Chem. Pharm. Bull. **42**(11) 2338—2341 (1994) Vol. 42, No. 11

Modeling Drug Release from Granules Coated with an Aqueous-Based System of Acrylate Methacrylate: Effect of Moisture Content on the Kinetics of Drug Release

Satoru WATANO,* Hiroko TAKAYA, Ikuko WADA, and Kei MIYANAMI

Department of Chemical Engineering, University of Osaka Prefecture, 1–1 Gakuen-cho, Sakai, Osaka 593, Japan.

Received June 10, 1994; accepted July 22, 1994

A simple model, which can be used to analyze data of the controlled release of a water-soluble drug from spherical particles coated with an aqueous-based system of acrylate methacrylate by a tumbling fluidized bed process, is presented. This model predicts that the fractional release of a drug is related to the exponential of release time. Drug release data of several samples prepared by various levels of operational moisture content were studied by the analytical equations, and the effect of operational moisture content on film thickness and permeability of a drug were investigated. It was found that the experimental results were very well represented by the analytical equations, and the mechanism of an aqueous coating was elucidated.

Keywords mathematical model; kinetics; drug release; aqueous polymeric coating; moisture content; tumbling fluidized bed

Conventional film coating processes for oral drugs have generally been conducted with an organic solvent-based system because of its favorable drying efficiency. In recent years, since environmental pollution and public health problems have become serious, a remarkable shift has been made from this conventional system to an aqueous-based system because of the latter's environmental and economic advantages. Aqueous film coating technology has advanced to a level of practical use; however, problems such as low operational efficiency due to the high heat required for vaporization and particle adhesion have not been sufficiently settled. In the previous study,[1] we reported a practical method for controlling drug release and reducing the agglomeration tendency by means of moisture control in an aqueous-based system. However, the effect of moisture content, which was regarded as the most important factor in the aqueous system, on the properties of film quality and the mechanism of the film forming process, have not been studied theoretically. To elucidate these mechanisms, mathematical models are needed.

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 using many different mathematical models. Higuchi[2] showed that the release rate of a drug under a perfect sink condition was inversely proportional to the square root of time. Flynn *et al.*[3] and Christensen *et al.*[4] used a pseudo-steady state assumption and obtained a solution. Lu and Lee[5] also used a pseudo-steady state assumption to analyze the 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. 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 standard operational manufacturing 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.

The purpose of this contribution is to analyze the data of the controlled release of a water-soluble drug from a spherical particle, coated with an aqueous-based system of acrylate methacrylate by a tumbling fluidized bed process, using a simple model derived from analysis. The drug release from coated particles prepared by various levels of operating moisture content were studied by this analytical equation, and the effect of operational moisture content on the drug release properties was investigated analytically. The results obtained in this work will be of practical significance for designing and producing desirable controlled-release products in an aqueous-based system.

Experimental

Materials As core particles, spherical granules made of crystalline cellulose (Selphere CP507, Asahi Chemical Industry Co., Ltd.) with a mean particle diameter of 600 μm and a true density of 1070 kg/m^3, were

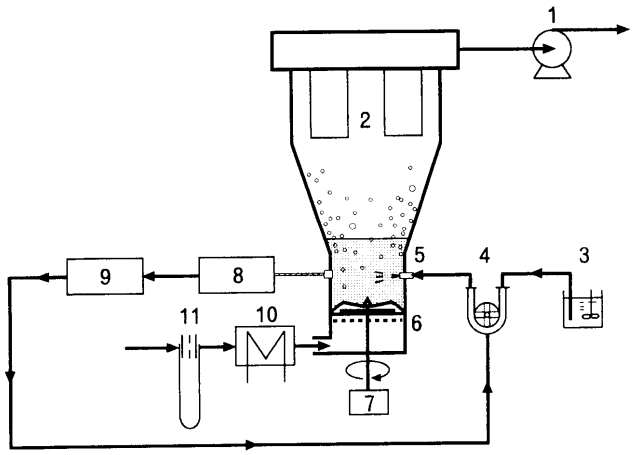

Fig. 1. Experimental Set-up

1, blower; 2, bag filter; 3, spray liquid; 4, tubing pump; 5, spray nozzle; 6, agitator blade; 7, motor; 8, IR moisture sensor; 9, PID controller; 10, heater; 11, orifice flow meter.

used. The aqueous dispersion of an acrylate methacrylate copolymer (Eudragit RS-30D, Rohm Pharma), which had a low quaternary ammonium (cationic) group content and was independent of pH, was adopted as the coating materials. The spraying liquid in this study contained 30 wt% of acrylic polymer, 1.5 wt% of triethylcitrate as a plasticizer, and 7.5 wt% of talc as a dispersant.

