Added Release Time in Diffusion/Dissolution Coupled Release

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Abstract: While increasingly sophisticated models have been developed to more accurately predict dispersed solute release from complex systems, distillation of their results into quantitative trends has been difficult. Here, the numerically calculated release profiles of coupled diffusion/dissolution systems are quantified by their cumulative release time (CRT) and compared against corresponding diffusion-controlled limits. The increase in CRT due to a finite dissolution rate was found to vary inversely with the second Damköhler number across several orders of magnitude, and also vary linearly with the amount of solid drug loaded in the system. The analytical nature of the relationship provides new physical insights into the system and appears to be indifferent to the form of the secondary rate-limiting step. This work provides a simple analytical expression with which one can not only predict the mean release time for a given set of parameter values, but understand precisely how each parameter value will affect it. The simplicity of the correlation and the lack of apparent limits to its validity also suggest the existence of an analytical pathway for its derivation, which may yield additional insights into the effect of secondary rate processes on controlled release.

1. Introduction.

One strategy for obtaining sustained release of a soluble drug is to disperse it in a matrix at a concentration well above its solubility. As dissolved drug diffuses out of the matrix it is replenished by dissolution of solid drug particles. Efforts to model this release were pioneered by Higuchi over a half-century ago using a pseudo-steady-state approximation.(1960, 1961, 1963) These were followed by exact transcendental functions for planar(Koizumi et al., 1975; Paul and McSpadden, 1976) and spherical(Abdekhodaie and Cheng, 1997) geometry and a variety of other approximate methods, notably the integral(Helbling et al., 2010a; Lee, 1980; Lin, 2008) and continuous field(Ayers and Lindstrom, 1977; Frenning et al., 2005; Lee et al., 1998) methods. Complexities such as external mass transfer resistance(Roseman and Higuchi, 1970; Tojo, 1985; Xiang and McHugh, 2011), finite reception volume(Harland et al., 1988; Helbling et al., 2010b; Zhou and Wu, 2002), variable diffusion coefficients(Chang and Himmelstein, 1990; Frenning and Strømme, 2003; Siepmann et al., 2002; Wu and Zhou, 1998), non-planar geometry(Cabrera and Grau, 2007; Helbling et al., 2011; Ritger and Peppas, 1987; Zhou and Wu, 1997), and additional rate-limiting steps (*e.g.* dissolution)(Cabrera et al., 2006; Chandrasekaran and Paul, 1982; Frenning, 2003; Kubota et al., 1994) have also been considered. As the complexity of the models increases, gleaning clear physical insights from them becomes more difficult, particularly for computational models. Modelers typically demonstrate the effect of a given variable visually, stepping through a range of input parameter values and plotting the resulting release profiles together to demonstrate a trend. The information gained is largely qualitative, particularly if multiple interdependent variables are studied. Quantification of these trends is frustrated by the inability to quantify the release profile curves themselves. Release profile quantification typically focuses on a single part of the profile

(*e.g.*, t_X , the time required to release X% of the solute; or a linear regression of an arbitrary portion of the curve).

The aim of this paper is not to develop an incrementally more accurate model, but rather to develop ways to more effectively express the information the model provides. In particular, it considers systems where the rate of diffusion is comparable to the rate of dissolution. While the exact release profile of such systems is not analytically solvable, extensive work has been done on modeling these systems to calculate approximate release profiles. In this paper, the continuous field approach is used to build a numeric model in which a variety of different dissolution kinetics can be incorporated. The resulting release profiles appear as sketched in Figure 1, plotting total released solute vs. time. When a planar monolith loaded evenly with dispersed solute is exposed to a perfect sink at time $t=0$, the solute immediately adjacent to the sink quickly diffuses out, providing an initial burst of release. This release slows, however, as solute near the surface is depleted and solute from deeper within the monolith releases. Since the time for solute to diffuse to the sink varies with the square of its initial distance to the sink, the release curve is essentially quadratic until the innermost solute is dissolved and the release curve begins to plateau, as shown in the solid release line in Figure 1. If a second rate process, free from this location dependence, is included in the system, then the release profile becomes more linear, as sketched by the dotted lines in Figure 1. For instance, if dissolution is much slower than diffusion, then the release rate will be much slower and, like the dissolution rate itself, much steadier.

Rather than quantifying an initial slope or a time for X% of the solute to release, this paper looks at the Cumulative Release Time (CRT) of the release curve, one of the few common metrics which encompasses the entire release profile. Conceptually, the CRT is the sum of the

times required by each solute molecule to release from the system, with units of (moles $\times$ time). Dividing by the total moles of solute released provides the mean release time, *i.e.* the average time required for a molecule to escape the system. The CRT is calculated from the release profile by integrating over time between the profile and the horizontal 100% release line which the profile asymptotically approaches, as shown in Figure 2. That figure also introduces a new metric, the Added Release Time (ART), which is simply the CRT of a system with a finite dissolution rate minus the CRT of the same system if the dissolution step were infinitely fast (*i.e.*, strictly diffusion-controlled). The ratio of the ART to the diffusion-controlled CRT quantitatively expresses the degree to which the additional rate-limiting step has altered the entire release profile rather than an arbitrarily chosen portion of it. More importantly, this paper demonstrates that the ART (and hence the mean release time) can be directly correlated to the ratio of the dissolution and diffusion rates with an integer power law relationship, apparently without regard to the nature of the dissolution kinetics.

