

Dissolution mechanism and rate of solid dispersion particles of nilvadipine with hydroxypropylmethylcellulose

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Abstract

The dissolution experiments on the solid dispersion particles of nilvadipine with hydroxypropylmethylcellulose were performed in stagnant and stirring water. The particles in stagnant water instantaneously gelatinized to the water content of 84.6% w/w after dipping and those dissolved very slowly through the penetration of water. However the particles in stirring water dissolved quickly at different rates depending on stirring rate, and both components in the solid dispersion dissolved at the same rate. Such experimental results seemed to suggest the important roles of erosion for gelatinized particles and mass transfer rate at the diffusion layer. The high concentrations of nilvadipine obtained after its nucleation and growth depend on complex formation. A new dissolution mechanism and rate equation were proposed on the basis of such experimental results and the availability of the rate equation was confirmed experimentally. © 1997 Elsevier Science B.V.

Keywords: Solid dispersion; Nilvadipine; Hydroxypropylmethylcellulose; Supersaturation; Complex formation; Dissolution mechanism; Dissolution rate

1. Introduction

For a drug such as nilvadipine (NiD), which is poorly soluble in water, it is possible to increase the dissolution rate and apparent solubility by the preparation of solid dispersion (SD) with hy-

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drophilic polymer, such as hydroxypropylmethylcellulose (HPMC). Usually, when SD particles are suspended in stirring water, such as the dispersed amount method, water penetrates quickly into SD particles and gelatinized SD is formed. The dissolution mechanism of gelatinized SD particles is very complicated because of mutual interaction among the drug, polymer, and water and also because of the stirring effect. Therefore, only a few papers on the stirring effect at the dissolution of SD and matrices have been presented.

Catellani et al. (1988), Harland et al. (1988), Peppas and Sahlin (1989), Ford et al. (1987) applied Eq. (1) to describe the dissolution rates of the drug from matrices when both diffusion and erosion contribute to dissolution.

$$W_t/W_\infty = k_1 t^n + k_2 t^p \quad (1)$$

where W_t/W_∞ = fraction of drug dissolved in time t , k_1 , k_2 are the kinetic constants, n , p are the diffusional and erosional exponents. But, these papers almost did not numerically clear the availability of Eq. (1) under the different conditions of stirring.

Nogami et al. (1966) studied the stirring effect on the dissolution rate constant defined in Noyes and Whitney (1897) equation, using the rotating disk method. Furthermore, Nogami et al. (1969) continued analytically the dissolution study with the drugs accompanying simultaneously phase change under different stirring rate. Takayama et al. (1980) studied the effect of rotational velocity on the dissolution parameters for SD using rotating disk method. But, these papers estimated the stirring effect as the influencing factor only for the thickness of diffusion layer, excepting erosion effect.

Although the majority of dissolution experiments of SD were performed using the rotating disk method, because of speed and accuracy of experiment, the dispersed amount method is very important for the estimation of the bioavailability of drugs. Nogami et al. (1969), Sekikawa et al. (1979) studied qualitatively the dissolution mechanism and rate of SD particles. Takayama et al. (1980), Sugimoto et al. (1982) estimated the dissolution parameters in the rate equations, in which the surface area of SD particles was not consid-

ered. Lu et al. (1993) simulated the dissolution rates of two lots of fine and coarse drugs using Noyes–Whitney equation, considering the size distribution and surface area of particles.

The purpose of this paper is to clear the gelatinizing and dissolution mechanisms and derive a new dissolution rate equation for SD particles composed of NiD and HPMC. The equation, including stirring effect, was confirmed to have a good availability through dissolution experiments.

2. Materials and methods

2.1. Materials

Nilvadipine (Fujisawa, Japan) and hydroxypropylmethylcellulose (Metholose[®], Shinetsu, Japan) were used and all other chemicals were of reagent grade.

2.2. Preparation of solid dispersion

In accordance with the method presented by Okuda and Aoi (1987), NiD of 1 g was dissolved in ethanol of 137.5 ml at 40°C and HPMC of 5 g was suspended in the solution for 5 min. After the evaporation of ethanol from the suspended mixture in vacuum at 40°C, the dried SD particles were screened using a 100- μ m sieve and the fine SD particles passed through the sieve were used for dissolution experiments.

