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Dimensionless presentation for drug release from a coated pure drug bead: 2. Experiment

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Abstract

The release of urea from a coated urea bead in water and in aqueous glycerol solutions is investigated experimentally. Experimental data of 19 release systems are analyzed and correlated using the dimensionless equations that have been discussed in part 1 of this work. The ratio of partition constants and the ratio of diffusivity to partition constant are determined.

Keywords: Urea bead; Ethyl cellulose coating; Aqueous glycerol solution; Release curve; Relative diffusivity

1. Introduction

In part 1 of this work, diffusion drug release from a coated pure drug bead in an elution liquid of known volume has been presented in dimensionless form. A release system consisting of a particle and an elution liquid is completely defined once dimensionless parameters ρ_u/C_s, s, and p are specified. The release behavior of a particle over its entire release life is described by using dimensionless cumulative release Y, dimensionless release rate dY/dX, and dimensionless time X. Fractional cumulative release and dimensionless release rate have been respectively unified with respect to parameter p. Systematic correlation and comparison of release data of different systems and sources are therefore made easy.

In this part of the work, experiments have been conducted to verify the results presented in part 1. A coated urea bead is used to release urea in water and in aqueous glycerol solutions of different concentrations.

2. Experimental

A urea bead of diameter about 15 mm is prepared and weighed. The bead is coated with ethyl cellulose. 2.5 g of ethyl cellulose powder (Ethocel 45STD, Dow Chemical Co.) is mixed with 50 ml acetone in a 125 ml tinted flask. After about 1 h of stirring, a clear colorless solution is obtained. The urea bead dipped in this solution is placed on a Teflon coated plate and is rolled around the plate to make the coating as uniform as possible. This coated bead is then dried in an oven at 50°C. The processes of dipping, rolling,

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and drying are repeated until a desired weight of coating has been added to the bead. For coating, high ethyl cellulose concentration is not desirable in that increased viscosity can cause the coated film to peel off from urea bead, low ethyl cellulose concentration is also not desirable in that excessive amounts of solvent and labor will be needed for a given amount of coating. In the first few layers of coating, urea may crystallize on the coated surface and thus may make the surface uneven. These crystals are rubbed off to prepare a smooth surface for the next coating. The finished particle has a smooth, yellow brown surface.

For release testing, a coated particle is placed in a 125 ml flask that contains 100 ml of an elution liquid. Four elution liquids, water, 10, 30, and 50% aqueous glycerol solutions, were used. The flask is mounted on an orbital shaker of 1 inch stroke and 120 rpm. The release temperature is 25°C. A particle with good coating was observed to remain at the bottom of the flask throughout the release test. The core bead which decreases in size with time is visible under light.

The cumulative release data are determined by using basically the method described by Lu and Lee (1992). At the end of a release lifetime, the concentration of urea in the elution liquid, $C_{\mathrm{e,end}}$, becomes invariant with time. The liquid inside the particle is then extracted by a hypodermic needle and its concentration of urea, $C_{\mathrm{c,end}}$, is determined. The hollow particle is a hard shell which may be cut open by a knife. The inner surface is not as smooth as the outer surface and shows printing of the surface pattern of the urea bead. For water as the elution liquid, the liquid stays clear during the release test. For 30% glycerol solution, when compared with 10 and 50% solutions, the liquid tends to have some white thread-like substance in the solution.

3. Results and discussion

3.1. About the tables

For the release of urea in water, the variables pertaining to each particle are tabulated in Table 1. The first column lists the names of the particles. The following columns show: W_1, the initial weight of a urea bead; W_2, the weight of a coated particle; W_{u}, the weight of urea after coating, obtained by summing up weights of urea assayed at the end of a release test; and $(W_1 - W_{\mathrm{u}})/W_1$, the relative loss of urea. The density of the coating layer, ρ_{film}, is 1.18 g/ml. Radii b and a, coating thickness $a-b$, and radius ratios a/b are then calculated and tabulated in the next four columns.