2. Methods.

2.1. Diffusion-limited release.

For a planar monolith loaded evenly with drug beyond its saturation concentration C_{Xs} , the drug is present in two forms: dissolved solute X and solid species Y. Any time the local X concentration is below saturation, Y instantly converts to X until either it is locally depleted or $C_X = C_{Xs}$. At time $t = 0$, the monolith is exposed to a perfect sink and X begins diffusing out at both interfaces. Species Y instantly dissolves, replenishing X until all the Y at the interfaces is gone. A moving front forms, sketched in Figure 3, behind which all Y is depleted and beyond which Y is still at initial concentration C_{Y0} . Since the monolith is symmetric, only half of it need

be considered, from the external interface ($z = \ell$) to the centerline ($z = 0$) which is considered impermeable due to its symmetry. A mass balance on species X yields

$$accumulation = [net\ flux\ in]_{z=0} + [net\ flux\ in]_{z=\ell} + generation \quad (\text{Equation 1})$$

Because the monolith is symmetric, there is no net flux at $z = 0$, and the generation of X can be calculated from the disappearance of Y:

$$generation = \frac{-dC_Y}{dt} = \frac{-d}{dt} (C_{Y0} A \ell') \quad (\text{Equation 2})$$

where A is the area of the interface and ℓ' is the location of the moving front.

While exact solutions to Equation 1 exist (Paul and McSpadden, 1976), the most straightforward solution, introduced by Higuchi (Higuchi, 1960), assumes that the dissolution front moves slowly relative to the diffusion rate of the solute. This pseudo-steady-state approximation implies a linear concentration profile of C_X behind the front, from saturation ($C_X = C_{Xs}$) at the front to $C_X = 0$ at the sink interface. With this linear concentration profile, the accumulation and net flux terms in Equation 1 can be expressed as

$$accumulation = \frac{d}{dt} \left[C_{Xs} A \ell' + \frac{C_{Xs} A (\ell - \ell')}{2} \right] \quad (\text{Equation 3})$$

$$[net\ flux\ in]_{z=\ell} = \frac{-A D C_{Xs}}{\ell - \ell'} \quad (\text{Equation 4})$$

Combining Equations 1-4,

$$\left(\frac{C_{Xs} A}{2} \right) \frac{d\ell'}{dt} = \frac{-C_{Xs} D A}{\ell - \ell'} - (C_{Y0} A) \frac{d\ell'}{dt} \quad (\text{Equation 5})$$

and integrating subject to the condition that the moving front starts at the interface (*i.e.*, $\ell' = \ell$) at time $t = 0$ yields

$$\ell' = \ell - \sqrt{\frac{2 D C_{Xs} t}{\frac{C_{Xs}}{2} + C_{Y0}}} \quad (\text{Equation 6})$$

Equation 6 is valid until all Y is consumed. This occurs at time t_L , when $\ell' = 0$.

$$t_L = \left(\frac{\ell^2}{D}\right) \left(\frac{C_{Y0}}{2C_{Xs}} + \frac{1}{4}\right) \quad (\text{Equation 7})$$

In the case of a swelling matrix, if the swelling front moves faster than ℓ' then one accounts for the swelling simply by using the swollen matrix thickness for ℓ in Equations 6 and 7. By integrating the $[net\ flux\ in]_{z=\ell}$ term over time, the total amount of X released from the half-monolith $M(t)$ is

$$M(t \leq t_L) = A \sqrt{2 D C_{Xs} \left(C_{Y0} + \frac{C_{Xs}}{2}\right) t} \quad (\text{Equation 8})$$

Until time t_L , the total solute released increases with the square root of time. This is the classic Higuchi result, which is most valid when $C_{Y0} \gg C_{Xs}$, though as $C_{Y0} \rightarrow C_{Xs}$, its deviation from the exact solution is less than 11.4%(Lee, 2011).

At time t_L , the monolith is devoid of Y but contains a near-linear concentration profile for C_X . The exact solution for $C_X(z,t)$ in this situation can be adapted from Carslaw and Jaeger(1959) as an infinite summation, though again the pseudo-steady-state approximation significantly simplifies the result with comparable accuracy to the $t < t_L$ case. Repeating the above analysis with no generation term,

$$\frac{d}{dt} \left(\frac{C_{X0} A \ell}{2} \right) = \frac{-C_{X0} A D}{\ell} \quad (\text{Equation 9})$$

where the left-hand-side is the accumulation and the right-hand-side is the net flux into the monolith at $z = \ell$. Here the solute concentration at $z = 0$, C_{X0} , is the dependent variable which decreases as the remaining solute releases from the monolith. Recalling that at $t = t_L$, $C_{X0} = C_{Xs}$, Equation 9 yields an expression for C_{X0}

$$C_{X0} = C_{Xs} \exp \left[\frac{-2 D (t - t_L)}{\ell^2} \right] \quad (\text{Equation 10})$$

