became progressively clearer as the drying temperature dropped. Changes in X-ray diffraction pattern also suggested that the fraction of new form in the sample increased at lower ranges of drying temperature. However, the new polymorph could not be isolated as a pure crystalline modification. Scanning electron photomicrographs showed that a small amount of crystals of form $\beta$ still remained and these were surrounded by the new form crystals in the sample obtained at 30 °C. The assumption that the new form might be a solvate was disproved by the results of both elemental analysis and TG.

The dissolution rates by the disc method (Wood et al 1965) and the solubility of samples in the U.S.P. dissolution test solution (U.S.P. 1975) were measured at 37 °C. Their behaviour, depending on drying temperature, was in good agreement. The solubility of the sample obtained at 30 °C was 1·5 times higher than that of the sample obtained at 120 °C, and the bioavailability of the new form crystals would be expected to compare with the other known forms.

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# Physical interpretation of parameters in the Rosin-Rammler-Sperling-Weibull distribution for drug release from controlled release dosage forms

FINN NORRING CHRISTENSEN, FLEMMING YSSING HANSEN, HELLE BECHGAARD*†, *Institute of Physical Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark and* †*Controlled Release Division, A/S Alfred Benzon, DK-1700 Copenhagen V, Denmark*

In recent years (see Langenbucher 1976; Gurny et al 1976; Goldsmith et al 1978) in vitro drug release has often been described in accordance with the general mathematical function originally proposed by Rosin et al (1933) and later by Weibull (1951). (The Rosin-Rammler-Sperling-Weibull RRSW distribution). This can take the following form when applied to drug release data:

$$\frac{C_{extr}(t)}{C_{extr}(\infty)} = 1 - \exp(-(t-\gamma)^{\beta}/\alpha) \quad .. \quad .. \quad (1)$$

Equation (1) gives the concentration $C_{extr}(t)$ in the extraction medium as a function of time t. $\alpha$, $\beta$ and $\gamma$ are adjustable parameters which may be calculated to give a least squares fit to observed data. $C_{extr}(\infty)$ is the concentration in the extraction medium when all of the drug has been released at $t = \infty$. $\gamma$ represents a change in the zero point for the time, and it is evident that equation (1) has a meaning only when $(t - \gamma) \geq 0$.

The flexibility of the distribution in equation (1) is obvious, and it has therefore also been applied to a large variety of distributions such as yield strength of fibres and steels, size of beans and insects (Rosin et al 1933). Thus the RRSW is not particularly designed to describe drug release, and there are no obvious physical reasons for using that particular distribution. This is a serious drawback of the method since it does not allow a prediction of a release profile for pellets of e.g. different sizes and with different coats. Besides, it is not possible to apply the parametric form in a simulation of in vivo release. In order to do so, it is necessary to consider a reasonable physical model for the release. In this study we describe the drug release as a quasi-stationary diffusion of drug through the coat which is the main obstacle for the release. We have considered pellets consisting of a core containing the drug and excipients surrounded by a uniform coat. For simplicity, it is assumed that the drug in the core is dissolved and that the diffusion coefficient in the coat is much smaller than in the core; thus we assume that the concentration of drug in the core at all times is uniform. It is also assumed that the drug concentration in the extraction fluid is uniform at all times due to effective stirring. We do not consider the initial swelling of pellets and dissolution of drug when dry pellets are put into an extraction medium. This may be accounted for by the introduction of a time lag ($\gamma$) as shown in equation (1).

Let us consider a spherical pellet where the radius of the core is b and the radius of the coated core is a; then the thickness of the coat is (a–b). Since we only consider radial diffusion, the diffusion equation for the coat is given by Fick's 2nd law (see Crank 1964),

$$\frac{\delta(rc)}{\delta t} = D\frac{\delta^2(rc)}{\delta r^2} \qquad b < r < a \quad .. \quad (2)$$

where D is the diffusion coefficient for the particular drug in the coat, r is the radius to a particular stage in the coat, and c is the concentration in the coat at that particular stage and time. We now impose stationarity upon the concentration profile in the coat, that is

* Correspondence.

$$\delta(rc)/\delta t = 0 \quad .. \quad .. \quad (3)$$

and from eqn (2) we find

$$C(r,t) = A(t) + B(t)/r \quad .. \quad .. \quad (4)$$

where A and B are constants (with respect to the radius r) to be determined from the boundary conditions. Since these vary with time, A and B are functions of time as indicated in eqn (4). Thus we consider a quasi stationary solution of the diffusion problem. At the boundaries r = b and r = a we have

$$\begin{aligned} C(b,t) &= A(t) + B(t)/b \\ C(a,t) &= A(t) + B(t)/a \end{aligned} \quad .. \quad (5)$$

from which A(t) and B(t) are found by

$$A(t) = C(b,t) - \frac{a}{a-b}\left[C(b,t) - C(a,t)\right] \quad .. \quad (6)$$

$$B(t) = \frac{ab}{a-b}\left[C(b,t) - C(a,t)\right]$$

Introduction of eqn (6) into eqn (4) gives

$$C(r,t) = C(b,t) + \left[\frac{ab}{a-b} \cdot \frac{1}{r} - \frac{a}{a-b}\right] \cdot \left[C(b,t) - C(a,t)\right] .. \quad (7)$$