The above columns are followed by columns for $C_{\mathrm{c,end}}/C_{\mathrm{e,end}}$ and K_b/K_a. $C_{\mathrm{c,end}}$ and $C_{\mathrm{e,end}}$ represent, respectively, the concentrations of urea in the core and in the elution liquid at the end of an experiment. As $C_{\mathrm{c},\infty}/C_{\mathrm{e},\infty} = K_b/K_a$ (see footnote of tables), the ratio $C_{\mathrm{c,end}}/C_{\mathrm{e,end}}$ is used to evaluate K_b/K_a. The difference between $C_{\mathrm{c,end}}$, $C_{\mathrm{e,end}}$ and $C_{\mathrm{c},\infty}$, $C_{\mathrm{e},\infty}$ is that the former are experimental values for which a small amount of elution liquid has to be taken for assaying urea concentration and the latter are theoretical values for which there is no such need. The column 'Adopt.' K_b/K_a shows the magnitudes of K_b/K_a adopted in calculation to obtain a good fit between the data and the equation. In Table 1, the maximum difference and the average relative difference between $C_{\mathrm{c,end}}/C_{\mathrm{e,end}}$ and K_b/K_a are found to be 6 and 2.5%, respectively.

The next two columns, 'Calc.' $M_{t\infty}$ (see footnote of tables) and 'Exp.' $M_{t\infty}$, show the calculated and the experimental total cumulative release. The maximum and the average relative differences between them are 1 and 0.5%, respectively.

Columns $N_1(\equiv (4\pi D / K_a/V_{\mathrm{e}})(ab/(a-b))$ and t_{s} list N_1 and critical time. They are determined by the linear regression of experimental cumulative release data in $t \le t_{\mathrm{s}}$ on equation $\ln(1-F) = -N_1 t$ (Lu and Lee, 1992). The results of regression are further checked by the fitness between the experimental data and the dimensionless equations in $t > t_{\mathrm{s}}$.

The following column shows $M_{t_{\mathrm{s}}}$ which is the cumulative release at $t = t_{\mathrm{s}}$. The column for D/K_a shows effective diffusivity relative to K_a. They are calculated from N_1. The last three columns show V_{r}, the volume ratio of elution liquid to

Table 1

Release data of urea beads coated with ethyl cellulose, in water ($\rho_{\text{film}} = 1.18$ g/ml, $\rho_u = 1.335$ g/ml, $C_s = 0.632$ g/ml, $\rho_u / C_s = 2.1123$)

Sample	u[a] Bead W_1 (g)	Coated, W_2 (g)	u Exp. W_u (g)	u Loss $(W_1 - W_u)/W_1$ (−)	b (cm)	a (cm)	$(a-b)$ (cm)	a/b (−)	$C_{c,\text{end}}/C_{e,\text{end}}$ (−)	Adopt. K_b/K_a (−)	Calc. $M_{t\infty}$ (g)	Exp. $M_{t\infty}$ (g)	N_1 (1/days)	t_s (days)	$M_{ts} = W_u - V_cC_s$ (g)	D/K_a (cm^2/s)	V_r (−)	s (−)	p (−)
0D	2.2778	2.4903	1.9592	0.1399	0.7050	0.7707	0.0657	1.0933	5.70	6.00	1.8006	1.8179	4.83$E-03$	21.3401	1.3503	5.38$E-08$	52.15	11.36	0.0510
0E	2.2491	2.4621	2.0578	0.0851	0.7166	0.7662	0.0496	1.0692	11.37	11.00	1.7595	1.7742	8.90$E-03$	23.4827	1.2749	7.40$E-08$	53.08	5.90	0.0202
0F	2.2100	2.4181	1.9060	0.1376	0.6985	0.7631	0.0646	1.0925	8.28	8.00	1.7106	1.7018	4.70$E-03$	28.8838	1.3077	5.25$E-08$	53.71	8.76	0.0379
0K	2.0992	2.1980	1.9009	0.0945	0.6979	0.7368	0.0389	1.0558	9.07	9.00	1.6850	1.6768	9.83$E-03$	15.6369	1.1993	6.86$E-08$	59.68	7.80	0.0196
0L	2.1226	2.2482	1.9112	0.0996	0.6992	0.7429	0.0437	1.0625	8.56	8.50	1.7039	1.6966	9.53$E-03$	15.2563	1.2178	7.39$E-08$	58.23	8.22	0.0234
0N	2.0543	2.1824	1.8939	0.0781	0.6970	0.7350	0.0379	1.0544	9.81	10.00	1.6586	1.6533	9.62$E-03$	17.8546	1.1577	6.56$E-08$	60.13	7.05	0.0172

[a] u, urea.