Inserting this expression into the net flux term in the right-hand-side of Equation 9 and integrating from time t_L ,

$$M(t \geq t_L) = M(t = t_L) + \frac{C_{Xs} A \ell}{2} \left[1 - \exp \left[\frac{-2 D (t - t_L)}{\ell^2} \right] \right] \quad (\text{Equation 11})$$

where $M(t=t_L)$ is determined by Equation 8.

$$M(t \geq t_L) = A \sqrt{2 D C_{Xs} \left(C_{Yo} + \frac{C_{Xs}}{2} \right) t_L} + \frac{C_{Xs} A \ell}{2} \left[1 - \exp \left[\frac{-2 D (t - t_L)}{\ell^2} \right] \right] \quad (\text{Equation 12})$$

Equations 8 and 12 provide the release profile at the limit of infinitely fast dissolution.

2.2. Mixed diffusion/dissolution-limited release: nanoporous monolith with conformal monolayer

There are many possible mathematical expressions for dissolution kinetics, depending on the physical system being modeled. Commonly the dissolution rate is proportional to the degree of unsaturation ($C_X - C_{Xs}$) and to the surface area of solid Y available to dissolve. In a nanoporous monolith whose pores are lined with a monolayer of solid Y, this surface area is proportional to the concentration of Y. In this case, the dissolution rate of Y, and hence the generation rate of X, can be expressed as

$$generation_X = k C_Y (C_{Xs} - C_X) \quad (\text{Equation 13})$$

where k is a dissolution rate constant, a thermodynamic property of the system. Y is immobile and X follows Fickian diffusion, so the local mass balances on these species are

$$\frac{\partial C_X}{\partial t} = D \frac{\partial^2 C_X}{\partial z^2} + k C_Y (C_{Xs} - C_X) \quad (\text{Equation 14})$$

$$\frac{\partial C_Y}{\partial t} = -k C_Y (C_{Xs} - C_X) \quad (\text{Equation 15})$$

with boundary conditions

$$\frac{\partial C_X}{\partial z}(z = 0, t) = 0 \quad C_X(z = \ell, t) = 0 \quad (\text{Equations 16, 17})$$

and initial conditions

$$C_X(z, t = 0) = C_{Xs} \quad C_Y(z, t = 0) = C_{Yo} \quad (\text{Equations 18, 19})$$

To make the model dimensionless, the dependent and independent variables are normalized by

$$\Psi_X \equiv \frac{C_X}{C_{Xs}} \quad \Psi_Y \equiv \frac{C_Y}{C_{Yo}} \quad \tau \equiv \frac{D t}{\ell^2} \quad h \equiv \frac{z}{\ell} \quad (\text{Equations 20-23})$$

whereupon Equations 14-19 become

$$\frac{\partial \Psi_X}{\partial \tau} = D \frac{\partial^2 \Psi_X}{\partial h^2} + \Phi \Psi_Y (1 - \Psi_X) \quad (\text{Equation 24})$$

$$\frac{\partial \Psi_Y}{\partial \tau} = -\frac{\Phi}{\gamma} \Psi_Y (1 - \Psi_X) \quad (\text{Equation 25})$$

$$\frac{\partial \Psi_X}{\partial h}(h = 0, \tau) = 0 \quad \Psi_X(h = 1, \tau) = 0 \quad (\text{Equations 26, 27})$$

$$\Psi_X(h, \tau = 0) = 1 \quad \Psi_Y(h, \tau = 0) = 1 \quad (\text{Equations 28, 29})$$

showing that the system depends on only two parameters, the ratio of the initial solid loading to its saturation concentration (γ) and the second Damköhler number (Φ) which is a ratio of the dissolution rate to the diffusion rate.

$$\gamma \equiv \frac{C_{Yo}}{C_{Xs}} \quad \Phi \equiv \frac{k C_{Yo} \ell^2}{D} \quad (\text{Equations 30, 31})$$

Similarly, the cumulative solute release $M(t)$ is normalized by the amount of dissolved solute the monolith can hold at saturation

$$\Theta \equiv \frac{M}{C_{Xs} A \ell} \quad (\text{Equation 32})$$

Equations 24-29 were solved with simple numerical methods, using the centered finite difference method to approximate the spatial second derivative and the explicit Euler method to approximate the time derivative. Balancing accuracy vs. computation time, 501 spatial nodes were used; an analysis of the effect of node size is included in the Supplementary Materials, along with the FORTRAN code used for the calculations. The time step was set at $\Delta \tau = 10^{-6}$, dictated by stability requirements rather than computational accuracy. Φ and γ were independently varied across several orders of magnitude, providing an array of release profiles of Θ vs. τ , each with a dimensionless CRT. The dimensionless CRT of the diffusion-limited case was calculated by non-dimensionalizing Equations 7, 8 and 12

$$\tau_L = \frac{\gamma}{2} + \frac{1}{4} \quad \text{(Equation 33)}$$

$$\Theta(\tau \leq \tau_L) = \sqrt{2\gamma\tau + \tau} \quad \text{(Equation 34)}$$

$$\Theta(\tau \geq \tau_L) = \gamma + 1 - \frac{1}{2} \exp[-2(\tau - \tau_L)] \quad \text{(Equation 35)}$$

and similarly integrating that release profile. Subtracting this diffusion-limited CRT from the CRT of each release profile gave its ART. The ART was then empirically correlated to Φ and γ .

