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Fundamentals of release mechanism interpretation in multiparticulate systems: the prediction of the commonly observed release equations from statistical population models for particle ensembles

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Summary

The kinetics of release from a population of microparticles is determined by the distribution of a small number of parameters governing the release function in a heterogeneous population. A general model for treatment of the distribution is developed for any release pattern common to a whole population, which is shown to lead to a variety of different cumulative release equations, including those hitherto considered to govern the release mechanism from microcapsules. Thus, the main case, that of constant release rate from individuals differing in rate constant, is shown to yield, according to the statistical distribution of the parameters, ensemble kinetics following first-order, square-root of time (Higuchi's equation), cube-root law (Hixson-Crowell) or a combination of initial zero-order followed by square-root of time relationships, all of which have been used to describe experimental systems studied. It is demonstrated that the cumulative release kinetics observed in a multiparticle system, being a function of the statistical distribution of parameters, does not characterize the basic release mechanism, which can only be determined directly from studies on individuals. The treatment also shows that in the case of first-order release by individuals, the ensembles cannot also observe first-order kinetics, except in the rare case of homogeneity of the determining parameters in the population.

Introduction

This paper is devoted to the development of the statistical models for the release kinetics of multiparticle systems. In the companion paper (Hoffman et al., 1986) the release behaviour of individual microcapsules was experimentally determined using a newly developed technique. In all the systems studied the overall release profile was seen to be entirely different from that of the single microcapsules, causing the release mechanism to be misinterpreted. Whereas the single microcapsules release their payload at constant rate, as predicted theoretically (Hoffman et al., 1985, 1986), the same microcapsules in ensembles observed first-order, or exponential behaviour. Such ex-

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ponential kinetics are in fact the norm, fitting far more experimental data than any other mathematical description. Exponential kinetics are, however, difficult to reconcile with chemical theories for release mechanisms of microencapsulated solids (Hoffman et al., 1986; Thies, 1982). This led to the search for a non-mechanistic explanation based on ensemble behaviour of a large number of statistically independent particles. The model described in this paper is the result.

When applied to populations of microcapsules that release their payload at constant rate, the model predicts exponential cumulative release for the ensemble whenever the time to complete release, which varies from one microcapsule to another in the population, follows a certain skewed distribution, and is statistically uncorrelated to the microcapsules' payload in a sense to be made precise in this paper. Using exploratory data analytical techniques, the data gathered for the four systems under study were shown (Hoffman et al., 1986) to be in substantial agreement with the statistical model, thereby lending experimental support to the present approach.

Apart from the work of Thies and his colleagues (Thies, 1982; Dappert and Thies, 1978a and b), there has been no appreciation or application of the statistical approach in the literature, despite its broad implications to release from all multiparticulate systems in a great variety of applications additional to drug delivery.

In the present work, the statistical model is developed in a manner that is sufficiently general to accommodate any ensemble of particles exhibiting a common type of release behaviour. The variation among particles in the ensemble is expressed in the model through the distribution of a small number of parameters governing their release function. Special attention is given to ensembles of constant release-rate particles. In addition to exponential ensemble kinetics, it is shown that models used in describing cumulative release from microcapsules, pellets and simple particulate dispersions, particularly of the first-order, square-root of time (Higuchi's matrix model) and the cube-root equation of Hixson and Crowell, 1931), discussed in the adjoining paper (Hoffman et al., 1986), are derivable from the model with basic statistical assumptions applied to the distribution of particle parameters.

Theoretical basis

The only paper entering into possible bases for understanding the release behaviour of heterogeneous particles is an important but apparently unapplied one. Dappert and Thies (1978a) proposed an elegant and simple statistical model for the kinetics of release of material from populations of microcapsules based on the release behaviour of individuals. They postulated the following general assumptions: (a) capsules release their payload independently of each other; (b) the external concentration of material in the medium remains constant or under sink conditions throughout the release process; and (c) the release functions of individual capsules in the ensemble have the same form and depend on a small number of physical parameters that vary from capsule to capsule.