$C_{c,\infty}/C_{e,\infty} = K_b/K_a$, calc. $M_{t\infty} = W_u/(1+(K_bV_c)/(K_aV_e))$, Eq. 22, 20 (Lu and Lee (1992)).

Table 2

Release data of urea beads coated with ethyl cellulose, in 10% glycerol solution ($\rho_{\text{film}} = 1.18$ g/ml, $\rho_u = 1.335$ g/ml, $C_s = 0.5745$ g/ml, $\rho_u / C_s = 2.3238$)

Sample	u[a] Bead W_1 (g)	Coated, W_2 (g)	u Exp. W_u (g)	u Loss $(W_1 - W_u)/W_1$ (−)	b (cm)	a (cm)	$(a-b)$ (cm)	a/b (−)	$C_{c,\text{end}}/C_{e,\text{end}}$ (−)	Adopt. K_b/K_a (−)	Calc. $M_{t\infty}$ (g)	Exp. $M_{t\infty}$ (g)	N_1 (1/days)	t_s (days)	$M_{ts} = W_u - V_cC_s$ (g)	D/K_a (cm^2/s)	V_r (−)	s (−)	p (−)
10D	2.2396	2.4626	1.8998	0.1517	0.6978	0.7683	0.0706	1.1011	11.1	10.50	1.6528	1.6566	6.49$E-03$	33.9110	1.4213	7.87$E-08$	52.63	6.69	0.0318
10E	2.4224	2.4558	1.8263	0.2461	0.6887	0.7685	0.0799	1.1160	11.4	11.00	1.5874	1.5802	5.24$E-03$	42.3282	1.6358	7.28$E-08$	52.59	6.65	0.0353
10F	2.1943	2.3883	1.8683	0.1486	0.6939	0.7602	0.0663	1.0955	9.6	10.00	1.6389	1.6488	9.00$E-03$	22.7234	1.3896	1.04$E-07$	54.34	7.15	0.0314
10G	2.1898	2.3904	1.9164	0.1249	0.6998	0.7598	0.0600	1.0857	10.9	11.00	1.6551	1.6625	9.41$E-03$	24.8724	1.3644	9.78$E-08$	54.43	6.33	0.0254
10H	2.1432	2.3846	1.7438	0.1864	0.6781	0.7614	0.0833	1.1229	19.8	21.00	1.3684	1.3616	1.07$E-02$	42.0608	1.3921	1.59$E-07$	54.08	3.65	0.0197
10I	2.1904	2.4360	1.8271	0.1659	0.6888	0.7663	0.0775	1.1125	15.0	15.50	1.5073	1.5091	9.18$E-03$	35.8511	1.4034	1.24$E-07$	53.06	4.71	0.0242
10J	2.1823	2.4388	1.8656	0.1451	0.6936	0.7661	0.0725	1.1046	18.3	18.00	1.4906	1.4822	8.87$E-03$	45.5426	1.3788	1.12$E-07$	53.10	3.98	0.0192

[a] u, urea.

$C_{c,\infty}/C_{e,\infty} = K_b/K_a$, calc. $M_{t\infty} = W_u/(1+(K_bV_c)/(K_aV_e))$, Eq. 22, 20 (Lu and Lee (1992)).