With increasing γ or decreasing Φ the time required for complete release becomes increasingly long. The minimum Φ value investigated for a given solute loading γ was dictated by the time required for 99.8% release; this had to occur within 2100τ . The same time limit determined the maximum γ value investigated for at a given Φ . As γ gets small and Φ gets large, small computational errors become significant, as does the error from the pseudo-steady-state approximation in the diffusion-limited case.

2.3. Mixed diffusion/dissolution-limited release: distributed shrinking spheres

A more common but significantly different kinetic expression for the dissolution rate involves tiny spheres of solid species Y distributed throughout the monolith. Their true dissolution rate is infinite but effectively limited by the rate at which dissolved solute can diffuse away from the sphere surface and into the bulk of the monolith. This, in turn, depends on the size of the sphere; smaller spheres have greater surface area-to-mass ratios and greater diffusional area per surface area at any given distance from the surface, so as the spheres dissolve their size decreases and their effective dissolution rate per mass increases in a fixed manner. If all the spheres at a given location start with the same initial radius R_o , they should dissolve at the same rate and disappear at the same time. During that time, the sphere radius R determines not only the Y concentration at that location, but also its effective dissolution rate. In this case, the flux from a sphere is (Cussler, 2009)

$$\text{flux from surface} = \frac{D}{R}(C_{Xs} - C_X) \quad (\text{Equation 36})$$

This flux, multiplied by the sphere's surface area ($4 \pi R^2$) must be equal to the decrease of Y in the sphere

$$\frac{D}{R}(C_{Xs} - C_X)(4 \pi R^2) = \frac{d}{dt} \left(C_{Yo} \frac{\frac{4}{3} \pi R^3}{\phi} \right) \quad (\text{Equation 37})$$

where ϕ is the initial volume fraction of Y in the monolith. This yields an expression for the change in particle radius over time:

$$\frac{dR}{dt} = \frac{\phi D}{C_{Yo}} \frac{(C_{Xs} - C_X)}{R} \quad (\text{Equation 38})$$

This expression is then used to find the rate of generation of X (and depletion of Y)

$$\frac{dC_Y}{dt} = \frac{d}{dt} \left(C_{Yo} \frac{\frac{4}{3} \pi R^3}{\frac{4}{3} \pi R_o^3} \right) = \frac{3 R^2 C_{Yo}}{R_o^3} \frac{dR}{dt} = \frac{3 \phi D}{R_o^2} R (C_{Xs} - C_X) \quad (\text{Equation 39})$$

By controlling the size of the spheres, one can control the effective dissolution rate, as demonstrated experimentally by Chandrasekaran and Paul(1982). Inserting this expression for the generation of X into a local mass balance, we get an equation analogous to Equation 14

$$\frac{\partial C_X}{\partial t} = D \frac{\partial^2 C_X}{\partial z^2} + \frac{3 \phi D}{R_o^2} R (C_{Xs} - C_X) \quad (\text{Equation 40})$$

Non-dimensionalizing as before, Equations 40 and 38, respectively, become

$$\frac{\partial \Psi_X}{\partial \tau} = \frac{\partial^2 \Psi_X}{\partial h^2} + 3\Phi(1 - \Psi_X)\Psi_Y \quad (\text{Equation 41})$$

$$\frac{\partial \Psi_Y}{\partial \tau} = - \left(\frac{\Phi}{\gamma} \right) \frac{1 - \Psi_X}{\Psi_Y} \quad (\text{Equation 42})$$

with the same boundary and initial conditions as in the previous section

$$\frac{\partial \Psi_X}{\partial h}(h = 0, \tau) = 0 \quad \Psi_X(h = 1, \tau) = 0 \quad (\text{Equations 26, 27})$$

$$\Psi_X(h, \tau = 0) = 1 \quad \Psi_Y(h, \tau = 0) = 1 \quad (\text{Equations 28, 29})$$

but where the second dependent variable, Ψ_Y , is now a measure of the particle radius and the Damköhler number is effectively a ratio of two characteristic diffusion rates, one from the particle surface to the bulk of the monolith, and one across the width of the monolith.

$$\Psi_Y \equiv \frac{R}{R_o} \qquad \Phi = \frac{\phi \ell^2}{R_o^2} \qquad \text{(Equation 43)}$$

Equations 41 and 42 were solved using the same computational methods described in the previous section to generate an array of release profiles and their corresponding CRT values, where Φ and γ were independently varied over several orders of magnitude. The FORTRAN code for the calculations is included in the Supplementary Materials. The CRT of the corresponding diffusion-limited release profile was subtracted from each calculated CRT to determine the ART for each system. These ART values were correlated against Φ and γ .