The fraction of the total population payload (M_∞ in their notation) released at time t, $M^*(t)$, is then the statistical average of the (dimensionless fraction $m^*(t)$ of total payload m_∞ of the single capsules in the ensemble. Thus if the single capsule (fractional) release function $m^*(t)$ is a function of some physical parameter α, then for the population fraction:

$$M^*(t) = \int_R m^*(t;\ \alpha)\psi(\alpha)\ d\alpha \tag{1}$$

where R is the set of possible values of the parameter α and $\psi(\alpha)$ is its density, i.e. $\psi(\alpha)\Delta\alpha$ represents the fraction of capsules in the population with parameter values between α and $\alpha + \Delta\alpha$. The parameter α in this formulation may represent a single real parameter or a vector of parameters.

Using this formulation, Dappert and Thies showed that the release function $M^*(t)$ for the total population at time t, although determined by the release function $m^*(t;\ \alpha)$ for the individual capsules through the process of averaging over α as given in Dappert and Thies (1978a), does not necessarily follow the same functional form as $m^*(t)$. Thus individual capsules may release their payload at a constant rate whereas the release function $M^*(t)$ for the total population (derived from Eqn. 1) may be exponential or first-order release. More precisely, if the release function $m(t)$ per capsule is a broken line, i.e.:

$$m(t) = \begin{cases} m_\infty \dfrac{t}{t_\infty} & \text{if } t < t_\infty \\ m_\infty & \text{if } t \geqslant t_\infty \end{cases} \tag{2}$$

and assuming absence of lag time or burst effects, then the fractional release function:

$$m^*(t) = m(t)/m_\infty$$

is characterized by one parameter t_∞, the time to complete release of its payload m_∞. If t_∞ is assumed to follow the gamma-distribution with shape parameter $m = 2$ and scale parameter K (Johnson and Kotz, 1970), then the fractional release function for the ensemble $M^*(t)$ derived from Eqn. 1 is exponential, i.e.:

$$M^*(t) = 1 - e^{-Kt} \qquad \text{for } t > 0 \tag{3}$$

To complete the specification of this model they assumed an unfamiliar distribution for the slope b, which in our notation reduces to the familiar gamma-distribution for t_∞; note that t_∞ is proportional to $1/b$ when m_∞ is constant in the population.

The gamma-distribution for the time to complete release is commonly used in the stochastic modelling of waiting times in queuing and other statistical theories, and has a density:

$$\psi(t_\infty) = K^2 t_\infty e^{-Kt_\infty} \qquad \text{if } t_\infty > 0 \tag{4}$$

We prefer the use of t_∞ to that of b, since the former is a waiting time for the termination of a physical process. A large number of possible distributions for modelling dispersion of waiting time exist in the literature (see Johnson and Kotz (1970) for example).

Although this result of Dappert and Thies may appear superficially to be a mere mathematical manipulation, its purpose was to demonstrate that the specific functional form of a population release function determined in laboratory experiments does not determine the functional form of release for individual capsules and need not be explained on that basis.

In their paper, the authors suggested that single capsule kinetic release behaviour may be determined in the laboratory for a sample of capsules and the "ingredients" of their formula (Eqn. 1), $\psi(\alpha)$ and $m^*(t;\ \alpha)$ be computed, thus "explaining" the ensemble behaviour determined experimentally.

A technique for determining single capsule release behaviour has been developed by some of the authors, and the program described above was carried out for several types of capsules (Hoffman et al., 1985).