2.3. Shape properties of HPMC and SD

The photographs of HPMC and SD were taken using JSM-840 scanning electron microscope (JEOL, Peabody, MA), and mean radius and axial length of each particle were determined through the measurements of both values for 20 particles on the photographs, assuming cylindrical shape. The mean values of radius and axial length of SD were calculated. The density of each particle was measured using a Beckman air comparison picnometer (Model 930, Beckman[®]). The weight of a SD was decided from the weight of a gelatinized SD described in the clause after the next.

2.4. Powder X-ray

Powder X-ray diffraction spectra of NiD, SD particles and physical mixture of NiD and HPMC which were mixed with mortar and pestle were measured using a Goniometer with nickel filtered Cu-K α radiation (Model 2171, Rigaku, Japan), operating at 4000 pulse/s as counting rate. The diffraction spectra was run at 2°/min in term of 2θ .

2.5. Measurement of radius, axial length, weight and water content of gelatinized SD

SD particles more than 30 were dipped into distilled water of 0.05 ml and spread over on a glass plate at 37°C. The shape change of SD particles was observed by photographs taken before and 5 min after dipping. The radii and axial lengths for 20 gelatinized SD were measured by the shape in photograph taken using an optical microscope attached camera (Nikon Optiphot), assuming cylindrical shape. The mean values of radius and axial length of gelatinized SD were calculated.

The measurement of weight of a gelatinized SD was carried out as follows. SD particles measured its weight accurately (about 1 g) were dipped into stagnant distilled water of 1 ml at 37°C for 5 min. The gelatinized SD thus obtained were put on a filter paper to remove adhering water. Furthermore, the gelatinized SD were inserted into a syringe of 1 ml attached 0.45- μ m cartridge filter (Millipore-HV) and slightly compressed to remove air included in gelatinized SD. After measuring the volume and the weight of the gelatinized SD in the syringe to decide the density, the water content in that SD was calculated from the weight difference between before and after drying of gelatinized SD removed from the syringe to a schale. The mean weight of a gelatinized SD particle can be calculated from the mean radius and axial length of the gelatinized SD particles in the photograph and its density.

2.6. Solubility of NiD

Excess NiD was added into the distilled water of 20 ml kept at 37°C. After stirring for 24 h, the suspension of NiD was filtered with a membrane filter of Teflon (Millipore-FG) and the concentration of NiD in filtrate was measured spectrophotometrically at 246 nm of UV spectrometer.

2.7. Dissolution rate

The dissolution rates of NiD from SD particles were measured according to the paddle method of the dissolution test in Japanese pharmacopoeia XII, using Riken dissolution tester (Miyamoto Riken, Japan). SD as for NiD from 1 to 100 mg were added into distilled water of 900 ml kept at $37 \pm 1^\circ\text{C}$ and the suspended solutions were stirred from 25 to 250 rpm. The concentrations of NiD in those solutions were measured with elapsed time, using UV spectrometer (HP-8451A, Hewlett Packard) with automatic sampling system. A 20- μ m filter was attached to the sampling device for suspended solution.

The HPMC concentrations in the solution were also measured with elapsed time by gel permeation chromatography using styrene column (Ultrastraygel-100A) recommended by Maclaren and Hollenbeck (1987).

3. Results and discussion

3.1. Shapes of HPMC and SD

Fig. 1 shows scanning electron microscope photographs of HPMC and SD particles. The shape of SD particles is almost same as that of HPMC and both shapes will be considered as cylindrical and similar to fiber. In the suspending process for the preparation of SD, even though NiD dissolved in ethanol, HPMC did not dissolve, but swelled. Referring to Fig. 1, it can be supposed that NiD is adsorbed in molecular size into swollen HPMC, together with ethanol, and NiD molecules homogeneously disperse in HPMC after the evaporation of ethanol. At the same time, HPMC particles in ethanol solution which was