3. Results.

3.1. Nanoporous monolith with conformal monolayer.

Figure 4 provides an example of typical release profiles from the nanoporous monolith model at $\Phi = 1$. Here the characteristic diffusion and dissolution times are comparable and the release profiles at various γ are initially identical, as shown in the inset. As γ decreases, however, Y near the surface is more quickly exhausted and those profiles deviate from the large γ profiles and plateau sooner, at a lower cumulative solute release Θ . The CRT, bounded by the release profile, the y-axis, and the horizontal Θ_∞ line, decreases with γ since Θ_∞ decreases linearly with γ .

Figure 5 provides an example of typical release profiles from the nanoporous monolith at $\gamma = 10$. Here the initial solid Y concentration is 10 times the saturation concentration of X , and every profile approaches the same $\Theta_\infty = 11$ asymptote. When the dissolution rate is ten times the diffusion rate (i.e., $\Phi = 10$) the release profile lays almost on top of the strictly diffusion-limited

case. The shape of the profiles changes substantially, however, as Φ decreases and the dissolution rate becomes slower than the diffusion rate. The profiles become more linear, taking much longer to approach the Θ_∞ and exhibiting a much larger CRT.

A partial table of ART values at various Φ , γ combinations is given in Table 1; a complete table is listed in the Supplementary Materials. Values for Φ and γ were chosen on a logarithmic scale in order to investigate several orders of magnitude in each parameter. The resulting ART values appear to similarly follow a logarithmic trend. Plotting the log of this dimensionless ART *vs.* $\log(\gamma)$, Figure 6 demonstrates a clear linear relationship, with slopes increasing marginally from 1.971 at $\Phi = 0.01$ to 2.029 at $\Phi = 316.2$, with an average value of 1.9894. Moreover, none of these regressions has an R^2 below 0.99994. Equally striking, the intercepts decrease steadily with increasing $\log(\Phi)$. Plotting the intercepts from Figure 6 *vs.* $\log(\Phi)$, Figure 7 shows a linear relationship with a slope of -1.02 ($R^2 > 0.999$) and an intercept near zero. This analysis yields the empirical correlation

$$ART = 1.01 \gamma^{1.99} \Phi^{-1.02} \quad \text{(Equation 44)}$$

Reversing the order of the analysis and first plotting $\log(ART)$ *vs.* $\log(\Phi)$, the slopes decrease marginally from -0.995 at $\gamma = 0.562$ (*i.e.*, less solid Y than dissolved X) to -1.068 at $\gamma = 1778$, as shown in Figure 8, with all R^2 values above 0.9992. Regressing the intercepts of the lines from Figure 8 *vs.* their corresponding $\log(\gamma)$, the slope is 2.01 ($R^2 > 0.999$) with an intercept near zero. This analysis yields the empirical correlation

$$ART = 1.03 \gamma^{2.01} \Phi^{-1.02} \quad \text{(Equation 45)}$$

Considering the correlations shown in Equations 44 and 45, it seems clear that for the nanoporous monolith system, the dimensionless ART, *i.e.*, the increase in the CRT due to a finite dissolution rate, can be estimated by the simple relationship

$$ART = \frac{\gamma^2}{\Phi} \quad \text{(Equation 45)}$$

3.2. Shrinking spheres

Performing the same sort of analysis on the system with small, evenly distributed spheres of Y, Figure 9 shows the same linear relationship between $\log(ART)$ and $\log(\gamma)$ (all $R^2 > 0.99999$), with essentially the same slopes (1.993 to 2.003, average 1.998). Regressing the intercepts of Figure 9 vs. their corresponding $\log(\Phi)$, the slope is -1.02 ($R^2 > 0.999$), essentially the same as in Figure 7. Remarkably, the only significant difference is that the intercept of this regression is -0.71, rather than 0.006 in Figure 7. This analysis yields the empirical correlation

$$ART = 0.19 \gamma^{2.00} \Phi^{-1.02} \quad \text{(Equation 46)}$$

Reversing the order of analysis and plotting $\log(ART)$ vs. $\log(\Phi)$ first, as shown in Figure 10, yields slopes of -0.987 to -1.039 (average -1.010, all $R^2 > 0.999$). Regressing the intercepts of these lines vs. $\log(\gamma)$ yields a slope of 1.990 and an intercept of -0.678 ($R^2 = 0.99999$). This analysis yields the empirical correlation

$$ART = 0.21 \gamma^{1.99} \Phi^{-1.01} \quad \text{(Equation 47)}$$

Considering the correlations shown in Equations 46 and 47, it seems clear that for the shrinking sphere kinetic system, the dimensionless ART can be estimated by the simple relationship