In the present paper, the statistical approach is carried one step further to model $M(t)$ rather than $M^*(t)$ and to investigate experimentally determined ensemble release functions. We show that common kinetic laws appearing to be applicable to release from experimental microcapsular systems (see refs. in Hoffman et al., 1985), such as Higuchi's law (Higuchi, 1963), postulating:

$$M(t) = K\sqrt{t} \tag{5}$$

for some constant K up to the release of 60–80% of the total population payload M_∞, can result from an inhomogeneous ensemble of capsules each of which releases its payload at contant rate. We also show that the commonly encountered population release function which starts out at constant rate for small values of t, and then develops continuously into Higuchi's law (Eqn. 5) may be similarly explained. Finally the experimentally derived law of Hixson and Crowell (1931) for dissolution release (Eqn. 6) during the early stages:

$$W_0^{1/3} - (W(t))^{1/3} = Kt \tag{6}$$

where $W(t) = M_\infty - M(t)$ represents the total payload remaining at time t and $W_0 = W(t = 0) = M_\infty$ represents the initial payload, is derived statistically from constant release rate capsules when t_∞ is constrained to vary in a finite interval (O, A) for all the capsules in the population and the statistical average of the capsule payloads in the subpopulation of capsules with a given release time t_∞ is proportional to t_∞.

All these empirical population release laws are shown to be possible in an ensemble of capsules or particles which follow constant rate release individually.

We also consider briefly a population of capsules with individual exponential release function following Eqn. 3. We show that such a population cannot display an exponential release rate unless the individual rate parameter K in Eqn. 3 is constant in the population. This result, together with Dappert and Thies' prediction of exponential release for the population from individual constant rate release constitute a striking example of a general principle which emerges from our investigation. That is, that in general the empirical release functional form yields little information about the underlying microprocess. Only direct measurements of release of single microcapsules reveal the basic kinetics involved.

This investigation also reveals the variety of population release rates which are, at least theoretically, possible with the same type of single capsule release behaviour as shown to be the preferred mechanism in the majority of cases (Hoffman et al., 1985, 1986). The empirical investigation of single capsule release behaviour together with population release behaviour of the same capsules under different physical conditions may lead to an understanding of the factors governing the distribution of parameters (such as t_∞ and m_∞) when capsules release their payload simultaneously into the same medium. One possibility may involve the introduction of "coupling" between capsules in the population that determines the distribution of their parameters in a given population.

The general population model

The purpose of this section is to extend the population release model as given in Dappert and Thies (1978a) to allow for statistical "coupling" or correlation between the parameter(s) α governing the fractional payload release function $m^*(t;\ \alpha)$ and the total single capsule payload m_∞. In the case of constant rate release for single capsules, $m^*(t;\ \alpha)$ is a function of t_∞, the time to complete release of the capsule. The parameter α here is one-dimensional and is identified as t_∞. In some populations the value of m_∞ and t_∞ of a capsule may be positively correlated. In such populations, capsules with larger payloads will tend to take longer to release them completely. If we adopt the basic assumptions (a)–(c), allowing, however, for a possible correlation between m_∞ and the parameters α, the total population material released by time t, M(t), will still be the sum of individual capsule material released by time t, m(t). If $\psi(m_\infty, \alpha)\Delta m_\infty \cdot \Delta\alpha$ designates the fraction of capsules having released $m_\infty \cdot m^*(t;\ \alpha)$ by time t, we conclude that:

$$M(t) = N\int_{R^+} m_\infty \cdot m^*(t;\ \alpha)\psi(m_\infty, \alpha)\ dm_\infty\, d\alpha \tag{7}$$

where R^+ denotes the range of values of (m_∞, α) and N the number of capsules in the population. We note parenthetically that α, which may be vector-valued, may include m_∞ among its components or may depend on m_∞ in other ways.

Our model, as formulated in Eqn. 7, can be easily seen to be an extension of Eqn. 3. To this end we introduce the notion of mean or average capsule payload $m_\infty(\alpha_0)$ in the subpopulation of capsules sharing the same value(s) of the parameter(s) α, say $\alpha = \alpha_0$. In statistical terminology this average is called the conditional expectation of m_∞ given $\alpha = \alpha_0$, and is a deterministic (non-random) function of α_0. If $f_{\alpha_0}(m_\infty)\Delta m_\infty$ denotes the fraction of capsules in the subpopulation of capsules with $\alpha = \alpha_0$ whose payload lies between m_∞ and $m_\infty + \Delta m_\infty$, and $g(\alpha_0)\Delta(\alpha_0)$ denotes the fraction of capsules in the total population with parameter(s) α between α_0 and $\alpha_0 + \Delta\alpha_0$, then we may rewrite Eqn. 7 as:

$$M(t) = N\int m_\infty(\alpha)m^*(t;\ \alpha)g(\alpha)\ d\alpha \tag{7'}$$

with:

$$m_\infty(\alpha_0) = \int m_\infty f_{\alpha_0}(m_\infty)\ dm_\infty \tag{8}$$

When $m_\infty(\alpha_0)$ does not depend on α_0, i.e., the average value of the payload subpopulations of capsules sharing a fixed value of $\alpha = \alpha_0$ (viz. subpopulations with a fixed functional release function $m^*(t;\ \alpha_0)$) does not depend on the specific value α_0, then this constant value must be equal to the average payload in the total population, say $\overline{m}_\infty$, satisfying $N\overline{m}_\infty = M_\infty$. Thus, if $m_\infty(\alpha_0)$ does not depend on α_0, we have:

$$M(t) = M_\infty \int m^*(t;\ \alpha) g(\alpha)\, d\alpha$$

which is a simple re-expression of Eqn. 1.

Quite generally, we may introduce the fraction $f(m_\infty)\,\Delta m_\infty$ of capsules in the population with payloads between m_∞ and $m_\infty + \Delta m_\infty$, and the average $\overline{m}_\infty$ of payloads in the population. We then have the twin relations:

$$\overline{m}_\infty = \int m_\infty f(m_\infty)\, dm_\infty \qquad \text{and} \qquad \overline{m}_\infty = M_\infty / N$$

Using both relations, we arrive at our final formulation of the expanded model:

$$M(t) = \frac{M_\infty \int m_\infty(\alpha) m^*(t;\ \alpha) g(\alpha)\, d\alpha}{\int m_\infty f(m_\infty)\, dm_\infty} \tag{7*}$$

Before applying this formula to specific micromodels (specific functional forms of $m^*(t;\ \alpha)$), we note that M_∞ and the integral in the denominator are population constants which do not depend on t and which will not affect the form of the population release function M(t), i.e. the form of M(t) will be completely determined by the specification of the function $m_\infty(\alpha)$ and the density (α) of the parameter α.

In this sequel, we shall divide models according to their functional payload release function form $m^*(t;\ \alpha)$, and then subdivide them according to their $m_\infty(\alpha)$ and $g(\alpha)$ forms.

Populations with constant release rate microcapsules

The basic constant rate model

The release function m(t) of a constant rate capsule (given by Eqn. 2) is characterized by two parameters, the total payload m_∞ and time to complete release t_∞. If we insert m(t) from Eqn. 2 into our general population release function as given in Eqn. 7*, we obtain:

$$\frac{dM(t)}{dt} = M'(t)$$

$$= (M_\infty / \overline{m}_\infty) \int_t^\infty \frac{m_\infty(t_\infty)}{t_\infty} g(t_\infty)\, dt_\infty \tag{9}$$

where $m_\infty(t_\infty)$ is the average payload for fixed values of t_∞, and $g(t_\infty)$ is the density of t_∞.

In the following subsections, we shall show that the exponential, the square-root function $Kt^{1/2}$ and the cube-root function $W_0^{1/3} - W(t)^{1/3} = Kt$, as well as other empirical release laws result from this basic model (Eqn. 9) for different combinations of $m_\infty(t_\infty)$ and $g(t_\infty)$.

In order to obtain overall zero-order release from a population, it is necessary generally that individuals releasing at constant rates have virtually identical values of t_∞, as may be seen from Eqn. 9. Their payloads, however, may follow any distribution, thus leading to an arbitrary distribution pattern for their rate constant $b = m_\infty / t_\infty$.

