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Short communication

Mass transfer from a coated pure drug bead

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Abstract

Drug release from a coated pure drug bead in a finite volume of stirred liquid may be expediently established by inspecting the rate at a particular time. The effects of various parameters on this rate and the ranges of parameters in applications have been discussed.

Keywords: Drug release; Analysis; Diffusion

1. Introduction

Mathematical models for coated sphere(s) were developed for describing release rate of drug with diffusion resistances (Chen and Lee, 2002; Li *et al.*, 2006; Liao and Lee, 1997; Lu and Chen, 1993, 1995; Lu and Lee, 1992; Lu, 1994; Lu *et al.*, 2007). The role of diffusional resistances was studied (Chen and Shih, 2006; Huang *et al.*, 2006; Kao and Li, 2006; Su *et al.*, 2006).

A coated pure drug bead contains the maximum amount of drug that can be enclosed inside a particle of the same radii. With a non-swelling coating, the release rate of drug in a well-stirred liquid at a given temperature is dependent on: core and particle radii, b and a; effective diffusivity of drug, D; volume of external liquid, V_e; partition constants at b and a, K_b, K_a; the ratio of drug density to drug solubility in the liquid, ρ_u/C_s. Fig. 1 shows six drug release systems, each in a liquid of volume 100 cm^3, inside an imaginary spherical container of radius r_e, systems (1a)–(1c) show particles of 1 mm coating but with different radii; and (2a)–(2c), 3 mm coating. Systems (1a) and (2a) show cases of small liquid to particle volume ratios; and (1c)–(2c), large ratios. The parameters of these systems are listed in Table 1.

Ignoring the very initial release stage, the release life of a particle is divided into two stages, $t < t_s$ and $t > t_s$. t is time and t_s is time at which solid drug in the core is exhausted. The release rates for different release systems are summarized in Fig. 2 in dimensionless form. The dimensionless quantities are defined by Eqs. (2a)–(2e) in next section. In a perfect sink, parameter s is infinity, and the release rate is zero order in the first stage but non-linear in the second. In a non-perfect sink, s is less than infinity. Release rate is affected by the magnitude of s. For a wide range of s, i.e., $\sim 15 < s < \infty$, this effect is less than $\sim$10% for systems with $\rho_u/C_s = 2.19$, and less than $\sim$50% with $\rho_u/C_s = 8$. Release experiments are often conducted in an abundant of liquid that is often low in viscosity. While in applications, situations that liquid is limited in volume arise. In either case, Fig. 2 shows that release rate at $t/t_s = 1$ may be taken as a landmark in a rate curve, and this, if known, will be useful in the design of a coated pure drug bead.

In this paper, a quantity that may be used to represent such a landmark is sought. As the release behavior of a system is a collective manifestation of all parameters that define the system, the effects of various parameters on this landmark and ranges of parameters in applications are investigated.

2. Analysis

For a coated pure drug bead releasing the drug in a well-stirred liquid of volume V_e, the dimensionless release rate at t_s is (Lu, 1994):

$$\left(\frac{dY}{dX}\right)_{X=X_s} = \exp\left(-\frac{p}{s}X_{ls}\right) \tag{1}$$

where

$$Y = \frac{M_t}{4\pi ab(a-b)C_s K_a/K_b}, \tag{2a}$$

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Nomenclature

a	core radius (m)
b	particle radius (m)
C_s	drug solubility (kg/m^3)
D	effective diffusivity of drug (m^2/s)
K_a	partition coefficient at $r = a$
K_b	partition coefficient at $r = b$
M_t	cumulative release quantity (kg)
p	dimensionless group defined in Eq. (2c)
r	radial direction (m)
s	dimensionless group defined in Eq. (2d)
t	time (s)
t_s	time when drug core is exhausted (s)
V_e	volume of external liquid (m^3)
V_τ	volume ratio
X	dimensionless group defined in Eq. (2b)
X_{ls}	X at $t = t_s$
Y	dimensionless group defined in Eq. (2a)