Table 3

Release data of urea beads coated with ethyl cellulose, in 30% glycerol solution ($\rho_{\text{film}} = 1.18$ g/ml, $\rho_u = 1.335$ g/ml, $C_s = 0.4987$ g/ml, $\rho_u / C_s = 2.6770$)

Sample	u[a] Bead W_1 (g)	Coated, W_2 (g)	u Exp. W_u (g)	u Loss $(W_1 - W_u)/W_1$ (–)	b (cm)	a (cm)	$(a-b)$ (cm)	a/b (–)	$C_{c,\text{end}} / C_{e,\text{end}}$ (–)	Adopt. K_b/K_a (–)	Calc. $M_{t\infty}$ (g)	Exp. $M_{t\infty}$ (g)	N_1 (1/days)	t_s (days)	$M_{t_s} = W_u - V_c C_s$ (g)	D/K_a (cm²/s)	V_r (–)	s (–)	p (–)
30G	2.1309	2.3182	1.8595	0.1274	0.6928	0.7520	0.0592	1.0855	25.1	25.00	1.3792	1.3903	$2.33E-02$	37.6055	1.4359	$2.44E-07$	56.13	2.87	0.0111
30H	2.1212	2.3164	1.8287	0.1379	0.6890	0.7523	0.0633	1.0919	26.1	26.00	1.3484	1.3515	$1.93E-02$	47.1029	1.4377	$2.17E-07$	56.08	2.81	0.0116
30I	2.0720	2.2750	1.7292	0.1654	0.6762	0.7487	0.0725	1.1071	27.2	28.00	1.2690	1.2663	$1.92E-02$	48.7194	1.4257	$2.53E-07$	56.89	2.76	0.0127
30J	2.2952	2.5234	1.9695	0.1419	0.7062	0.7743	0.0681	1.0965	21.8	21.50	1.4952	1.4998	$1.45E-02$	52.1884	1.5590	$1.67E-07$	51.42	3.15	0.0148
30K	2.1715	2.4205	1.9563	0.0991	0.7046	0.7627	0.0581	1.0825	26.8	26.00	1.4166	1.4050	$1.25E-02$	81.4974	1.4403	$1.24E-07$	53.80	2.62	0.0103
30L	2.1065	2.3567	1.9983	0.0514	0.7096	0.7547	0.0451	1.0635	23.8	23.00	1.4865	1.4872	$1.42E-02$	60.4490	1.3596	$1.10E-07$	55.54	2.90	0.0088

[a] u, urea.

$C_{c,\infty} / C_{e,\infty} = K_b / K_a$, calc. $M_{t\infty} = W_u / (1 + (K_b V_c)/(K_a V_e))$, Eq. 22, 20 (Lu and Lee (1992)).

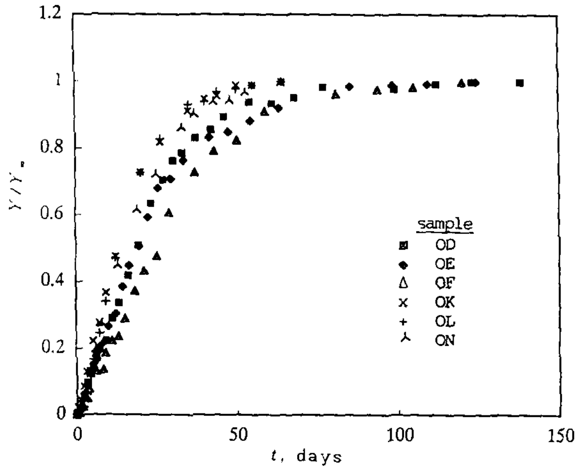

Fig. 1. Fractional cumulative release vs time, in water.

particle, and s and p, the dimensionless parameters. The magnitudes of ρ_{film}, ρ_u, C_s, ρ_u/C_s are listed at the end of the table title.

Tables 2 and 3 are like Table 1 but are for cases with 10 and 30% glycerol solutions as the elution liquid. In the following sections, the release of urea is discussed according to the elution liquid.

3.2. In water

Fig. 1 shows experimental fractional cumulative release vs time. This is the conventional plot that is often used to present experimental results. In this paper, however, the experimental data are analyzed and presented in dimensionless forms. Once the dimensionless parameters like those shown in Table 1 are determined, the release data are describable by the dimensionless equations given in part 1.