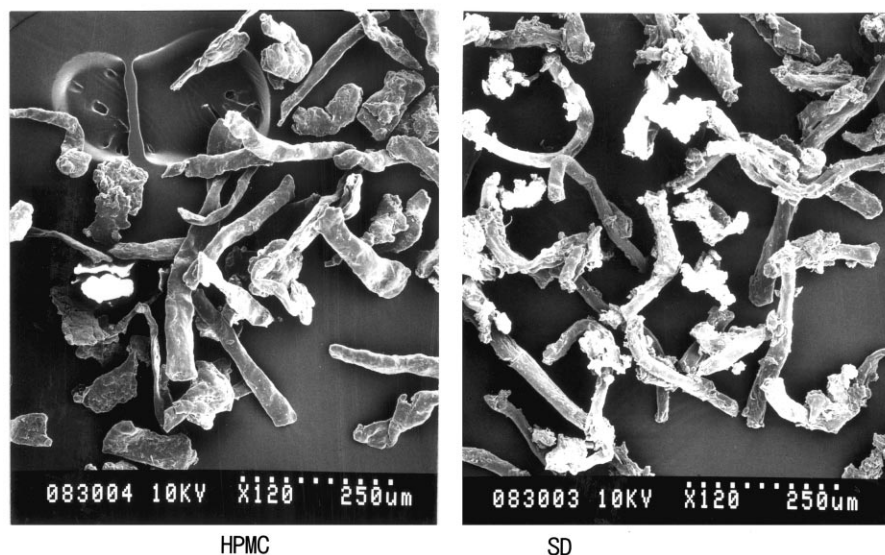


Fig. 1. SEM of HPMC and SD particles.

dissolving NiD did not deform by the suspension process, and the shape of HPMC was kept almost unchangeably after the preparation of SD. The mean physical properties calculated by the measurement with both 20 particles in SEM photographs are listed in Table 1. Although all properties of SD particles were almost the same as those of HPMC, the slight increases in the axial length, the slight decrease in the radius length and weight of SD particle were recognized through the SD preparation. It is supposed that the increase of axial length of SD would be axially expanded and the decrease of radius length of SD would be shrunken by the preparing process for SD, in which SD is swollen by ethanol and is dried under vacuum conditions. The reason, in which the weight ratio of SD to HPMC became 1.07 smaller than 1.2 of the stoichiometrical value, would be defaced by screening-dried coarse SD particles with a 100- μm sieve.

3.2. Powder X-ray

Fig. 2 shows the powder X-rays of NiD, SD and the physical mixture. The crystalline peaks of NiD are observed in the diffraction spectra of

NiD and the physical mixture. However, the peaks cannot be observed in that of SD, suggesting the molecular dispersion of NiD in HPMC.

3.3. Radius, axial length and water content of gelatinized SD

Fig. 3 shows the shape change of SD particles in the photographs taken by the optical microscope before and 5 min after dipping into the distilled water. The SD particles instantaneously gelatinized to about 2-fold by the absorption of water. Although the shape of gelatinized SD particles remained unchanged visually until 10 min after dipping, the gelatinized SD particles gradually became larger by the absorption of water. The radius and axial length were measured with 20 gelatinized SD particles in the photograph, assuming a cylindrical shape.

The mean physical properties of gelatinized SD are also listed in Table 1. The total surface area of gelatinized SD particles at the initiation of dissolution was calculated using the mean values.

The mean water content of gelatinized SD measured by the described method was 84.6% w/w as listed in Table 1.

Table 1
Mean physical properties of HPMC, SD and gelatinized SD

Sample	Radius (μm)	Axial length (μm)	Density ($\mu\text{g}/\text{ml}$)	Weight (μg)	Water content (% w/w)
HPMC	22.2	125.0	1.38×10^6	0.26	—
SD	21.8	137.0	1.36×10^6	0.28	—
Gelatinized SD	43.6	234.3	1.01×10^6	1.41	84.6

3.4. Dissolution characteristics of NiD from SD

As shown in Fig. 4, NiD concentrations in bulk solution after the dissolution of SD including 10, 14, 24 and 30 mg as for NiD increase very steeply at the initiation step of dissolution, and attain to each maximum value which is the high supersaturation in comparison with the intrinsic solubility measured with NiD alone. The maximum concentrations obtained for SD including 24 and 30 mg as for NiD decrease very quickly due to the high nucleation rate of NiD and high growth rate of nuclei, corresponding to the high degree of supersaturation. The final NiD concentrations after nucleation and growth are about 2.5 times higher than the solubility of NiD alone, as described by Matsumaru et al. (1977).