Greek symbol

ρ_u	drug density (kg/m^3)

$$X = \frac{Dt}{K_a(a-b)^2}, \tag{2b}$$

$$p = 3\frac{K_a}{K_b}\frac{a}{b}\left(\frac{a}{b} - 1\right), \tag{2c}$$

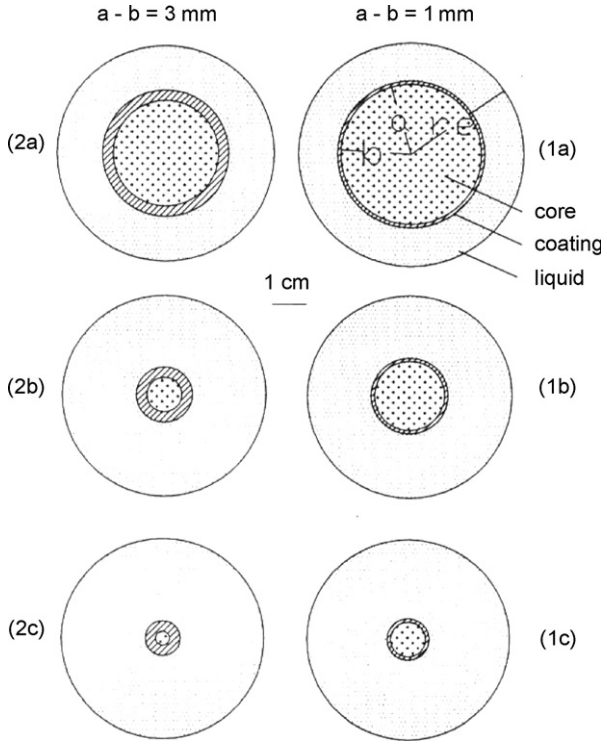

Fig. 1. A coated pure drug bead in an imaginary spherical container of radius r_e. Other parameters are shown in Table 1.

Table 1
Parameters of the system shown in Fig. 1

Fig. 1	$a - b$ (mm)	b/a	b (cm)	a (cm)	r_e (cm)	V_p (cm^3)	V_e/V_p
1a	1	1.05	2.0	2.1	3.21	38.8	2.6
1b	1	1.10	1.0	1.1	2.93	5.6	17.9
1c	1	1.20	0.5	0.6	2.89	0.9	111
2a	3	1.20	1.5	1.8	3.10	24.4	4.1
2b	3	1.60	0.5	0.8	2.90	2.1	46.6
2c	3	2.50	0.2	0.5	2.88	0.5	191

$V_e = 100$ cm^3.

$$s = \frac{K_a}{K_b}V_\tau\left(\frac{a}{b}\right)^3, \tag{2d}$$

$$X_{ls} = -\frac{s}{p}\ln\left(1 - \frac{\rho_u/C_s - 1}{s}\right). \tag{2e}$$

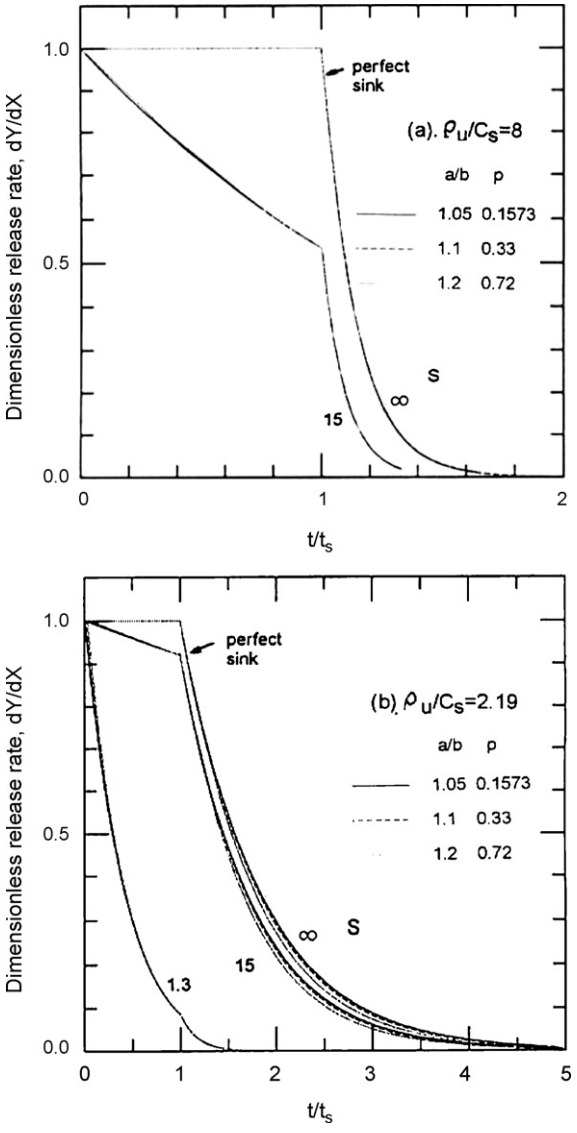

Fig. 2. Dimensionless release rate vs. dimensionless time for different release systems. Data quoted from Lu (1994). $V_e = 100$ cm^3 and $K_b/K_a = 1$.