Under the boundary conditions

$$-V_{core} \cdot \frac{\delta C_{core}(t)}{\delta t} = A_{core} \cdot J_b \quad .. \quad .. \quad (8)$$

and

$$V_{extr} \cdot \frac{\delta C_{extr}(t)}{\delta t} = A_{coated\ core} \cdot J_a .. \quad .. \quad (9)$$

where A denotes the surface area, V denotes the volume and $J_r$ is the flux of drug through a spherical surface with the radius r.
By inserting the radial formulation of Fick's 1st law (see Crank 1964)

$$J = -D\frac{\delta c}{\delta r} \quad .. \quad .. \quad .. \quad .. \quad (10)$$

into eqns (8) and (9) and allowing for an adsorption phenomenon at the boundaries by introducing the constants $K_b$ and $K_a$ defined by

$$C_{core}(t) = K_b \cdot C(b,t) \text{ and } C_{extr}(t) = K_a \cdot C(a,t) \quad (11)$$

we get

$$\frac{\delta C(r,t)}{\delta t} = \frac{3}{b} \cdot \frac{D}{K_b} \cdot \frac{\delta C(r,t)}{\delta r}; \quad r = b \quad .. \quad .. \quad (12)$$

and

$$\frac{\delta C(r,t)}{\delta t} = -\frac{4\pi a^2}{V} \cdot \frac{D}{K_a} \cdot \frac{\delta C(r,t)}{\delta r}; \quad r = a \quad .. \quad (13)$$

from which C(a,t) and C(b,t) can be determined. Introduction of eqn (7) in eqn (12) and (13) leads to:

$$\frac{\delta C(b,t)}{\delta t} = -\frac{3}{b} \cdot \frac{D}{K_b} \cdot \frac{a}{(a-b)b}\left[C(b,t) - C(a,t)\right] \quad (14)$$

and

$$\frac{\delta C(a,t)}{\delta t} = \frac{4\pi a^2}{V} \cdot \frac{D}{K_a} \cdot \frac{b}{(a-b)a}\left[C(b,t) - C(a,t)\right] \quad (15)$$

Equations (14) and (15) are two coupled differential equations which are easily solved by subtracting eqn (15) from eqn (14) followed by integration. We find:

$$\left[C(b,t) - C(a,t)\right] = \left[C(b,0) - C(a,0)\right] \cdot \exp\left[-\left(\frac{a^2}{bK_b} + \frac{b^2}{aV'K_a}\right)\frac{3D}{(a-b)ab} \cdot t\right] \quad .. \quad (16)$$

with the relative volume V′ given by

$$V' = V \Big/ \frac{4\pi a^3}{3}$$

In order to find the concentration of drug in the extraction medium we only have to calculate C(a,t) and multiply with $K_a$ (eqn (11)). This is easily done by introducing eqn (16) in eqn (15) followed by a simple integration. We find:

$$C(a,t) = C(a,0) - \frac{C(b,0) - C(a,0)}{\left[1 + V' \cdot \frac{K_a}{K_b} \cdot \frac{a^3}{b^3}\right]} \cdot \left[\exp\left(-\left(\frac{a^2}{bK_b} + \frac{b^2}{aV'K_a}\right)\frac{3D}{(a-b)ab} \cdot t\right) - 1\right] \quad (17)$$

Since there is no drug in the extraction medium at t = 0 (C(a,0) = 0), eqn (17) may be reduced to

$$\frac{C_{extr}(t)}{C_{extr}(\infty)} = 1 - \exp\left[-\left(\frac{a^2}{bK_b} + \frac{b^2}{aV'K_a}\right)\frac{3D}{(a-b)ab} \cdot t\right] \quad .. \quad .. \quad .. \quad (18)$$

Comparison with equation (1) shows the similarity between the two expressions. In the above derivation, equation (18), we have not allowed for any time lag as initially described, but that is easily achieved by replacing t with $(t-\gamma)$ as done in equation (1). It is seen that if $\beta = 1$ in equation (1) the RRSW distribution corresponds to a quasi-stationary diffusion of the drug through the coat. In that case the $\alpha$ parameter is given by:

$$\frac{1}{\alpha} = \left[\frac{a^2}{bK_b} + \frac{b^2}{aV'K_a}\right] \frac{3D}{(a-b)ab} \quad .. \quad .. \quad (19)$$

The time lag may be determined in the same way as for the RRSW distribution.

