Modeling and Simulation of Drug Release from Granule Coated with an Aqueous-Based System of Acrylic Copolymer[1)]

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In a previous paper, [Watano *et al.*, *Chem. Pharm. Bull.*, 42, 2338 (1994)], we proposed a simple model which could be used to analyze data of controlled release of a water-soluble drug from spherical particles coated with an aqueous-based system of acrylic copolymer by a tumbling fluidized bed process. The model predicted that the fractional release of drug was related to exponential of release time, and drug release data of several samples prepared with various levels of operational moisture content were studied to determine the effect of this content on film thickness and drug permeability.

In this study, to confirm the method's validity, we simulated the drug release rate at various moisture content and coating levels using the proposed model. The simulated results were compared with the experimental data to evaluate the accuracy of the model. The mechanism of aqueous coating was also described using the simulated results.

Key words drug release; Fick's diffusion law; aqueous polymeric coating; moisture content; coating level; tumbling fluidized bed

Modeling of the controlled release of a drug from polymeric devices has been the subject of considerable research and many authors have worked to find a drug release pattern with many different mathematical models.

The first systematic investigation of drug release was conducted by Higuchi,[2)] who showed that release rate of a drug under a perfect sink condition was inversely proportional to the square root of time. Thereafter, Flynn *et al.*[3)] and Christensen *et al.*[4)] used a pseudo-steady state assumption to obtain a solution; Lu and Lee[5)] also used this assumption to analyze drug release data. Tojo *et al.*[6)] simulated the transient and steady-state release characteristics of a membrane-moderated controlled release of an active agent from a core matrix, while Crank[7)] described various diffusion problems. Fan and Singh[8)] presented solutions to different problems of controlled release. However, there is no mathematical model which takes into consideration operational conditions on the kinetics of drug release. It is very important for researchers who engage in the design or preparation of particles with desirable drug release properties to theoretically investigate the effect of operating conditions on the kinetics of drug release.

In a previous study,[1)] we derived a drug release model based on Fick's diffusion law, which predicted that the fractional release of drug from polymeric devices was related to exponential of release time. We used the model to investigate the contribution of operational moisture content to the film forming process of aqueous polymeric coating by tumbling fluidized bed.

In this study, to confirm the model's validity, we here simulated drug release rate at various operational moisture content and coating levels. Accuracy of the proposed model was then evaluated by comparing the simulated results with experimental data. It was found that the drug release rate could be predicted with high accuracy under perfect sink conditions, and drug release behavior was controllable by varying operational moisture content and coating level. The mechanism of drug release from polymeric devices prepared by tumbling fluidized bed was also discussed here.

Experimental

Materials As core particles, spherical granules made of crystalline cellulose (Celphere CP507, Asahi Chemical Industry Co., Ltd.) with a mass median diameter of 600 μm, were used. Aqueous dispersion of an acrylic copolymer (Eudragit RS-30D, Rohm Pharma) which had a low content of quaternary ammonium (cationic) group and was independent of pH was adopted as the coating material. Spraying liquid contained 30% of acrylic copolymer, 1.5% of triethylcitrate as a plasticizer and 7.5% of talc as a dispersant.

Preparation of Particles A tumbling fluidized bed[9–11)] (NQ-Labo, Fuji Paudal Co., Ltd.) was used for the coating operation. Moisture content during this operation was continuously measured by an IR moisture sensor[9–11)] (Wet-Eye, Fuji Paudal Co., Ltd.). The details of the equipment and the principle of moisture measurement were described earlier.[1,9–11)]

Table 1 gives the operating conditions applied in this study. The coating experiment was conducted as previously reported.[1)] Core particles of 300 g were first undercoated with a water solution of pigment (Blue No.1, Toushoku Pigment Co., Ltd.) selected as a model drug. After drying the particles in the coater, dispersion of the Eudragit RS30D was sprayed while moisture content was controlled. The coated particles were then dried in the coater until the moisture content was less than 1.0%. These operations were conducted automatically using the IR moisture control system developed previously.[9–11)]

Evaluation of the Coated Particles Dissolution tests of the coated particles were performed in 900 ml purified water using the paddle method (Dissolution tests, JP XII, 100 rpm and 37 °C). The release of drug (Blue No. 1 pigment) was continuously analyzed by spectrophotometry at 630 nm.