Y is the dimensionless representative of cumulative release M_t, and X, of time. X_{ts} is X at t_s. p and s are dimensionless parameters. V_τ is volume ratio of the external liquid to the coated particle, V_e/V_p. Substitute Eq. (2a)–(2e) into Eq. (1) and rearrange the resulting equating equation as follows:

$$y = \left(\frac{dM_t/dt}{4\pi DC_s/K_b}\right)t_s = \frac{(a/b)(a-b)}{(a/b-1)^2}\left[1 - \frac{4\pi}{3V_e}\frac{K_b}{K_a}\left(\frac{a-b}{a/b-1}\right)^3\left(\frac{\rho_u}{C_s}-1\right)\right] \quad (3)$$

y define as above, differs from dY/dX in that it does not contain the radii. Y is a quantity that may be used to represent the landmark in a rate curve. Eq. (3) thus shows how y is affected by the radii, V_e, K_b/K_a and ρ_u/C_s.

3. Results and discussion

Plots of y versus a/b according to Eq. (3) for particles with 1 mm coating are shown in Fig. 3. For a quick grasping of a real situation, b and V_p are also included in the figure.

Fig. 3 shows that for a given V_e, there is a a/b at which $y = 0$, or $(dM_t/dt)_{t_s} = 0$, i.e., drug release ends at the exhaustion of solid drug. For $(a/b) < (a/b)_{y=0}$, drug release ends with solid drug still present in the core and thus is without t_s. However, for the problem to be realistic, there is a limit to the magnitudes of a/b. This limit is dependent on the conditions of the systems. For $(a/b) > (a/b)_{y=0}$, t_s exists. y increases quickly to a maximum and then decreases gradually. Most release experiments are located on the right side of the maximum. At increased a/b, all curve converge to the curve for a perfect sink ($s = \infty$). Large a/b implies small b and a, and thus, even with small V_e, V_e is still large relative to a, and thus, V_τ, and therefore s, are sufficiently large for the approximation of a perfect sink.

Fig. 3(a) and (b) show the effect of K_b/K_a on y, and (b) and (c) show the effect of ρ_u/C_s on y. The effect of increase in coating thickness, not shown here, is to shift the curves