Exponential population release

If m_∞ and t_∞ are not correlated in the population, $m_\infty(t_\infty) = \overline{m}_\infty$, as explained in "General population model" section and

$$M'(t) = C \int_t^\infty \frac{1}{t_\infty} g(t_\infty)\, dt_\infty$$

where C stands for a generic constant independent of t. If t_∞ follows the gamma-distribution with shape parameter m = 2 and scale K > 0 then

$$g(t_\infty) = K^2 t_\infty e^{-Kt_\infty} \qquad \text{if } t_\infty > 0 \qquad \text{and}$$

$$M'(t) = Ce^{-Kt}$$

leading to

$$M(t) = \int_0^t M'(m)\, dm = C(1 - e^{-Kt_\infty})$$

which is the common exponential release function with $C = M_\infty$. Exponential release for the population may also be obtained from constant rate capsules in other ways, e.g. when t_∞ and m_∞ are correlated in such a way that

$$m_\infty(t_\infty) = \text{Const.} \cdot t_\infty \qquad (\text{Const.} > 0)$$

and t_∞ has an exponential distribution with scale parameter $\alpha > 0$ and density

$$g(t_\infty) = \alpha e^{-\alpha t_\infty} \qquad \text{for } t_\infty > 0$$

then according to Eqn. 9

$$M'(t) = \text{Const.} \int_t^\infty e^{-\alpha t_\infty}\, dt_\infty = \text{Const.} \cdot e^{-\alpha t}$$

and

$$M(t) = \text{Const.}(1 - e^{-\alpha t}) \qquad \text{for } t > 0$$

The last formula (with positive constant) depicts again first-order global behaviour. Note that the exponential distribution is but a special case of a

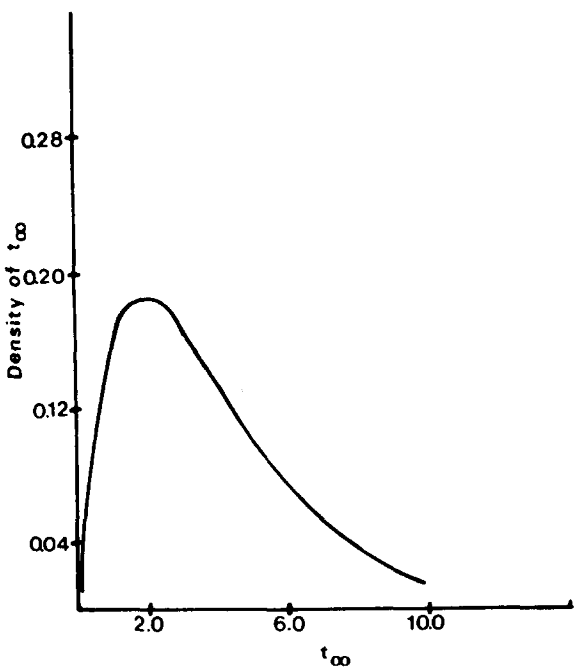

Fig. 1. Gamma density distribution of t_∞ with shape parameter $m = 2$ and scale $K > 0$.

gamma-distribution with shape parameter $m = 1$.

To relate these results to experimental situations, one may expect first-order behaviour in a population of constant rate capsules when their payloads and times to complete release are uncorrelated and the marginal density of their release times t_∞ follows the general form described in Fig. 1.

This density falls off exponentially with t_∞ but vanishes at $t_\infty = 0$. As mentioned in the Introduction it is widely used in statistical modelling of waiting time phenomena and resembles the log-normal density of particle size distribution which often serves to model physical phenomena (Carstensen and Musa, 1972; Irani and Callia, 1963; Martin et al., 1969). First-order behaviour is also expected where the density of t_∞ is exponential and the scatter of t_∞ and m_∞ in the ensemble indicates a linear dependence of m_∞ on t_∞ with noise.

As previously stated, the majority of experimental data on release from ensembles of microcapsules and other dispersed systems follows exponential kinetics.