Preparation of Particles Figure 1 shows the experimental set-up used. A tumbling fluidized bed[1,9] (NQ-Labo, Fuji Paudal Co., Ltd.) was used for the coating operation. Moisture content during the operation was continuously measured by an IR moisture sensor[1,9] (Wet-eye, Fuji Paudal Co., Ltd.). Due to the measuring principle of the IR sensor, this sensor can detect particle surface moisture content. By using the correlation between the absorbance of IR ray and the moisture content measured by the drying method, a mass basis moisture content was calculated.

The operational variables listed in Table I were measured continuously, and the main operational variables, such as agitator rotational speed, air flow rate and inlet air temperature, were feedback controlled to maintain stable operation. Details of the equipment and the principle of the measurement of the IR moisture sensor have been described in previous reports.[1,9]

The coating experiment was conducted as follows. 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. Once the particles in the coater were dry, dispersion of the Eudragit RS30D was sprayed while moisture content was controlled. After having sprayed the dispersion, the coated particles were dried in the coater until the moisture content was reduced to less than 1.0%. These operations were conducted automatically using the IR moisture control system developed previously.[1,9]

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

Film thickness was measured by scanning electron microscope (SEM) photographs of a cross section of the coated particles. The SEM photographs showed a coat of even thickness which was around 6 μm for polymer coating ratio of 5%.

Mathematical Models Figure 2 illustrates the schematic diagram of drug release from a coated particle. The diameter of the core particle and the coated particle are represented by r_1 and r_2, respectively. The initial drug concentration in the core particles is C_0, which is less than the saturation concentration, C_{sat}. The coating film was initially free of drug ($t=0$, $C=0$), and the coated particle was immersed in a well stirred extraction medium of volume V_2. In this study, since the model drug (pigment blue No. 1) was water soluble and the core particle (crystalline cellulose) had strong water absorbing power, the drug was assumed to be dispersed uniformly in the core particle.

TABLE I. 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.)
Agitator rotational speed	5.0 rps

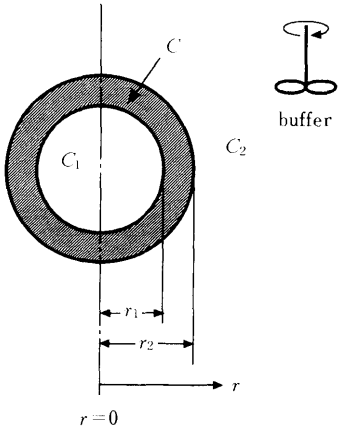

Fig. 2. Schematic Diagram of Drug Release from Coated Particle

The mass transfer equation based on Fick's law for the coated particle is

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

This result is subject to two conditions

$$\begin{aligned} t>0,\quad & r=r_1,\ C=C_{m1} \\ & r=r_2,\ C=C_{m2} \end{aligned} \tag{2}$$

where, C_{m1} and C_{m2} expressed the interfacial concentration between core and film, and film and extraction medium, respectively.

With a steady state assumption, $\frac{d}{dr}\left(r^2\cdot\frac{dC}{dr}\right)=0$, Eq. 1 can be easily solved to give

$$C=\frac{r_1C_{m1}-r_2C_{m2}}{r_1-r_2}-\frac{1}{r}\cdot\frac{r_1r_2}{r_1-r_2}(C_{m1}-C_{m2}) \tag{3}$$

By using Fick's law, which defined mass flux J as $J_{r=r2}=-D\,(dC/dr)$, the dissolution mass rate is expressed as

$$\begin{aligned} \frac{dM_t}{dt}&=J_{r=r2}\cdot(4\pi r_2^2) \\ &=4\pi D\cdot\frac{r_1r_2}{r_2-r_1}(K_1C_1-K_2C_2) \end{aligned} \tag{4}$$

In Eq. 4, we used the following equations

$$\begin{aligned} C_{m1}&=K_1C_1 \\ C_{m2}&=K_2C_2 \end{aligned} \tag{5}$$

where K_1 and K_2 are partition coefficients, which show the equilibrium between core and film, or film and extraction medium concentration. In this study, K_1 and K_2 are assumed to be constant regardless of drug concentration.

Since the amount of drug existing in the film is negligible compared to that in the extraction medium, the drug concentration of particle C_1 and of extraction phase C_2 are expressed as

$$C_1=(M_1-M_t)/V_1,\quad C_2=(M_2+M_t)/V_2 \tag{6}$$

In Eq. 6, M_1, M_2 and M_t show the amount of drug existed in the initial core particle, initial extraction phase, and the extraction phase at time t. Also, V_1 and V_2 express volume of the particle and the extraction medium.