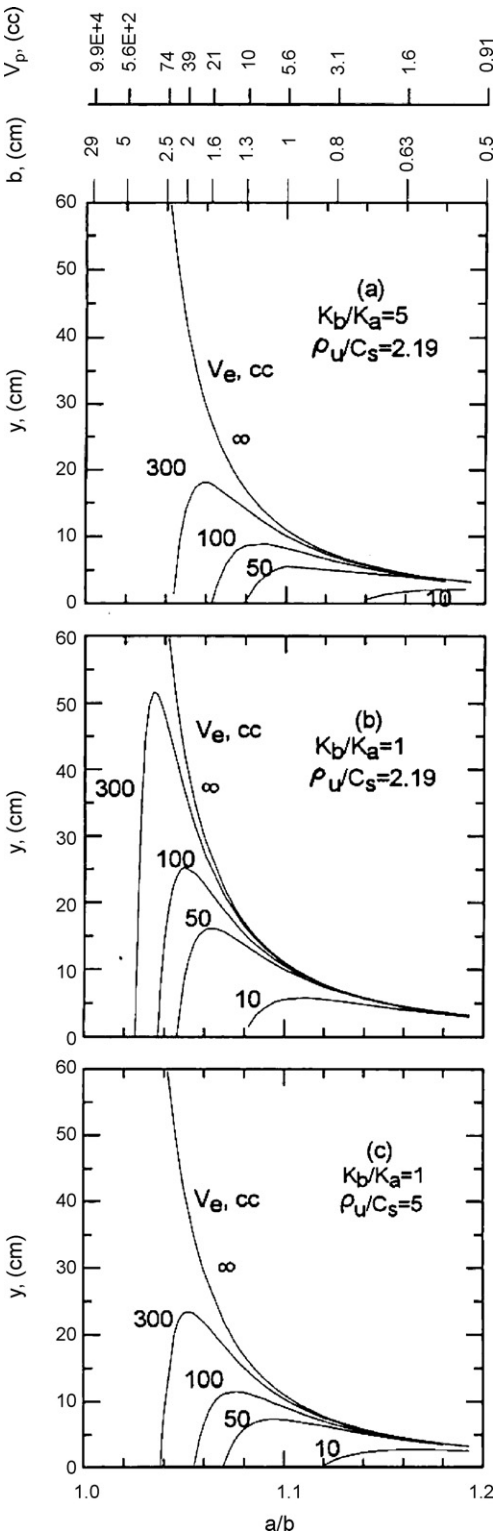

Fig. 3. y vs. a/b at various V_e, for $a - b = 1$ mm, and K_b/K_a and ρ_u/C_s as indicated.

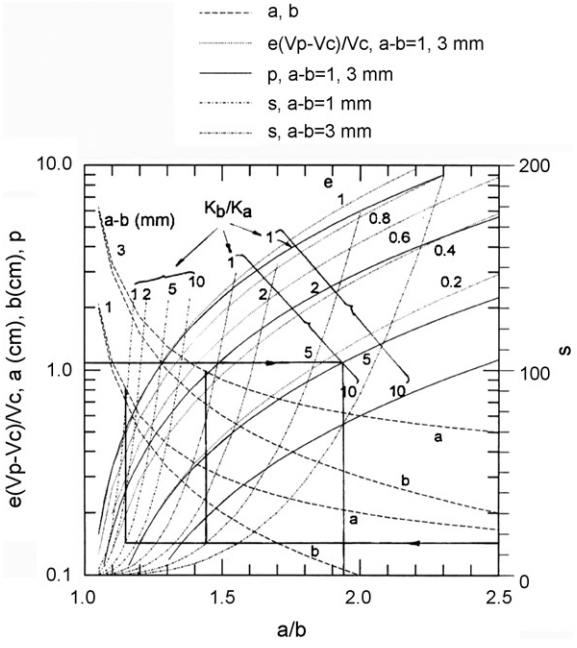

Fig. 4. Particle radii, b and a, parameters p and s, and pore volume fraction at various a/b. For $V_e = 100$ cm^3 and the indicated $a - b$ and K_b/K_a.

rightward with attenuated maxima. From Fig. 3, for $a/b = 1.16$, find $b = 0.63$ cm, $a = 0.73$ cm, $V_p = 1.6$ cm^3, and that release in a liquid with $V_e \geq 50$ cm^3 are nearly equal to that in a perfect sink while with $V_e = 10$ cm^3, deviation is greater especially under the conditions of (a) and (c). Cases of small V_e are encountered in release from multiple particles.

For Fig. 2(b) where $\rho_u/C_s = 2.19$ and $K_b/K_a = 1$, it has been shown in Lu (1994) that $dY/dX = \sim 1$ is attained if $p \leq \sim 1.17$ and $s \geq \sim 15$. These limitations also apply when $K_b/K_a > 1$. The ranges of real variables of release systems that are within these limitations may be found from Fig. 4 where a, b, p, s, and $e(V_p - V_c)/V_c$ are plotted, respectively, against a/b for the conditions indicated. For simplicity, take $p = 1.1$ for $p \leq \sim 1.17$and consider a system with a particle 1 mm in coating, $V_e = 100$ cm^3, $\rho_u/C_s = 2.19$ and $K_b/K_a = 5$. From Fig. 4, find: (1) by p curve, $a/b = 1.943$, and by a, b curves, $a = 0.206$ cm and $b = 0.106$ cm and (2) by s curve, with $s = 15$, $a/b = 1.146$, and by a, b curves, $a = 0.783$ cm and $b = 0.683$ cm for particles with a/b in 1.146–1.943, or a in 0.783–0.206 cm, or b in 0.683–0.106 cm (similarly, for particles 3 mm in coating, find a/b in 1.439–1.943, or a in 0.983–0.618 cm, or b in 0.683–0.318 cm), $dY/dX \sim 1$ can be attained and y is almost equal to that for a perfect sink. For particles with $a/b < 1.146$, or $b > 0.683$ cm, or $a > 0.783$ cm, the effect of the sink (imperfect) on release rate increases with decreasing a/b. dY/dX falls below 1 and y eventually becomes zero. For particles with $a/b > 1.943$, or $b < 0.106$ cm, or $a < 0.206$ cm, drug release may be assumed to be in a perfect sink. However, as $p > 1.1$, thus, $dY/dX < 1$. This may be explained physically by the following example. For a particle with 3 mm coating and $a/b = 2.5$, Fig. 4 shows that $b = 0.2$ cm, $a = 0.5$ cm, $p = 2.25$ if $K_b/K_a = 5$, and $s = 597$ (not shown) if $V_e = 100$ cm^3. s is so large that a perfect sink may be assumed. By $e(V_p - V_c)/V_c$ curve where V_c is core volume and e is porosity, assuming $e = 0.4$, fine $e(V_p - V_c)/V_c = 5.85$. Liquid volume holdup is 5.85 times the core volume. For $\rho_u/C_s = 2.19$, then drug holdup in the coating layer at the exhaustion of solid drug is less than that under a pseudo steady state. Thus, $dY/dX = 1$ cannot be attained. An analysis more rigorous than that used in Lu (1994) is needed to describe this situation. However, for high ρ_u/C_s, drug holdup in the coating layer will be low and the analysis may be used. The system shown by Fig. 1(2c) is an example that may behave as has been described depending on the drug and the liquid used.