On the other hand, the maximum concentrations obtained for SD, including 10 and 14 mg as for NiD, are appreciably lower than former two values and the decreasing rate of NiD concentration is also lower. The maximum NiD

concentrations (C_{NMAX}) increased with the increase of amount of SD dissolved, as shown with solid line in Fig. 5. The calculation values C_{NMAX} shown with dotted line were calculated as the NiD concentrations which all SD dissolved without nucleation and growth. The disagreement between both C_{NMAX} values at the larger amount of NiD than 20 mg is considered that the nucleation and growth of NiD simultaneously occur with the dissolution of SD, because of the higher degree of supersaturation.

Although C_{NMAX} increases with the increase of amount of dissolved SD, the maximum C_{NMAX} converges upon $40 \mu\text{g}/\text{ml}$. Such a converged C_{NMAX} will be considered as the critical supersaturation of NiD at the dissolution of gelatinized SD.

Fig. 6 shows the dissolution rates of NiD and HPMC from SD. Referring to the almost similar rates of both species, the following dissolution mechanism, in which both species in gelatinized SD particles transfer together to bulk solution through diffusion layer is reasonable. Such an experimental result suggests a different dissolution mechanism from the model presented by Higuchi (1961), in which the molecular diffusion of drug proceeds through gelatinized layer.

Fig. 7 shows the effect of stirring rate on the dissolution rate of SD particles. The dissolution rate gradually becomes higher corresponding to the increase of stirring rate. The acceleration of dissolution rate by the stirring rate primarily comes from the decrease of the thickness of diffusion layer adhered at the outside of gelatinized SD. Moreover, the other important role of stirring will be the erosion of gelatinized SD as pointed out on the drug release mechanism from gelatinized matrix tablet by Ford et al. (1987).

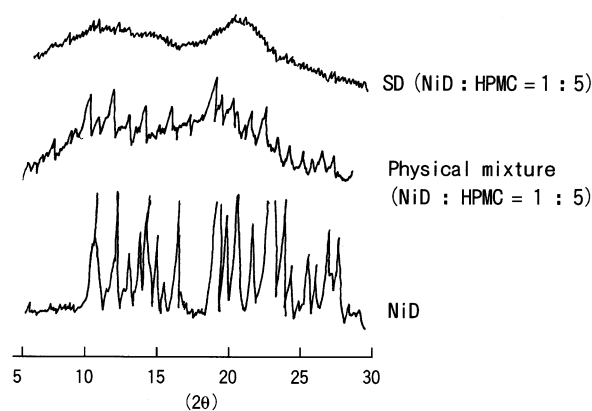


Fig. 2. Powder X-rays of NiD, SD and physical mixture.

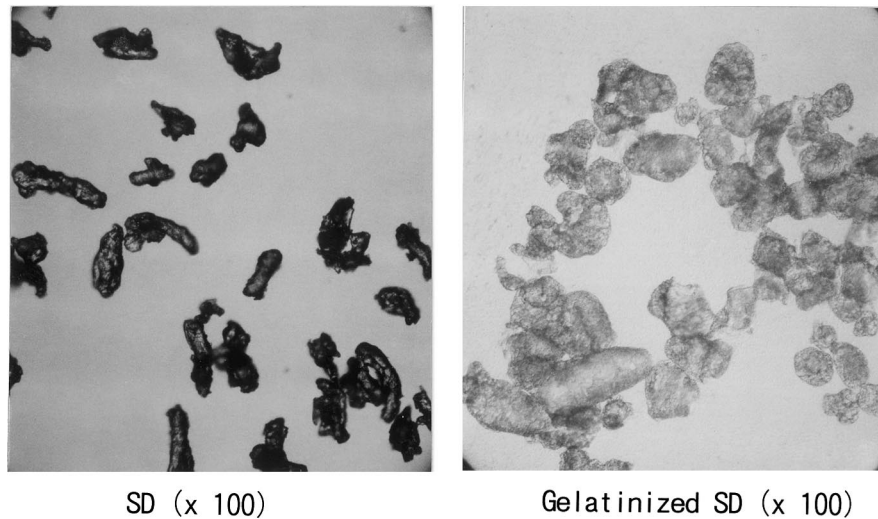


Fig. 3. Photographs of SD and gelatinized SD (5 min after dipping).