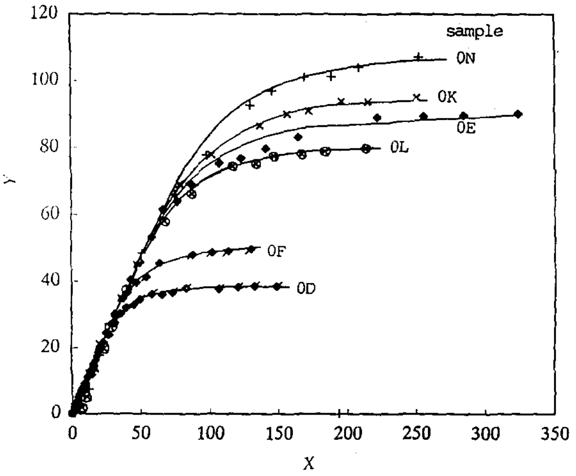

Fig. 2. Dimensionless cumulative release vs dimensionless time, in water.

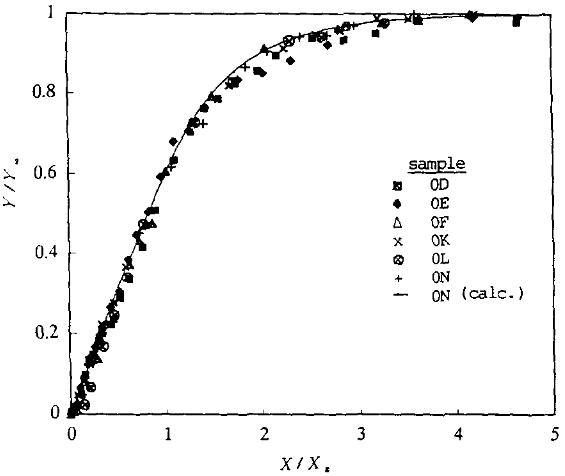

Fig. 3. Fractional cumulative release vs X/X_s, in water.

Fig. 2 shows dimensionless cumulative release vs dimensionless time. Symbols represent the experimental data and solid curves the results of calculation. This figure is after Fig. 1a of part 1. Table 1 shows that each particle sample is different from the others. The last four samples, how-

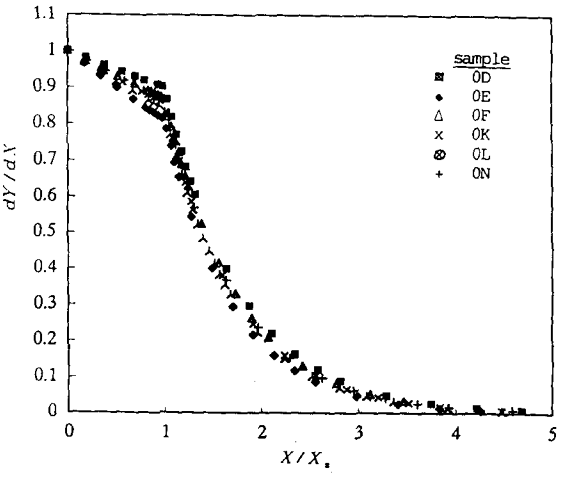

Fig. 4. Dimensionless release rate vs X/X_s, in water.

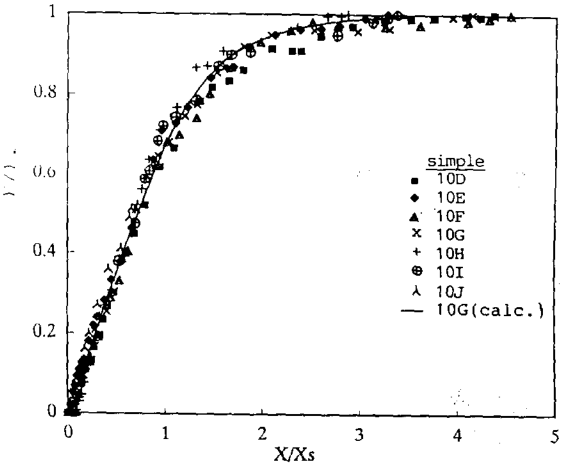

Fig. 5. Fractional cumulative release vs X/X_s, in 10% aqueous glycerol solution.