By substituting Eq. 6 into Eq. 4 and rearranging it based on the assumption that the volume of the extraction medium is significantly larger than that of the particle ($V_2 \gg V_1$), the following equation is obtained. Here, the initial condition that $M_t=0$ at $t=0$ is used.

$$\frac{M_t}{M_1}=1-\exp\left(\frac{4\pi DK_1}{V_1}\cdot\frac{r_1r_2}{r_1-r_2}t\right) \tag{7}$$

In this equation, M_1 is considered to be equal to M_∞ if we assume that the amount of drug in the core particle is released perfectly into the extraction phase. Therefore, Eq. 7 can be denoted as

$$\frac{M_t}{M_\infty}=1-\exp(-Bt) \tag{8}$$

where

$$B=\frac{4\pi DK_1}{V_1}\cdot\frac{r_1r_2}{\delta} \tag{9}$$

By introducing the permeability K_p ($=K_1D/\delta$), B is easily rewritten as

$$B=\frac{3K_p}{r_1^2}\cdot(r_1+\delta) \tag{10}$$

where δ ($=r_2-r_1$) is a film thickness.

In this study, drug release properties were analyzed using Eq. 8.

Results and Discussion

Application of the Mathematical Model to Drug Release Properties Figure 3 shows the drug release profiles obtained by various levels of operational moisture content. Here, the value of 100% release was determined by spectrophotometrically measuring the total amount of drug in coated particles. From Fig. 3, the drug release was increasingly suppressed with an increase in moisture content. Taking into account the fact that the amount of polymer sprayed was theoretically the same in each experiment, properties of the film or the coating efficiency would thus largely be influenced by operational moisture content.

Unlike a free film made by a casting method, a diffusion coefficient of the film layered onto the coated particles cannot be easily measured because it is impossible to tear off the film from the core. In addition, it is impossible to use the free film prepared by a polymer solution comprising the same component as the coating spray liquid, because the tumbling and compacting motion cannot be experienced with the free film. Therefore, general techniques in which a diffusion coefficient is measured by a diffusion cell, the optical method or the laser Doppler light scattering method cannot be applied. In order to analyze the mechanism or the process of the aqueous coating, the proposed model was adopted to the drug release data obtained.

Figure 4 shows plots of $-\ln(1-M_t/M_\infty)$ as a function of dissolution time t.

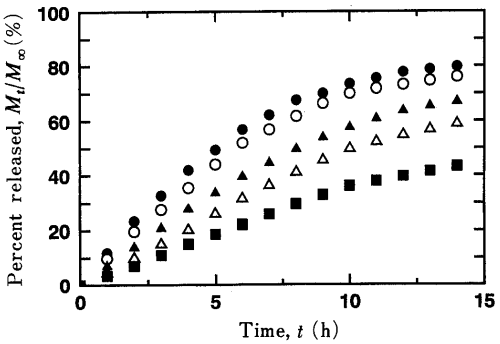

Fig. 3. Drug Release Profiles Obtained by Various Levels of Operational Moisture Content

●, moisture content $W=6\%$; ○, $W=8\%$; ▲, $W=10\%$; △, $W=12\%$; ■, $W=14\%$.

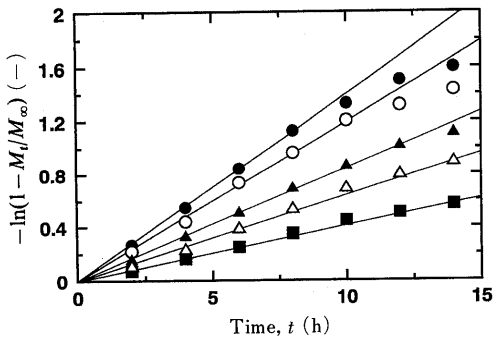

Fig. 4. Plots of $-\ln(1-M_t/M_\infty)$ as a Function of Dissolution Time t

●, moisture content $W=6\%$; ○, $W=8\%$; ▲, $W=10\%$; △, $W=12\%$; ■, $W=14\%$.

In this figure, the symbols represent the experimental data and the solid lines express the approximation of the data. The experimental results can be approximately expressed by a linear equation, and the slope of lines, which is equivalent to the value of B, decreases with the increase in moisture content. However, the plots of high percent released data ($W=6\%$ and $W=8\%$ after $t=10$ h) had smaller values than the simulated results; this was because the driving force of drug release decreased under an imperfect sink condition.[8] From Fig. 4, this model can be applied to drug release data under a perfect sink condition of $M_t/M_\infty<0.6$ or 0.7.