3.5. Dissolution mechanism of gelatinized SD

Considering the experimental results already shown in previous figures, the following dissolution mechanism of gelatinized SD is reasonable.

1. SD particles gelatinize to a water content of 84.6% w/w after dipping into water and the total concentration of NiD and HPMC in gelatinized SD is written as C_{GO} .

2. The finely crushed gelatinized SD are continuously produced on the surface of gelatinized SD by the attrition of stirring paddle— SD and SD–SD, and these finely gelatinized SD diffuse to bulk solution through diffusion layer. The water content of gelatinized SD increase at the diffusion process in the diffusion layer. After the arrival to bulk solution, each gelatinized SD homogeneously disperses into bulk solution at perfect mixing state and the total concentration of NiD and HPMC in bulk solution is written as C_{GS} . In such a mass

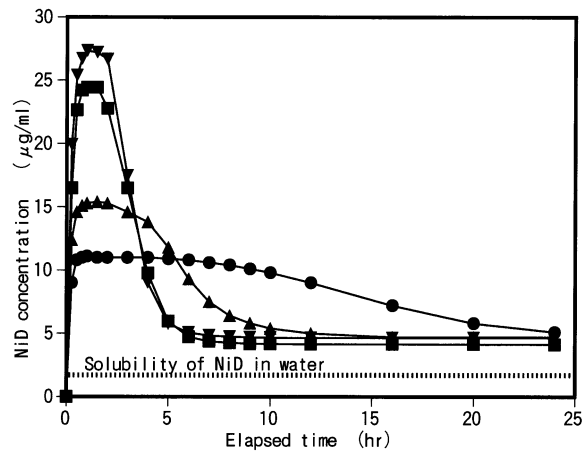


Fig. 4. Dissolution profiles of NiD from SD for three different amounts at 37°C and 100 rpm: (●) 10 mg; (▲) 14 mg; (■) 24 mg and (▼) 30 mg as NiD.

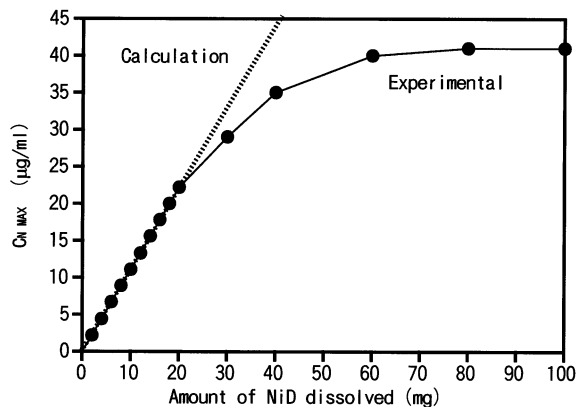


Fig. 5. Relationship between measured and calculated C_{NMAX} at 37°C and 100 rpm.

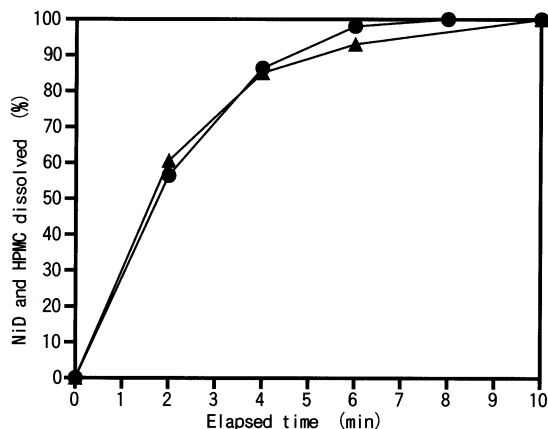


Fig. 6. Dissolution rates of NiD and HPMC from SD (20 mg NiD) at 37°C and 100 rpm: (●) NiD and (▲) HPMC.

transfer model the driving force can be written as $(C_{GO} - C_{GS})$, as shown in Fig. 8.