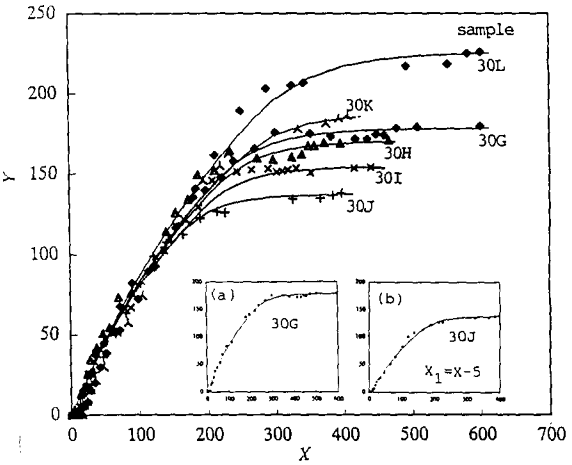

Fig. 7. Dimensionless cumulative release vs dimensionless time, in 30% aqueous glycerol solution.

ever, have K_b/K_a and s closer to each other in magnitudes. The average K_b/K_a and the average s for the four samples are 8.9 and 8. Fig. 2 and Table 1 show that excepting sample 0E for which s is minimum, the curve moves upward as a/b decreases. Coating technique and surface condition of the pure drug bead are important for producing particles of similar release behaviors.

Fig. 3 shows Y/Y_∞ vs X/X_s. Symbols denote experimental data and the solid curve represents a calculated result. Only one calculated result is shown to avoid crowding the figure. Table 1 shows that $K_b/K_a \gg 1$, i.e., $K_a/K_b \ll 1$. Therefore, in Fig. 3, the curve traced out by the data points of a given release system represents the limiting curve which is independent of p, i.e., the system is dependent only on s and ρ_u/C_s.

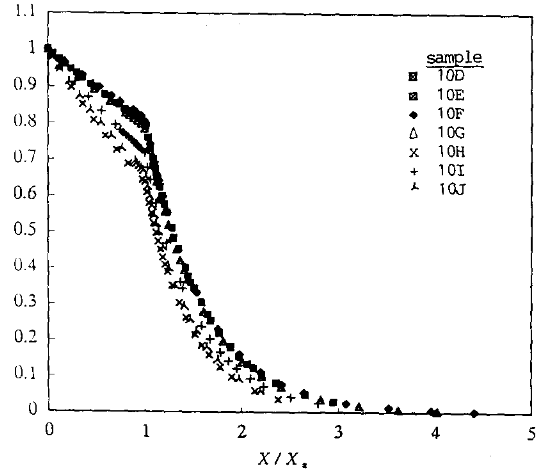

Fig. 6. Dimensionless release rate vs X/X_s, in 10% aqueous glycerol solution.

The rate curves are shown in Fig. 4. The rates are calculated as described in part 1. The calculated results are nevertheless represented by symbols so the rates of different samples can be recognized by different symbols. For the magnitudes of s shown in Table 1, the drop in rate at critical time is less than 20%.

3.3. Particle in aqueous glycerol solutions

For particles releasing urea in 10% glycerol solution, the results are shown in Table 2 and Fig. 5 and 6. Table 2 shows that the magnitudes of s for the first four samples are closer to each other. The average K_b/K_a and the average s for the four samples are 10.6 and 6.7, respectively. The ratio of the maximum s to the minimum s is about 2, the same as that in Table 1. However, the spread in data shown in Fig. 5 and 6 are greater than that shown in Fig. 3 and 4. This is because the s in Table 2 are in general smaller than the s in Table 1.