The $Kt^{1/2}$ population release (apparent Higuchi's Law)

This type of release is characteristic of non-homogeneous capsule population. We show that it arises in the basic model for constant rate capsules (Eqn. 9) when t_∞ is highly dispersed in the population and m_∞ and t_∞ are related in a simple way, namely when

$$m_\infty(t_\infty) = a + bt_\infty$$

for some positive constants a and b. The density of t_∞ is given by:

$$g(t_\infty) = \left(\frac{\sqrt{ab}}{\pi}\right) \cdot \frac{1}{\sqrt{t_\infty}\,(a + bt_\infty)} \qquad \text{if } t_\infty > 0$$

and is of the form given in Fig. 2.

This is the density of the square-root of a Cauchy variable. Its dispersion is much higher than that of a Gaussian variable since its density falls off as $1/\sqrt{t_\infty}(a + bt_\infty)$ as t_∞ increases; its mean is infinite, although its median is of course

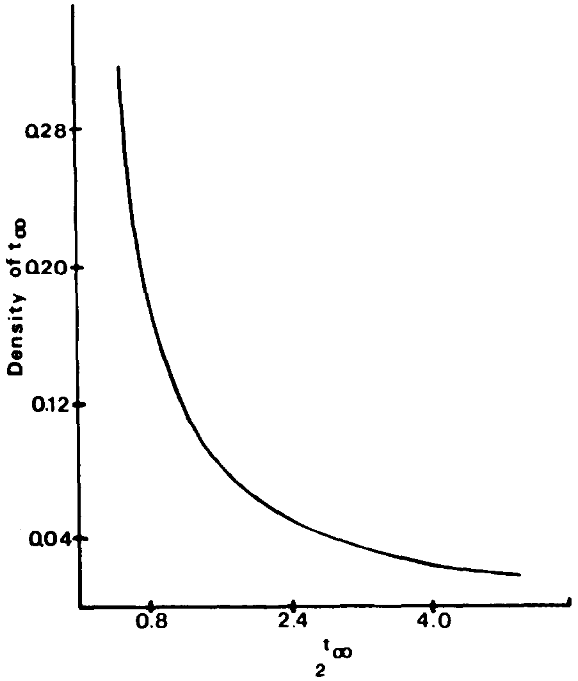

Fig. 2. Density of t_∞ when t_∞^2 follows the standard Cauchy distribution.

finite. Upon integrating Eqn. 9 with these (conditional) mean payload and density of t_∞ we obtain:

$$M(t) = \frac{4\sqrt{ab}}{\pi} \cdot \sqrt{t}$$

The assumptions leading to Higuchi's equation provide a possible mathematical expression to the notion of non-homogeneous populations. If, for instance, some capsules are not separated and form an entity comprised of several capsules which would separately follow a constant-rate release, then the effective release time would be much larger than the single capsule release time, the effective payload would be a multiple of the original payload and the two would be positively correlated.

Many systems do in fact observe apparent Higuchi release behaviour (see Hoffman et al., 1986) and this may result from population distribution following the above form. We see (Fig. 2) that the sample distribution includes groups having very short and very long release durations. The source may well be non-uniformity arising in the production process, some microcapsules having multiple cores providing extended release times while others break into smaller particles giving rapid release of their contents, with the possibility of lowered efficiency of coating in the process.

Constant rate followed by apparent Higuchi's equation

In some experimental situations the population release function M(t) appears to display constant rate initially followed by a $\sqrt{t}$ law. This macrobehaviour may arise from a non-homogeneous population with $m_\infty(t_\infty) = bt_\infty$ for some $b > 0$ and

$$g(t_\infty) = \tfrac{1}{2}\sqrt{\eta} \cdot \frac{1}{t_\infty^{3/2}} \qquad \text{if } t_\infty > \eta \qquad (10)$$

for some constant $\eta > 0$. In other words the time to complete release of a single capsule always exceeds some threshold $\eta > 0$ and large values of t_∞ are very likely. In fact the proportion of cap-

