous in payload (m_∞). Lower graph B: individual release curves. Upper graph A: ensemble release curve.

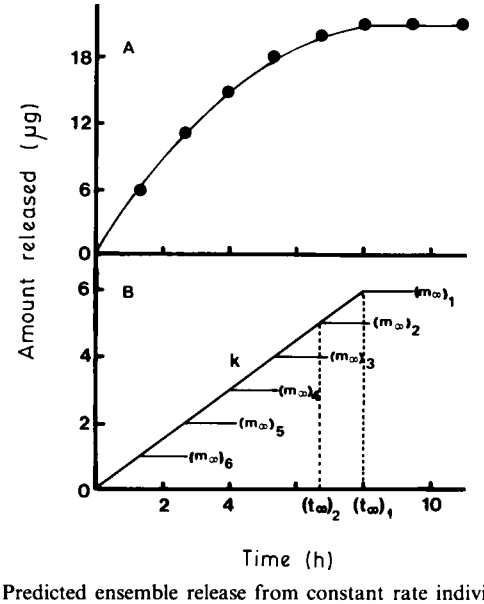

FIG. 5. Predicted ensemble release from constant rate individuals homogeneous in release rate constant (k) but heterogeneous in payload (m_∞). Lower graph B: individual release curves. Upper graph A: ensemble release curve.

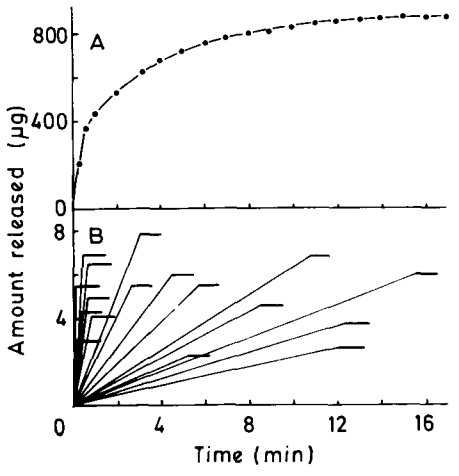

FIG. 6. Predicted change in ensemble kinetics from constant rate individuals with bimodal parameter distribution, showing apparent 'burst' effect. Lower graph B: individuals. Upper graph A: cumulative.

The discussion has been simplified to cases in which only one or two release parameters undergo variation in the ensemble. The presence of a third release-controlling parameter varying among the individuals can give rise to a number of interesting changes in the forms of the ensemble release curves, an important example involving lag time having been demonstrated earlier experimentally (Fig. 2). The apparent equation for overall behaviour of the population is identifiable by curve fitting techniques, such as regression procedures and computer simulations and will be valid for describing the particular heterogeneous experimental system. However, as is self-evident, inferences about the mechanism of the kinetic processes occurring in the individuals cannot be made from the cumulative behaviour. Still more so, changes of mechanism postulated to occur during release for the sole purpose of obtaining better curve-fitting of different parts of an overall release curve to more than one standard equation cannot be validated, since the curve characteristics are determined by the nature of the heterogeneity and the number of essential parameters involved in the release kinetics, as well as the individual release profiles. It is impossible to determine the true mechanisms or the nature of the heterogeneous distribution without extensive studies on individuals in populations.

References

Alpar, H. O., Walters, V. J. (1981) J Pharm. Pharmacol. 33: 410–422
Benita, S., Donbrow, M. (1982a) J. Pharm. Sci. 71: 205–210
Benita, S., Donbrow, M. (1982b) J. Pharm. Pharmacol. 34: 77–82
Benita, S., Donbrow, M. (1982c) Int. J. Pharm. 12: 251–264
Benita, S., Hoffman, A., Donbrow, M. (1985a) J. Pharm. Pharmacol. 30: 65–67
Benita, S., Hoffman, A., Donbrow, M. (1985b) J. Microencapsulation 2: 207–222
Benita, S., Babay, D., Hoffman, A., Donbrow, M. (1988) Pharm. Res. in press
Donbrow, M., Benita, S. (1982) J. Pharm. Pharmacol. 34: 547–551
Donbrow, M., Benita, S., Hoffman, A. (1984a) Israel Patent Application 70431
Donbrow, M., Benita, S., Hoffman, A. (1984b) J. Appl. Biochem. Biotechn. 10: 245–249
El Samaligy, M., Rohdewald, P. (1983) Int. J. Pharm. 13: 23–34
Gross, S. T., Hoffman, A., Donbrow, M., Benita, S. (1986) Ibid. 29: 213–222
Hoffman, A., Donbrow, M., Gross, S. T., Benita, S., Bahat, R. (1986a) Ibid. 29: 195–211
Hoffman, A., Donbrow, M., Benita, S. (1986b) J. Pharm. Pharmacol. 38: 764–766
Jun, H. W., Lai, J. W. (1983) Int. J. Pharm. 16: 65–77
Kondo, T. (1978) in: E. Matijevic (ed.) Surface and Colloid Science, Vol. 10. Plenum Press, New York, pp 1–43
Madan, P. L., Madan, D. K., Price, J. C. (1976) J. Pharm. Sci. 65: 1476–1479
Madan, P. L., Shanbhag, S. R. (1978) J. Pharm. Pharmacol. 30: 65–67
Nixon, J. R., Walker, S. E. (1971) Ibid. Suppl. 23: 1475–1479
Thies, C. (1982) Crit. Rev. Biomed. Eng. 8: (4) 335–383
Vidmar, V., Smolcic-Bubalo, A., Jalsenjak, I. (1984) J. Microencapsulation 1: 131–136
Yalabik-Kas, H. S. (1983) Drug Devel. Ind. Pharm. 9: 1047–1060