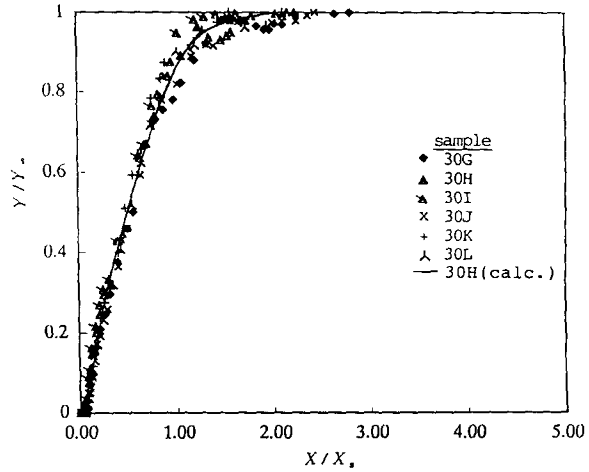

Fig. 8. Fractional cumulative release vs X/X_s, in 30% aqueous glycerol solution.

For particles releasing urea in 30% glycerol solution, the results are shown in Table 3 and Fig. 7–9. Table 3 shows that s are rather small and excepting sample 30J, the magnitudes of s are relatively close to each other. For these five samples, the average s is 2.79 and the average K_b/K_a is 25.7. Fig. 7 shows Y vs X. Insets (a) and (b) are for samples 30G and 30J. The solid curve in inset (b) is calculated using $X_1 = X - 5$ instead of $X_1 = X - 1/6$. This results in better fit between the calculation and the experiment especially in $t < t_s$. This implies that initial stage lasted longer than that accountable by equation $X_1 = X - 1/6$. This tendency has been noticed in data obtained with glycerol solutions of high concentration. The extended lag time may be due to time taken by the liquid to permeate the coating layer.

Fig. 7 when compared with Fig. 2 shows that experimental data are either less smoothly behaved or less satisfactorily fitted by equations, especially at the bending of the curves. With 50% glycerol solution as the elution liquid, fitting of experimental data to equations becomes difficult. This may due to viscosity, increased glycerol concentration, and fixed rpm used in the experiments. Fig. 8 shows the plot of Y/Y_∞ vs X/X_s. The solid curve represents a calculated result. Fig. 9 shows rate curves. At critical time, the dimensionless rate dropped to around 0.4.

3.4. Comparisons of the results

Comparison of Tables 1–3 shows that as the concentration of glycerol solution is increased from 0 to 30%, ρ_u/C_s increased from 2.11 to

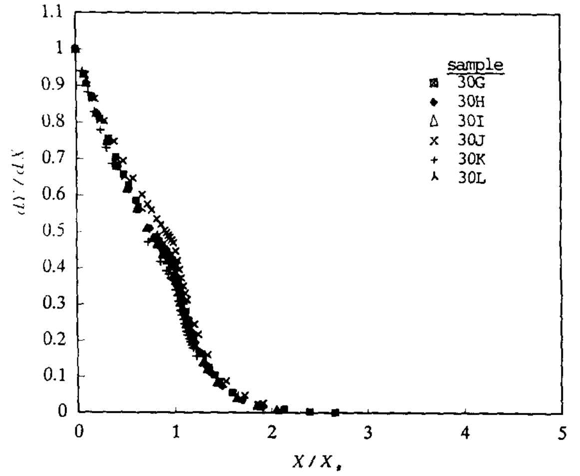

Fig. 9. Dimensionless release rate vs X/X_s, in 30% aqueous glycerol solution.

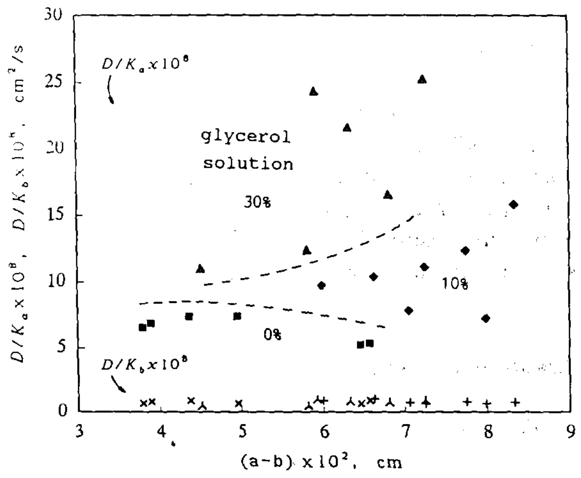

Fig. 10. D/K_a and D/K_b vs coating thickness.