- The radius and axial length listed in Table 1 are used for the calculation of the surface area of gelatinized SD at the initiation of dissolution.

3.6. Dissolution rate of NiD from SD

When an SD particle composed of NiD of W_N and HPMC of W_H absorbs water of 5.49 ($W_N + W_H$), corresponding to a water content of 84.6% w/w after the dipping into water, the concentration (C_{GO}) of NiD and HPMC in the gelatinized SD can be expressed as follows.

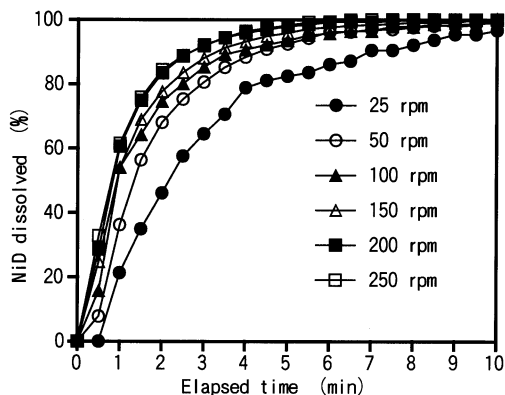


Fig. 7. Dissolution rates of NiD from SD (2 mg NiD) at six different stirring rates at 37°C.

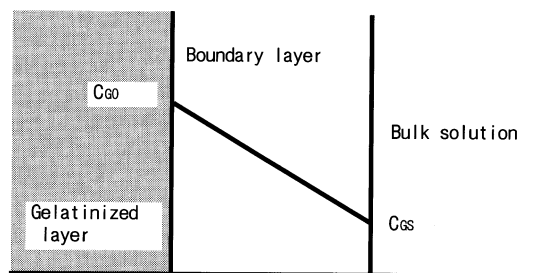


Fig. 8. Dissolution model of gelatinized SD.

$$C_{GO} = \frac{\rho_G}{6.49} \quad (2)$$

where ρ_G is the density of gelatinized SD.

Assuming that each gelatinized SD dissolves keeping the cylindrical shape, and the axial length, radius, and weight of gelatinized SD become l_G , r_G , W_G at the elapsed time of θ from the initiation of dissolution, the dissolution rate at θ is expressed as Eq. (3), which is the same as the equation applied by Noyes and Whitney (1897), Lu et al. (1993).

$$-\frac{n}{v} \frac{dW_G}{d\theta} = \frac{D}{t} n(2\pi \cdot r_G \cdot l_G + 2\pi \cdot r_G^2) (C_{GO} - C_{GS}) \quad (3)$$

$$C_{GS} = \frac{n(W_{GO} - W_G)}{v} \quad (4)$$

where n is the number of dissolved SD particles, v is the volume of distilled water, π is the ratio of the circumference of a circle to its diameter, D is the diffusion coefficient of the gelatinized SD finely crushed, t is the thickness of the diffusion layer, W_{GO} is the initial weight of gelatinized SD, C_{GO} calculated by Fig. 3, and water content of 84.6% w/w and maximum C_{GS} calculated by maximum C_N in Fig. 4. Therefore, C_{GS} is negligibly small in comparison with C_{GO} .

Under the condition that the bulk concentration C_{GS} is negligibly small in comparison with C_{GO} , namely perfect sink, Eq. (3) can be simplified, and integrated as Eq. (5).

$$W_G = 2/3 \pi^{1/3} k_d \cdot v(a + 1)(a\rho_G)^{-2/3} C_{GO} \cdot \theta \quad (5)$$

where $k_d = D/t$ is the mass transfer coefficient and $a = l_0/r_0$ is the ratio of axial length to radius of gelatinized SD.