Mathematical Models The mass transfer equation based on Fick's law for reservoir type devices is

$$\frac{\partial C}{\partial t}=\frac{D}{r^2}\cdot\frac{\partial}{\partial r}\left(r^2\cdot\frac{\partial C}{\partial r}\right) \quad (1)$$

where C, D, r and t indicate drug concentration in the film layer, drug

Table 1. Operating Conditions

Inlet air velocity	1.0 m/s
Inlet air temperature	308 K
Spray air pressure	1.5×10^5 Pa
Spray nozzle insert	1.0 mm (i.d.)
Nozzle location	Side
Agitator rotational speed	5.0 rps

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diffusion coefficient, radius of the particle and release time, respectively.

With a steady state assumption,

$$\frac{d}{dr}\left(r^2 \cdot \frac{dC}{dr}\right)=0 \tag{2}$$

Eq. 1 can easily be solved to give a following equation.

$$\frac{dM_t}{dt}=4\pi D \cdot \frac{r_1 r_2}{r_2-r_1}(K_1C_1-K_2C_2) \tag{3}$$

where M_t, r_1, r_2, C_1 and C_2 show amount of drug release to extraction phase, core diameter, coated particle diameter, drug concentration in the core and that in the extraction medium, respectively. Also, K_1 and K_2 indicate partition coefficients between core and film, and film and extraction medium concentration.

By solving Eq. 3, the percent drug release M_t/M_∞can be denoted as

$$\frac{M_t}{M_\infty}=1-\exp(-Bt) \tag{4}$$

where

$$B=\frac{3DK_1}{\delta}\cdot\frac{r_1+\delta}{r_1^2}=3\left(\frac{D_a}{\delta}\right)\cdot\left(\frac{r_1+\delta}{r_1^2}\right) \tag{5}$$

In Eq. 5 we defined D_a as an apparent diffusion coefficient ($=DK_1$) for the following two reasons: i) partition coefficient K_1 could not be obtained by experiment, and ii) we wished to separate film thickness from partition coefficient[1] ($K_p=DK_1/\delta$), because film thickness δ varied with moisture content and coating level.

In this study, we assumed that the drug diffusion and partition coefficient were constant, regardless of release time.

Results and Discussion

Drug Diffusion Coefficient Our investigation up to this time had eliminated the notion that the quality of film and coating efficiency in polymeric coating by tumbling fluidized bed were seriously affected by operational moisture content. To understand the film forming mechanism and to predict drug release behavior, drug release simulation is required. However, no quantitative investigation have yet been made to determine the effect of moisture content on film quality and coating efficiency; this had to be done before simulation of the drug release.

Figure 1 shows the plots of apparent diffusion coefficient D_a against moisture content when the coating level was 2.5%. The diffusion coefficient D_a decreased linearly with an increase in moisture content within the region $6\% \leqq W \leqq 14\%$. As Lehmann reported,[12] if water transfer rate was too rapid, polymer particles did not form a continuous film and the polymer film peeled or was rubbed off. By contrast, sufficient operational moisture content during aqueous coating (*i.e.*, adequate drying speed) was found to enhance the membrane properties; if the coating was conducted at high moisture content, the polymer particles sprayed on the surface of the core were able to move freely, which resulted in the formation of continuous and well-packed film. In addition, when the polymer particles were deformed by surface tension and capillary forces during the film forming process, the deformation rate of the particles exceeded the dehydration speed when the moisture content was high. In this case, since there were sufficient quantities of water and thermal energy during the deformation, the packing condition of polymer particles was improved.

As shown in Fig.1, apparent diffusion coefficient, D_a was found to be expressed linearly as a function of moisture content. An empirical equation based on least squares method was as follows:

$$D_a=-8.80\times10^{-5}W+1.38\times10^{-3} \tag{6}$$

Coating Efficiency Drug release rate is determined by film thickness and drug diffusion coefficient, which was determined linearly as a function of moisture content (Fig. 1). As previously reported,[1,9] film thickness was seriously affected by operational moisture content; the effect of spray drying, in which the sprayed polymer particles were dry before adhering to the core particle, could not be disregarded. Therefore, to simulate drug release rate, quantitative evaluation of the spray drying effect is necessary. We thus calculated the coating efficiency to evaluate the drying efficiency.

Figure 2 shows coating efficiency plots against operational moisture content. Here, coating efficiency was calculated by the following equation:

$$E=\frac{\text{weight of polymer film}}{\text{polymer feed weight}} \tag{7}$$

where weight of polymer film was calculated by film thickness obtained by scanning electron microscopy (SEM) observation and polymer density ($=1230\,kg/m^3$).