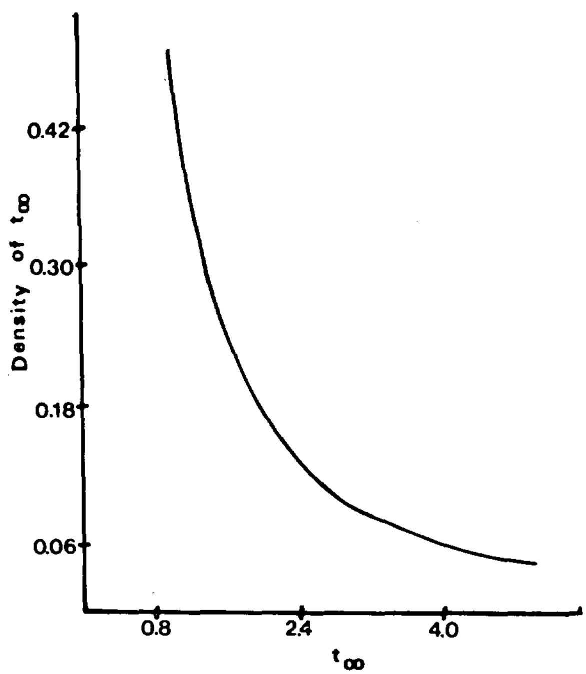

Fig. 3. Pareto density distribution of t_∞.

sules with t_∞ exceeding a fixed value $a > \eta$ is

$$\int_a^\infty \tfrac{1}{2}\sqrt{\eta}\,\frac{1}{t_\infty^{3/2}} = 1 - \left(\frac{\eta}{a}\right)^{1/2}$$

which falls off to zero at the rate of $1/\sqrt{a}$. Using Eqn. 9 again we find that

$$M(t) = \begin{cases} bt & \text{if } t < \eta \\ b\eta\left(2\sqrt{t}/\sqrt{\eta} - 1\right) & \text{if } t \geqslant \eta \end{cases}$$

The distribution of t_∞ given by Eqn. 10 is the Pareto distribution often used by econometricians to model income distribution. It is characterized by its positive threshold of minimum income η and its slow descent to zero for high incomes (Fig. 3). The difference between the square-root of Cauchy distribution and the Pareto distribution (Figs. 2 and 3) is that the latter has a larger value for the minimal t_∞, the time up to which no microcapsule has released all its contents. This applies to all systems in which summation of the constant rate lines (none of which are terminated) gives a cumulative straight line. This explains the zero-order behaviour during the initial period found by many investigators, as for example, where the square root of time relationship starts after 25% release (Madan et al., 1974). Another system showed similar behaviour but also appeared to observe square root time behaviour throughout (Jalsenjak et al., 1980).

Apparent Hixson and Crowell release law

This empirical population release law (Eqn. 6) is applicable for small values of t, or in the initial stages of release. It was shown to fit empirical release curves in populations of capsules that tend to disintegrate prior to completion of their payload release (Benita and Donbrow, 1982).

We shall display a model for constant rate capsules that predicts

$$M'(t) = C(A - t)^2 \qquad \text{for } 0 \leqslant t \leqslant A$$

for some positive constants A and C, with $C = 3\ K^3$ and $A = M_\infty^{1/3}/K$. The parameters M_∞ and K are the total payload and slope parameters defined in Eqn. 6.

For this model

$$M(t) = C/3\left(A^3 - (A - t)^3\right) \qquad \text{for } t \leqslant A$$

which constitutes a mere rewriting of Eqn. 6 as Hixson and Crowell's law for $t \leqslant A$.

The functional forms needed for $m_\infty(t_\infty)$ and $g(t_\infty)$ here are:

$$g(t_\infty) = \frac{2}{A^2}(A - t_\infty) \qquad \text{if } 0 \leqslant t_\infty \leqslant A$$

and

$$m_\infty(t_\infty) = \text{Const.} \cdot t_\infty$$

Upon inserting these into the model (Eqn. 9) we obtain the desired result.

The density chosen here for t_∞ puts into mathematical form the empirical requirement that all capsules in the medium disintegrate or otherwise release their payload by some specific time A. Furthermore, the chosen form of $m_\infty(t_\infty)$ postulates that the average payload of all capsules in the medium that release all their payload at t_∞ increases linearly with t_∞.