2.68, the averaged K_b/K_a increased from 8.9 to 25.7, the order of magnitude of D/K_a increased from 10^{-8} to 10^{-7}, and the averaged s decreased from about 8 to 2.79. In the present experiments, V_r are around 55. The main factor that affected the magnitude of s is K_b/K_a.

Comparison of Fig. 3, 5, and 8 shows that the curve shifts toward the left-hand side when glycerol concentration is increased. This is due to the increase in ρ_u/C_s and also to the decrease in s. The increase in ρ_u/C_s is not large, but the decrease in s is substantial. Comparison of Fig. 4, 6, and 9 shows that decrease in dY/dX at critical time increased from about 20% to about 60%.

D/K_a and D/K_b of all samples are plotted against coating thickness in Fig. 10. D/K_b are calculated from the columns D/K_a and K_b/K_a in the tables. In Fig. 10, the filled symbols refer to D/K_a and other symbols to D/K_b. The dashed curves separate D/K_a data into three regions according to the concentration of glycerol solutions. For all samples, D/K_b are smaller than D/K_a, and in contrast to D/K_a, D/K_b is relatively constant with respect to coating thickness. The maximum, average, and minimum of D/K_b of all samples are 1.042×10^{-8}, 0.7621×10^{-8}, and 0.4781×10^{-8} cm^2/s, while for D/K_a, they are 25.31×10^{-8}, 15.85×10^{-8}, and 5.252×10^{-8} cm^2/s.

4. Conclusions

Experimental release data of urea from a coated urea bead in water and in aqueous glycerol solutions show that for elution liquids up to around 30% of glycerol solution, the data may be correlated according to the dimensionless equations presented in part 1. Systematic correlation and comparison of data of different systems and sources are therefore made easy.

Acknowledgement

The support of project NSC81-0402-E002-19 by National Science Council is acknowledged.

Nomenclature

a	radius of particle, cm
b	radius of drug bead, cm
C	concentration of urea in coating layer; C_a, C at $r = a$; C_b, C at $r = b$; g/cm^3
C_c	concentration of urea in core; $C_{c,end}$, C_c at the end of a release experiment; $C_{c,\infty}$, theoretical C_c at the end of a drug release for which no liquid samples are taken for assaying the drug, g/cm^3
C_e	concentration of urea in elution liquid; $C_{e,end}$, C_e at the end of a release experiment; $C_{e,\infty}$, theoretical C_e at the end of a drug release for which no liquid samples are taken for assaying the drug, g/cm^3
C_s	saturation concentration of drug in elution liquid, g/cm^3
D	effective diffusivity of coating layer, cm^2/s
F	$\equiv (K_b V_c / K_a V_e)(M_t/(V_c C_s))$, –
K_a,K_b	$K_a \equiv C_e/C_a$, $K_b \equiv C_c/C_b$, –
M_t	cumulative release per particle at t; M_{t_s}, at t_s; $M_{t\infty}$, at t_∞, g
N_1	$\equiv (4\pi Dab)/(K_a V_e(a-b))$, –
p	$\equiv 3(K_a/K_b)(a/b)(a/b-1)$, –
s	$\equiv (K_a/K_b)(V_r)(a/b)^3$, –
t	time; t_∞, infinite time; t_s, time at which solid urea in the core is just exhausted; s
V	volume, cm^3; V_e, volume of elution liquid; V_r, volume ratio of elution liquid to coated particle, –
W_u	weight of urea after coating, g
W_1	initial weight of urea bead, g
W_2	weight of coated urea bead, g
X	dimensionless time, $\equiv Dt/(K_a(a-b)^2)$; X_s, at $t = t_s$, –
Y	dimensionless cumulative release, $\equiv (M_t)/(4\pi ab(a-b)C_s(K_a/K_b))$; Y_∞, Y at t_∞, –
ρ	density: ρ_u, of drug; ρ_{film}, of coating; g/cm^3

Reference

Lu, S.M. and Lee, S.F., Slow release of urea through latex film. *J. Controlled Release*, 18 (1992) 171–180.