Coating efficiency increased linearly with an increase in moisture content (Fig. 2), indicating spray drying was prevented by the increased moisture content. This was because the drying efficiency decreased due to the high feed rate of spray liquid when the moisture content was high. In this case, polymer particles sprayed were difficult

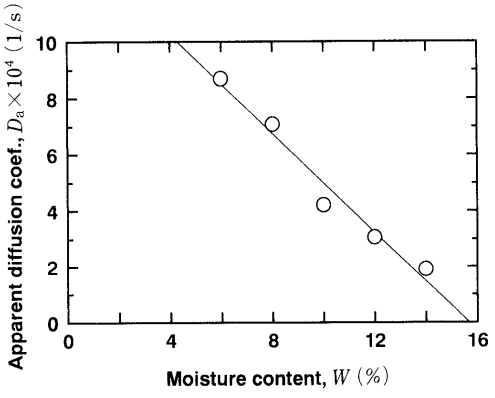

Fig. 1. Plots of Apparent Drug Diffusion Coefficient against Moisture Content

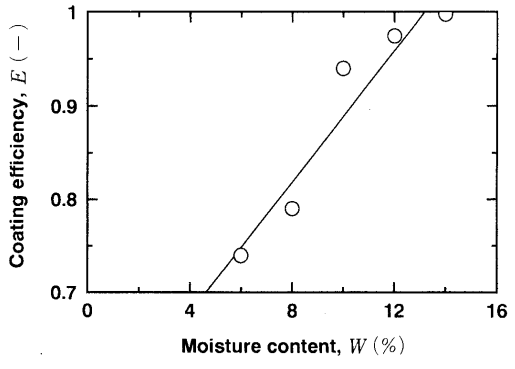

Fig. 2. Plots of Coating Efficiency against Moisture Content

to dry before adhering to the core; thus, the proportion of the spray drying decreased, and the coating efficiency increased.

Thus coating efficiency was expressed by operational moisture content as

$$E=3.505\times10^{-2}W+0.538 \quad (8)$$

Simulation of Drug Release Rate Simulation of drug release rate at various operational moisture content and coating levels was conducted using the following procedure. First, operational moisture content and coating level were determined. Apparent drug diffusion coefficient, D_a was calculated by substituting moisture content W into Eq. 6. Coating efficiency, E was obtained from the operational moisture content using Eq. 8.

Secondly, film thickness was calculated theoretically using the polymer balance equation. Before starting the coating experiment, only core particles were present in the fluidized bed. At this time,

$$\frac{4}{3}\pi r_1^3\rho_c\cdot N=m \quad (9)$$

where ρ_c, N and m indicate density of core granules ($=1490\,kg/m^3$), number of core particles and core particle feed weight. After the coating operation was over, polymer balance equation was

$$N\cdot\frac{4\pi}{3}(r_2^3-r_1^3)\cdot\rho_p=m\cdot R\cdot E \quad (10)$$

where ρ_p and R show density of polymer ($=1230\,kg/m^3$) and coating level, respectively. Here, density of core particle and polymer were used based on the manufacturer's information. With this success (Eq. 10), radius of a coated particle (r_2) could be estimated, and the film thickness δ ($=r_2-r_1$) as a function of moisture content and coating level was obtained theoretically.

Substituting of apparent drug diffusion coefficient and film thickness into Eq. 5 obtained parameter B. Then, the percent drug release M_t/M_∞ could be calculated theoretically using Eq. 4.

Figure 3 illustrates the percent drug release plots as a function of coating level at $W=8\%$. Plots indicate experimental results and solid lines show the results of simulation. As shown, adequate correlation was obtained between the results of simulation and those of experiments. Also, drug release was suppressed with the increase in coating level. These results implied that the drug release at various moisture content and coating levels were very well represented by the proposed model. The experimental plots of $R=1.0$ and 2.5%, however, showed smaller value than the simulated results when M_t/M_∞ was over 0.6 or 0.7. This phenomenon was due to the driving force of drug release decreasing under imperfect sink conditions,[8] since we used a steady state assumption and perfect sink condition as prior conditions. This model thus can be applied to drug release data under perfect sink conditions of $M_t/M_\infty<0.6$ or 0.7.