Figure 5 illustrates the relation between B and moisture content W. The plot of parameter B has a linear correlation with the moisture content. It is obvious from Fig. 5 that the kinetics of drug release can be analyzed by using the proposed model.

Effects of Operational Moisture Content on Drug Release It is important to investigate the permeability of a drug through a membrane when we design controlled release particles. From Eq. 10, parameter B is expressed as a function of film thickness, radius of the core and drug permeability. Since the core particles were already sieved to a median particle size of 600 μm, r_1 in Eq. 10 is a known number. If the film thickness is investigated, permeability can be calculated.

Figure 6 shows the plots of film thickness δ as a function of operational moisture content W. Here, the film thickness was measured by SEM photographs of cross sections of coated particles. From Fig. 6, the film thickness increased linearly with an increase in moisture content. Since the amount of polymer sprayed was theoretically constant,

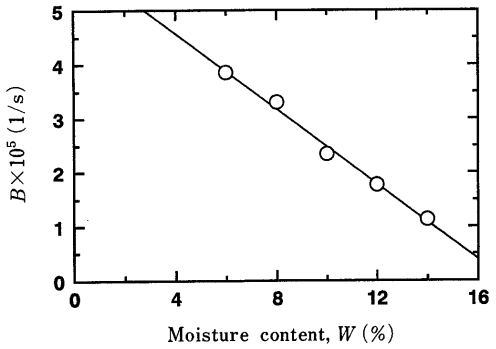

Fig. 5. Relation between B and Moisture Content W

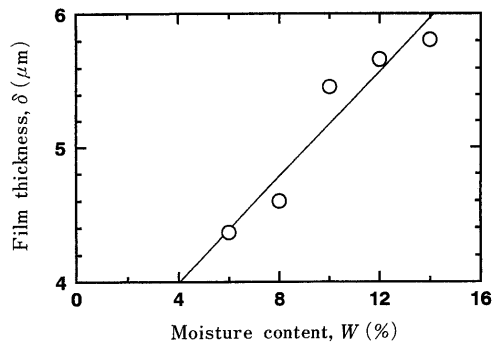

Fig. 6. Plots of Film Thickness δ as a Function of Operational Moisture Content W

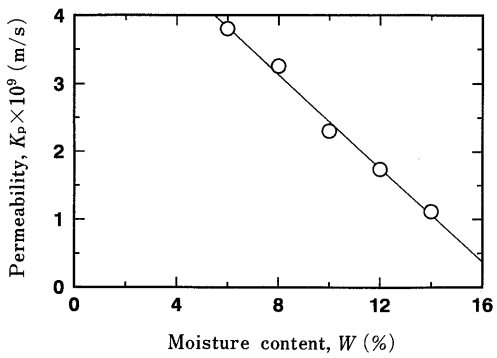

Fig. 7. Plots of Permeability K_p as a Function of Operational Moisture Content W

coating efficiency must be affected by the amount of polymer practically adhered on the core; when the moisture content was high, drying efficiency decreased due to the high feed rate of spray liquid. In this case, it was difficult to dry the sprayed polymer particles before they adhered to the core; thus, the proportion of the spray drying decreased, and the film thickness increased. By contrast, when the moisture content was low, sprayed polymer particles were easy to dry before being captured by the core due to their high drying efficiency.

Figure 7 shows the plots of K_p as a function of operational moisture content W. The permeability K_p decreased linearly with an increase in moisture content. The decrease in permeability meant the suppression of drug release through the membrane. Operational moisture content, *i.e.* surface moisture content during aqueous coating, was found to facilitate membrane properties; if the coating was conducted with high moisture content, the polymer particles sprayed on the surface of the core were able to move freely, which resulted in the formation of a continuous and well packed film. In addition, when the polymer particles were deformed by surface tension and capillary forces during the film forming process,[10] the deformation rate of the polymer particles exceeded the dehydration speed when the moisture content was high. In this case, since there was a sufficient quantity of water and thermal energy during the deformation, the packing condition of the polymer particles was improved.

However, when the operational moisture content was low, dehydration speed exceeded the deformation rate of the polymer particles, leading to an imperfect film.

As a result, drug release from spherical particles coated with an aqueous-based system of acrylate methacrylate was elucidated by using the proposed model. It was also found that the drug release rate could be controlled by operational moisture content.

Conclusions

Drug release from spherical particles coated with an aqueous-based system of acrylate methacrylate by a tumbling fluidized bed process was studied analytically and experimentally. By using a simple model, which predicted that the fractional release of drug was related to an exponential of time, drug release from the coated particles prepared with various levels of operational moisture content was well simulated. This mathematical model provides a way to analyze the kinetics of drug release from coated granules.

References

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