Populations of exponential rate individual microcapsules

Here we assume that the single capsule release function is given by:

$$m(t) = m_\infty(1 - e^{-Kt}) \qquad (11)$$

for $t > 0$, which is characterized by the capsule total payload m_∞ and a one-dimensional positive parameter K. In the micro-model described by Dappert and Thies (1978a), K and m_∞ are related by the equation:

$$K = \frac{\Gamma(C_i(0) - C_e)}{m_\infty}$$

where $C_i(t)$ is the (assumed) concentration in the region of the internal wall of the capsule ($C_i(t) \approx C_i(0)$ at $t = 0$) and C_e is the (assumed) constant concentration at its external wall region; Γ is a parameter which depends entirely on the geometric properties of the capsule and may vary from one capsule to another in the population.

When m(t) from Eqn. 11 is inserted into our general model (7*) we obtain

$$M(t) = C\int_0^{\infty} m_{\infty}(K)(1 - e^{-Kt})g(K)\, dK \qquad (12)$$

where C is some positive constant, $m_{\infty}(K)$ is the mean payload in the subpopulation of capsules with a constant rate K and g(K) is the density of K in the population. Eqn. 12 provides a general formula for deriving the global function M(t) for microcapsules with individual exponential release.

It is natural to expect that a population of exponentially releasing microcapsules will display global exponential release as in Eqn. 3. This is, however, not the case, except in the unlikely population of capsules that release their payload at the exact same rate K_1. Translated into the mathematical terms of Eqn. 12, global first-order will result only if the density g(K) of K is concentrated at some constant $K_1 > 0$; in other words g(K) is degenerate at K_1. This assertion is valid under some general assumptions (Eqn. 13) that stipulate that $m_{\infty}(K)$ be a "nice" function of K. These mild assumptions are expected to be obeyed in any realistic physical system. We conclude then that first-order behaviour cannot arise in populations of exponentially releasing capsules, unless the capsules are extremely homogeneous and thus share the same release rate K.

We include the proof of our assertion for the sake of completeness.

The "nice" behaviour of $m_{\infty}(K)$ is translated into the condition that

$$\int_0^{\infty} e^{rK} m_{\infty}(K)g(K)\, dK < \infty \qquad (13)$$

for some $r > 0$. If M(t) of Eqn. 12 is to equal $M_{\infty}(1 - e^{-K_1 t})$ for all $t > 0$ and some $K_1 > 0$ then for all $i = 0, 1, 2, \ldots$

$$\int_0^{\infty} K^i m_{\infty}(K)g(K)\, dK = CK_1^i \qquad (14)$$

for some $C > 0$. Under the conditions of Eqn. 13 the only density g(K) to satisfy Eqn. 14 is the degenerate density that concentrates all its mass as $K = K_1$ thus proving our assertion.

Although exact first order may not exist in a population of exponentially releasing individual capsules, release behaviour that appears "almost" exponential is possible, as may be seen from Eqn. 12 by assuming different forms for the functions $M_{\infty}(K)$. This exercise is fruitless, however, unless an empirical model is available for the population and the individual capsules are exponential.

Conclusions

(1) The theory of release of contents from an ensemble of single particles such as microcapsules has been developed for the case of individuals releasing at constant rate based on simple assumptions (a)–(c). Four types of kinetics used in the literature for populations have been derived on the basis of different statistical distributions of the parameter t_{∞}. Many other types of release kinetics may also be understood using the same basic theory.

(2) In the event that conditions (a)–(c) are not observed, it is possible that these or other kinetic profiles may be followed.

(3) In all cases, the overall kinetics is determined by the micro-behaviour and its distribution.

(4) Where individuals follow first order behaviour, the cumulative release data cannot be exponential unless all the particles have identical parameters. As this situation is extremely rare, overall exponential release proves individual non-exponential release, and derives from statistical distribution phenomena of the types presented and analyzed.

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