4. Conclusions

Overall drug release behavior from a coated pure drug bead in a well-stirred liquid may be predicted expediently by using the rate at the exhaustion of solid drug. The effects of various parameters on this rate and the ranges of real variables in applications have been made clear.

References

Chen, B. H. and D. J. Lee, "Finite Element Analysis of Slow Drug Release through Deformed Coating Film: Effects of Morphology and Average Thickness of Coating Film," *Int. J. Pharm.*, **234**, 25 (2002).

Chen, P. H. and H. C. Shih, "A Chemical Kinetics Model for Oxide Chemical Mechanical Polishing," *J. Chin. Inst. Chem. Engrs.*, **37**, 401 (2006).

Huang, J. F., C. H. Jien, and L. S. Lee, "Effects of Co-solvents on the Solubility of Beta-carotene in Supercritical Carbon Oxide," *J. Chin. Inst. Chem. Engrs.*, **37**, 329 (2006).

Kao, C. Z. and M. H. Li, "Diffusion Coefficients of Aqueous *N*,*N*-Diethylethanolamine, *N*,*N*-Dimethylethanolamine, Monoisopropanolamine, Piperazine, and Sulfolane Solutions," *J. Chin. Inst. Chem. Engrs.*, **37**, 341 (2006).

Li, S. J., Y. Shen, W. K. Li, and X. Hao, "A Common Profile for Polymer-based Controlled Release and Its Logical Interpretation to General Release Process," *J. Pharm. Pharm. Sci.*, **9**, 238 (2006).

Liao, Y. C. and D. J. Lee, "Slow Release from a Coated Sphere with Slight Deformation of Coating Film and Drug Matrix," *J. Pharm. Sci.*, **86**, 92 (1997).

Lu, S. M. and S. F. Lee, "Slow Release of Urea through Latex Film," *J. Control. Release*, **18**, 171 (1992).

Lu, S. M. and S. R. Chen, "Mathematical-Analysis of Drug Release from a Coated Sphere," *J. Control. Release*, **23**, 105 (1993).

Lu, S. M., "Dimensionless Presentation for Drug Release from a Coated Pure Drug Bead. Part I. Analysis," *Int. J. Pharm.*, **112**, 105 (1994).

Lu, S. M. and S. R. Chen, "Dimensionless Presentation for Drug Release from a Coated Pure Drug Bead. Part II. Effects of Initial Conditions and Methods of Solution," *Int. J. Pharm.*, **119**, 11 (1995).

Lu, S. M., S. L. Chang, W. Y. Ku, H. C. Chang, J. Y. Wang, and D. J. Lee, "Urea Release Rate from a Scoop of Coated Pure Urea Beads: Unified Extreme Analysis," *J. Chin. Inst. Chem. Engrs.*, **38**, 295 (2007).

Su, W. B., J. R. Chang, T. B. Lin, and H. C. Shen, "Internal and External Mass Transfer Effects for Commercial Acid Resin Catalysts in TAME Synthesis," *J. Chin. Inst. Chem. Engrs.*, **37**, 249 (2006).