$$ART = 0.2 \frac{\gamma^2}{\Phi} \quad \text{(Equation 48)}$$

4. Discussion.

Delivery systems with competing rate processes are often described by coupled, non-linear partial differential equations such as Equations 14 and 15, which must be solved numerically. The flux of solute at the system interface and the cumulative release over time (*i.e.*, the release profile) must therefore also be calculated numerically. The ability to gain predictive

insights from a numeric model rests on the ability to characterize the output parameter of interest and correlate its change to the change of an input parameter. In the case of coupled diffusion/dissolution-limited release, this is typically done qualitatively by plotting a series of release profiles based on the change in an input parameter and noting a trend, as this paper does with Figures 4 and 5. To develop a clearly-defined mathematical correlation, the release profile must be quantified more precisely. Most efforts to precisely quantify a release profile focus exclusively on one part of the profile, for instance its initial slope or the time point at which a specific fraction of the drug has been released. This is problematic because most applications require information about multiple locations in the release profile and the choice of focus location is inherently arbitrary. Moreover, analytical correlations between such an output parameter and the input parameters are typically limited to a small range of values.

The Cumulative Release Time is unique in that it encompasses information from the entire release profile. It shares a common weakness with the other types of output parameters mentioned above because applying it to a specific application still requires an understanding of the general profile shape and how it will change in response to an input parameter. However, unlike the other types of output parameters mentioned above, the CRT can be precisely correlated to the diffusion and dissolution rates over several orders of magnitude, as indicated in Equation 45. Mathematically, the CRT is analogous to the “Leakage” of a reactive barrier membrane: the integration of the moles of solute which have penetrated the membrane over time. For solutes that slowly react with the contents being protected by the barrier membrane, the Leakage is directly correlated to the degree of damage done by the solute. Furthermore, the Leakage has been shown to vary inversely with the membrane’s second Damköhler number, though the governing equations are not analytically solvable. (Nuxoll and Cussler, 2005)

Similarly, Equations 14 and 15 have no known analytical solution, and even the diffusion-controlled limit of Section 2.1 is typically approximated rather than solved exactly. Yet Figures 6-10 indicate that the area between their resulting release profiles can be expressed analytically, demonstrating simple integer power-law relationships between the ART, γ , and Φ . Φ was investigated at logarithmically-regular intervals across 4.5 orders of magnitude, from strongly diffusion-limited systems ($\Phi = 316$) to strongly dissolution-limited systems ($\Phi = 0.01$). Similarly, γ was investigated across 3.75 orders of magnitude, from systems where the initial concentration of solid drug was 3162 times its solubility limit to systems where there was initially more dissolved drug than solid drug. The entire range of Φ could not be investigated at every γ , and vice-versa, but most series include at least ten data points spanning over two orders of magnitude. In every series, the power-law correlation between ART and Φ , or ART and γ , is remarkably strong. Moreover, the exponents of the correlation are simple integers.

Equally striking, this relationship appears to be independent of the kinetics of the dissolution. The dissolution rate in a shrinking sphere kinetic system changes very differently than the dissolution rate of a conformal monolayer, as demonstrated by the markedly different forms in Equations 25 and 42. From Equation 42, we see that as the particle radius shrinks, its rate of shrinking actually accelerates until it suddenly disappears. (As a sidenote, this is a rare instance in which explicit numerical methods are inherently more stable than implicit ones. Though not required for stability purposes in the shrinking sphere model, the timestep $\Delta\tau$ was still kept at 10^{-6} for uniformity with the conformal monolayer model.) Nonetheless, the correlation between ART and Φ and γ in the shrinking sphere model is identical to the correlation in the nanoporous monolayer model, except for the leading coefficient of 0.2 instead of 1.0. Without an analytical pathway to Equations 45 and 48, it is difficult to discern how the coefficient

changes with the kinetic expression, though determining the coefficient for a different kinetic system could be done quickly with the same analysis shown in Section 2. In any case, for estimates on the effect of dissolution rate and solids loading over several orders of magnitude, the effect of the coefficient would be comparatively small.

The CRT of the diffusion-limited system, obtained by subtracting the integral of Equations 34 and 35 over time from the integral of Θ_∞ over time (where Θ_∞ is simply constant at $\gamma + 1$), varies with γ^2 , as shown by

$$CRT(\text{diffusion-limited}) = \frac{\gamma^2}{6} + \frac{5\gamma}{12} + \frac{5}{12} \quad \text{(Equation 49)}$$

This may be expected, as increasing γ increases both the number of molecules being released and the total time required to release them all. Dividing by the moles of solute released, we see that the mean release time for each molecule increases roughly linearly with solid loading.