Because the dissolution rate of gelatinized SD is expressed by Eq. (5), the concentration of NiD and HPMC in bulk solution C_{GS} becomes Eq. (6).

$$C_{GS} = \frac{n[W_{GO} - \{\frac{2}{3} \pi^{1/3} k_d \cdot v(a+1)(a\rho_G)^{-2/3} C_{GO} \cdot \theta\}]}{v} \quad (6)$$

Therefore, the concentration of NiD in the bulk solution C_{NS} becomes Eq. (7).

$$C_{NS} = \frac{W_N \cdot C_{GS}}{(W_N + W_H)} \quad (7)$$

3.7. Availability of dissolution rate equation

Because NiD in SD is less than 20 mg, as for NiD completely dissolved without nucleation of NiD, as shown in Fig. 5, k_d values from data indicated with symbols in Fig. 9 can be estimated by non-linear least squares regression analysis using Gauss–Newton method with Eqs. (6) and (7). The k_d values obtained for five different amounts of dissolved SD are almost constant and the mean value of k_d and the standard deviation become $1.59 \times 10^{-12} + 0.13 \times 10^{-12}$ cm/min. The five dotted lines in Fig. 9 show the simulation of dissolution rates calculated using the mean k_d value. Considering the good coincidence of the simulation curves with experimental data, these

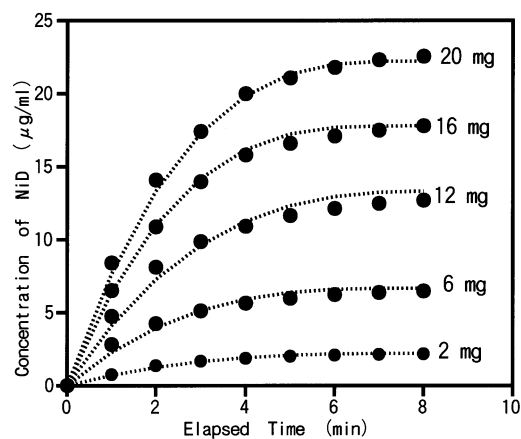


Fig. 9. Measured and simulated dissolution rates of NiD from various amount of SD with elapsed time at 37°C and 100 rpm; (●) measured and (---) simulated values.

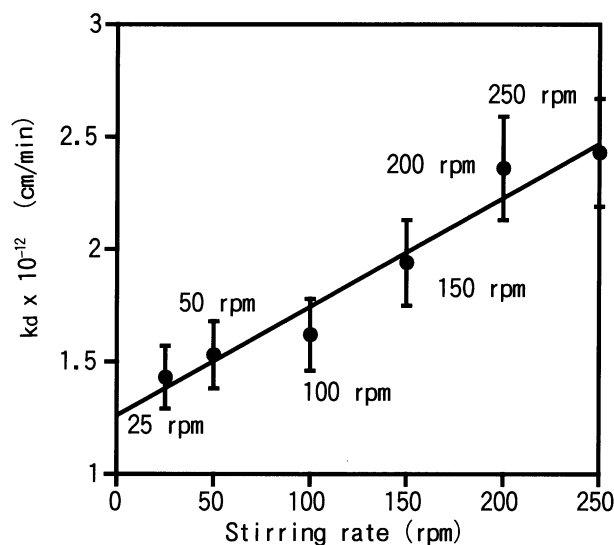


Fig. 10. Relationship between k_d and stirring rate. Each value represents the mean \pm S.D.

dissolution mechanism and rate equations can be used for the estimation of dissolution rate of SD particles.

Finally, the dependency of k_d on the stirring rate calculated from Fig. 7 is shown in Fig. 10. The reason why k_d value increases with increase in stirring rate will be considered that the thickness of diffusion layer adhered at the outside of gelatinized SD particles decreases with the increase of stirring rate and the acceleration of erosion of gelatinized SD.

4. Conclusions

The SD particles composed of NiD and HPMC instantaneously adsorbed water of 84.6% w/w after dipping into stagnant distilled water and dissolved slowly. When the SD particles were suspended in stirring-distilled water, the dissolution of SD particles proceeded and corresponded to the stirring rate after quick gelatinization. NiD and HPMC diffused to the bulk solution at the same transfer rate. Assuming that finely crushed gelatinized SD are produced by the erosion of SD particles and the concentration of the crushed particles is the same as the concentration of NiD

and HPMC in gelatinized SD, the dissolution rate was estimated under the experimental conditions, in which SD particles were less than 20 mg, as for NiD dissolved without nucleation and growth. As the results of dissolution experiments, a good coincidence was obtained between experimental data and simulation.

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