It has been shown that the quasi-stationary diffusion description of the drug release formally leads to an expression of the same form as the RRSW distribution when $\beta = 1$. For such a case we have established a relation (eqn 19) between the various parameters used for characterizing the release profile. The important difference between the two methods is that the parameters in the diffusion model are physical parameters of the pellets which is not the case with the RRSW parameters.

As an illusion we have applied the diffusion model to the prediction of the release profile of pellets with a known diffusion coefficient D and a coat thickness (a–b). Two experimental and calculated release profiles of dextropropoxyphene hydrochloride pellets, coated with different amounts of a synthetic coat (Pedersen 1974) are shown in Fig. 1. Curve A corresponds to pellets with a thin coat (8%) and Curve B to pellets with a thick coat (10%). Since the coating material is the same, it is assumed that the diffusion coefficients are identical in both cases which implies that the difference in release profiles is due to a different thickness of the coating. The diffusion model should be able to reproduce this difference if the model reflects essential features of the process, whereas the RRSW distribution function method will not allow such predictions.

Since release experiments are done with a large number of pellets, it is important that a product with a narrow size distribution is chosen in order to test the simple quasi-stationary diffusion model. However, it is easy to generalize the model to include products with any size distribution, but it will just complicate the matter unnecessarily at this point. The dimensions of the pellets (a and b) were obtained from microscopy of a series of microtome sections of the pellets. It was found that $b = 459{\cdot}2\ \mu m$ and $a = 475{\cdot}0\ \mu m$ and $478{\cdot}8\ \mu m$, respectively. Since adsorption phenomena were considered unimportant, $K_a$ and $K_b$ are set equal to 1. The relative volume $V' = 75$. Equation (18) was then applied to fit data points for pellets with the thin coat (Curve A) in order to obtain a value for the diffusion coefficient and the lag time $\gamma$. It was possible to fit the data points (Curve A) with $\gamma \cong 0$ and $D = 390\ \mu m^2\ h^{-1} \sim 1{\cdot}08 \cdot 10^{-9}\ cm^2\ s^{-1}$. The order of magnitude of D is in good agreement with diffusion coefficients reported for similar systems (Samuelov et al 1979). Curve B was now calculated from eqn (18) with the relevant b and a, and the predicted release profile is seen to be in very good agreement with the experimental data.

The quasi-stationary description may be expected to be valid, particularly in the case of relatively thin coats since their capacity is small. Deviation from the simple quasi-stationary diffusion may be absorbed more or less

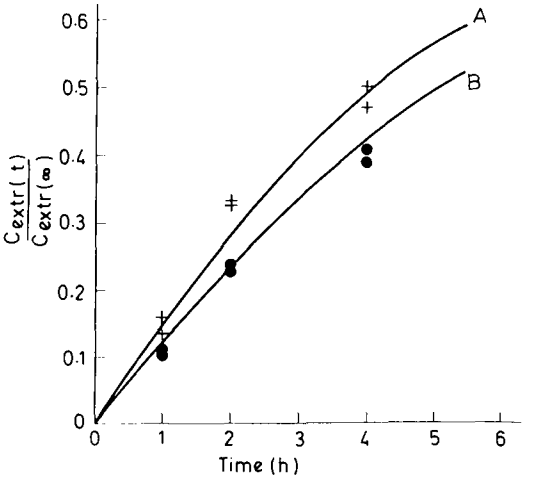


FIG. 1. A, release profile calculated from eqn (18) when $a = 475{\cdot}0\ \mu m$, $b = 459{\cdot}2\ \mu m$, $V' = 75$, $K_a = K_b = 1$ to give the least squares fit to experimental data. The diffusion coefficient is determined at $1{\cdot}08 \cdot 10^{-9}\ cm^2\ s^{-1}$. Corresponding to $\alpha = 5{\cdot}9$ h. B, predicted release profile of pellets when $a = 478{\cdot}8\ \mu m$, $b = 459{\cdot}2\ \mu m$, $V' = 75$, $K_a = K_b = 1$ and $D = 1{\cdot}08 \cdot 10^{-9}\ cm^2\ s^{-1}$. Corresponding to $\alpha = 7{\cdot}3$ h.

successfully by optimizing the $\beta$-parameter in the RRSW function. Such deviations may in the diffusion model approach be accounted for by using a general solution of the diffusion problem without introducing the simplifying assumptions leading to the present results. Such solutions are also fairly easy to extend to include systems with any size distributions of pellets.

The perspective of the diffusion model approach is that it may be used to predict in vitro release profiles and, coupled to an appropriate pharmacokinetic compartment model, in vivo profiles.

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