Similar to Equation 49, Equations 45 and 48 indicate that the increase in CRT due to a finite dissolution rate also scales with the square of the solids loading. However, this is actually an artifact of the non-dimensionalization. The ART in Equations 45 and 48 is dimensionless. Re-dimensionalizing it using Equations 22 and 32 (as the dimensionless ART is an integral of Θ over τ), the dimensional form of Equation 45 for the nanoporous monolith becomes

$$ART(\text{dimensional}) = \left(\frac{C_{Xs} A \ell^3}{D} \right) ART(\text{dimensionless}) = \gamma \left(\frac{A \ell}{k} \right) \quad \text{(Equation 50)}$$

In dimensional terms, the ART for a nanoporous monolayer with mixed diffusion/dissolution control increases only linearly with the initial solids loading. The increase in the mean release time of a molecule (the ART divided by the total moles released) due to a finite dissolution rate is in fact independent of the initial solids loading. The effect of additional solids on the mean release time is accounted for in the infinitely-fast-dissolution limit as indicated in Equation 49,

but the increase in mean release time due to slower dissolution kinetics is independent of the amount of solids involved. It does, however, increase exactly inversely with the dissolution rate constant per volume, as indicated in Equation 50. Similarly, for the case of shrinking-sphere dissolution kinetics, the dimensional form of Equation 48 becomes

$$ART(dimensional) = \left(\frac{C_{Xs} A \ell^3}{D} \right) ART(dimensionless) = 0.2 \gamma \left(\frac{\rho_Y}{MW_Y} \right) \left(\frac{A \ell R_o^2}{D} \right) \quad (\text{Equation 51})$$

where ρ_Y and MW_Y are the density and molecular weight, respectively, of solid Y; their ratio is equivalent to C_{Y0}/ϕ . Again the dimensional ART increases only linearly with the amount of solid Y, indicating that the increase in the mean release time of a molecule due to dissolution limitations is independent of the initial solids content. However, Equation 52 shows that the simple inverse relationship between the dimensional ART and the dissolution rate constant indicated in Equation 50 is not universal. If it were, then by analogy with Equation 50, the dissolution rate constant for the shrinking sphere system would be $(MW_Y/\rho_Y) (D/R_o^2)$. However, the effective dissolution rate (*i.e.*, the rate of decrease of solid Y) for this system is given in Equation 39, and by substituting $\phi = C_{Y0} MW_Y / \rho_Y$ and $C_Y = C_{Y0} (R^3 / R_o^3)$ into that equation the dissolution rate expression becomes

$$\frac{dC_Y}{dt} = \frac{3 \phi D}{R_o^2} R(C_{Xs} - C_X) = \left(\frac{MW_Y}{\rho_Y} \right) \left(\frac{D}{R_o^2} \right) \left(3 R_o C_{Y0}^{2/3} \right) C_Y^{1/3} (C_{Xs} - C_X) \quad (\text{Equation 52})$$

The effective dissolution rate constant is not merely $(MW_Y/\rho_Y) (D/R_o^2)$, but also multiplied by a factor of $3 R_o C_{Y0}^{2/3}$. For systems with different kinetic expressions, a separate dimensional analysis of the system is required to determine Φ and the corresponding dimensional expression for the ART. Nonetheless, this analysis should allow a predictive, quantitative analytical expression for release profiles as a function of the relative diffusion and dissolution rates.

5. Conclusions.

Dispersing drug in a matrix at a concentration well above its saturation limit is a longstanding method of obtaining sustained release. When the dissolution rate of the drug is comparable to its diffusion rate in the matrix, the concentrations of dissolved and solid drug are usually described most accurately by coupled, non-linear partial differential equations with no known analytical solution, driving decades of research on computational models for calculating the resulting release profiles. These efforts typically result in set of model release profiles qualitatively demonstrating a relationship between the profile and a given input parameter. To quantitatively correlate the release profile to an input parameter, the profile itself must be quantified. The mean release time is one such metric. This paper introduces the Added Release Time, which is the difference between the mean release times of a system with infinitely fast dissolution and a corresponding system with a finite dissolution rate. Through computational modeling using a continuous field approach with simple numeric methods, the release profiles and corresponding ARTs were calculated over a wide range of dissolution rates, ranging from dissolution-dominated to diffusion-dominated release. Similarly, a wide range of solid drug loadings were investigated, ranging from solids contents smaller than the dissolved solute concentration to solids contents thousands of times larger than the dissolved solute concentration. Across the entire range investigated, both parameters showed a strong power-law relationship with the ART, with integer exponents. Moreover, this relationship appears to be independent of the dissolution kinetics, as systems with significantly different dissolution rate expressions yielded the same relationship, differing only in the coefficient. Rather than resort to computational modeling to determine the mean release time of a system with mixed dissolution/diffusion control, this work provides a simple analytical expression with which one can not only predict the mean release time for a given set of parameter values, but understand

precisely how each parameter value will affect it. The simplicity of the correlation and the lack of apparent limits to its validity also suggest the existence of an analytical pathway for its derivation, which may yield additional insights into the effect of secondary rate processes on controlled release.

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Figure Captions and Table Headings.

Figure 1. Effect of Finite Dissolution Rate of Release Profile. As the dissolution rate decreases, release becomes slower and more linear with respect to time.