Figure 4 also demonstrates percent drug release plots as a function of coating level at $W=12\%$. At higher moisture content, adequate correlation was also obtained

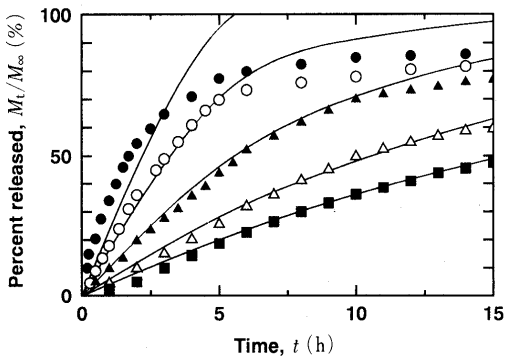

Fig. 3. Drug Release as a Function of Coating Level at $W=8\%$

●, coating level $R=1.0\%$; ○, $R=2.5\%$; ▲, $R=5.0\%$; △, $R=7.5\%$; ■ $R=10.0\%$. ——, simulated result.

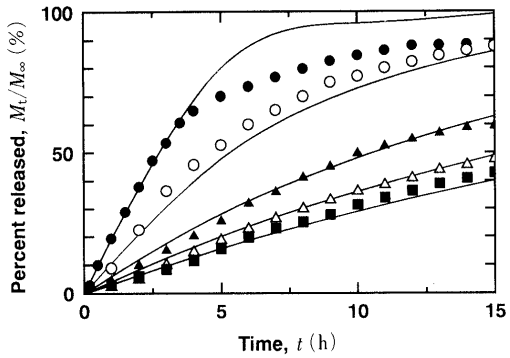

Fig. 4. Drug Release as a Function of Coating Level at $W=12\%$

●, coating level $R=1.0\%$; ○, $R=2.5\%$; ▲, $R=5.0\%$; △, $R=7.5\%$; ■, $R=10.0\%$. ——, simulated result.

between the results of simulation and those of experiments. Comparison of Fig. 4 with Fig. 3 shows the drug release data at $W=12\%$ to be more suppressed than that at $W=8\%$.

Drug release at various moisture content and coating levels was thus well simulated by the proposed model. Recognizing that the model is applicable to different coating levels and moisture content, the film forming process was speculated to be as follows: when the core particle is covered with polymer particles, the particles are deformed and a continuous thin monolayer is formed. Repetition of this process causes construction of a polymer film layer. It is therefore suggested that the moisture content uniformly affects each polymer layer during the film forming process, regardless of coating level. This also implies that the parameters of moisture content and coating level can be handled independently of each other.

Conclusions

Using the proposed model, which predicted that the fractional release of drug was related to exponential of release time, drug release at various moisture content and coating levels was well simulated. Adequate correlation was obtained between the results of simulation and those of experiments under perfect sink conditions of $M_t/M_\infty=0.6$ or 0.7. The results also indicated that the parameters of moisture content and coating level could be handled independently in the model, because moisture

content uniformly affected each polymer layer during the film forming process.

References

1) Watano S., Takaya H., Wada I., Miyanami K., *Chem. Pharm. Bull.*, **42**, 2338 (1994).
2) Higuchi T., *J. Pharm. Sci.*, **50**, 874 (1961).
3) Flynn G. L., Yolkowsky S. H., Roseman T. J., *J. Pharm. Sci.*, **63**, 495 (1974).
4) Christensen F. N., Hansen F. Y., Bechgaard H., *J. Pharm. Pharmacol.*, **32**, 580 (1980).
5) Lu S. M., Lee S. F., *J. Controlled Release*, **18**, 171 (1992).
6) Tojo K., Miyanami K., Fan L. T., *Powder Technol.*, **35**, 89 (1983).
7) Crank J., "The Mathematics of Diffusion," ed. by Oxford University Press, London, 1975.
8) Fan L. T., Singh S. K., "Controlled Release," ed. by Springer Verlag, London, 1989.
9) Watano S., Yoshikawa K., Miyanami K., *Chem. Pharm. Bull.*, **42**, 663 (1994).
10) Watano S., Harada T., Terashita K., Miyanami K., *Chem. Pharm. Bull.*, **41**, 580 (1993).
11) Watano S., Fukushima T., Miyanami K., *Powder Technol.*, **81**, 161 (1994).
12) Lehmann K., Dreher D., *Drugs Made in Germany*, **16**, 126 (1973).