Figure 2. Cumulative Release Time (CRT) and Added Release Time (ART). The CRT (shaded in both gray tones) for the diffusion/dissolution coupled release profile (dotted line) is bounded by the profile, the y-axis, and the 100% release plateau. Dividing the CRT by the plateau value gives the Mean Release Time (MRT), the average time required for a molecule to escape the system. The ART (light gray) is bounded by the coupled release profile and the diffusion-limited release profile.

Figure 3. Pseudo-steady-state Release from Monolith. Solute concentration is assumed to be initially saturated, but quickly diffuses into external sink at right. As the local solute concentration drops it is replenished by dissolution of solid Y until the local solids concentration C_Y drops to zero. A moving front forms (its location designated ℓ') beyond which $C_Y = 0$ and behind which $C_Y = C_{Y0}$. The rate at which this front advances to the left is determined by the flux of dissolved solute to the right, approximated by assuming a linear concentration gradient from $C_X = C_{Xs}$ at ℓ' to $C_X = 0$ at the external sink.

Figure 4. Effect of Solid Chemical Loading γ on Release Profile. Release profiles with comparable diffusion and dissolution rates (Damköhler number $\Phi = 1$) at various solids loading. Profiles are initially identical (shown at inset) but diverge as local solids are exhausted at different times. Fast dissolution limit (dashed line) is for $\text{Log}(\gamma) = 1.0$ case.

Figure 5. Decreased Relative Dissolution Rate Linearizes Release Profile. Release profiles at uniform solids loading $\gamma = 10$ show that as the ratio of dissolution to diffusion rate (Φ) decreases, the profile becomes more linear. $\text{Log}(\Phi)$ value for each profile is indicated in parentheses next to the profile; infinitely fast dissolution case is shown with dashed line.

Figure 6. Correlation Between Added Release Time and Solids Loading in Monolayer Release System. $\text{Log}(\text{ART})$ is linear with respect to $\text{Log}(\gamma)$ across several orders of magnitude and over a wide range of $\text{Log}(\Phi)$ values (given in parentheses next to corresponding series). Linear trendline results are listed beneath each series indicating that ART is proportional to $\gamma^{2.0}$ with high precision (all $R^2 > 0.99994$). Series at intermediate $\text{Log}(\Phi)$ values (e.g., -1.75, -1.25, -0.75, ...2.25) were omitted due to space constraints, but have comparable trendlines.

Figure 7. Intercepts of $[\text{Log}(\text{ART}) \text{ vs. } \text{Log}(\gamma)]$ Correlate Linearly to $\text{Log}(\Phi)$. The series in Figure 6 ($\text{Log}(\text{ART})$ vs. $\text{Log}(\gamma)$) are equally spaced, as shown by plotting their intercepts vs $\text{Log}(\Phi)$ across 4.5 orders of magnitude. This indicates that ART is proportional to $\Phi^{-1.0}$.

Figure 8. Correlation Between Added Release Time and Dissolution Rate in Monolayer Release System. $\text{Log}(\text{ART})$ is linear with respect to $\text{Log}(\Phi)$ across several orders of magnitude and over a wide range of $\text{Log}(\gamma)$ values (given in parentheses next to corresponding series). Linear trendline results are listed beneath each series indicating that ART is proportional to $\Phi^{-1.0}$ as indicated in Figure 7.

Figure 9. Correlation Between Added Release Time and Solids Loading in Shrinking Sphere System. Log(ART) is linear with respect to Log(γ) across several orders of magnitude and over a wide range of Log(Φ) values (given in parentheses next to corresponding series). Linear trendline results are listed beneath each series indicating that ART is proportional to $\gamma^{2.0}$ with high precision (all $R^2 > 0.99999$). Series at intermediate Log(Φ) values (e.g., -1.75, -1.25, -0.75, ...1.25) were omitted due to space constraints, but have comparable trendlines.

Figure 10. Correlation Between Added Release Time and Dissolution Rate in Shrinking Sphere System. Log(ART) is linear with respect to Log(Φ) across several orders of magnitude and over a wide range of Log(γ) values (given in parentheses next to corresponding series). Linear trendline results are listed beneath each series indicating that ART is proportional to $\Phi^{-1.0}$.

Table 1. Log(ART) Values for Nanoporous Monolith with Conformal Monolayer. A more extensive dataset is presented as Table S1 of the Supplementary Materials.

Table1 Log (Φ)	Log (γ)				
	1	1.25	1.5	1.75	2
-1	3.002				
-0.75	2.753	3.252			
-0.5	2.504	3.002	3.501		
-0.25	2.256	2.754	3.252	3.751	
0	2.009	2.505	3.003	3.502	4.001
0.25	1.763	2.257	2.754	3.252	3.751
0.5	1.517	2.010	2.506	3.003	3.501
0.75	1.270	1.761	2.256	2.753	3.251
1	1.019	1.511	2.008	2.502	3.000
1.25	0.762	1.257	1.753	2.250	2.749
1.5	0.492	0.996	1.496	1.995	2.494
1.75		0.723	1.232	1.735	2.236
2		0.425	0.953	1.465	1.971

Figure3

Figure 5

Figure 6

Figure7

Figure 8

Figure 9

Figure 10