Sustained Release Mechanisms of Wax Matrix System for Controlled Release

Yasutomi KATO,*,[a] Hisakazu SUNADA,[a] Yorinobu YONEZAWA,[a] and Ryuzo ISHINO[b]

Faculty of Pharmacy, Meijo University,[a] 150, Yagotoyama, Tempaku-ku, Nagoya 468, Japan and Pharmaceutics Research Laboratory, Tanabe Seiyaku Co., Ltd.,[b] 16–89, Kashima 3-chome, Yodogawa-ku, Osaka 532, Japan.
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In order to elucidate the influence of the particle size of water-soluble ingredients in a wax matrix and the solubility of drugs on the drug dissolution rate from a dosage form, reservoir devices were prepared from a wax matrix layer consisting of hydrogenated caster oil (HCO) and lactose, a drug reservoir and a water non-permeable layer of HCO, and dissolution tests were then carried out. Drug permeability and water penetrability of the wax matrix layer were affected by the particle size of lactose incorporated into the wax matrix layer. Drug permeability and water penetrability could be decreased by using smaller lactose particles. Tortuosity in the wax matrix layer after the dissolution of lactose could be increased inversely proportional to the particle size. Permeability of the wax matrix layer differed depending on the kinds of drugs forming the drug reservoir, which was attributed to differences in the solubility and viscosity of the drug saturated solution formed in the drug reservoir.

Keywords wax matrix; sustained release; reservoir device; particle size; tortuosity; viscosity

Application of a wax matrix dosage form, in which drugs are incorporated into inert water insoluble matrix materials, has been attempted in many types of matrix forms, including granules[1] and tablets,[2,3] in an effort to obtain an effective sustained release system. In the previous paper,[4,5] we reported that after dissolution of the active or water-soluble ingredients in a wax matrix, the wax matrix system becomes porous without disintegrating[1b,2] and this porous structure is used as a barrier for control of the drug dissolution rate, as is the insoluble polymer membrane.[6] Therefore, Fick's law can be applied to the drug dissolution rate from a reservoir device, and it is clear that the drug dissolution rate depends on the component and the thickness of the wax matrix as a barrier for controlled release. We think that the structure of a diffusion pathway could affect the dissolution rate, too. The objective of the present study is to clarify the effect of the particle size of the water-soluble ingredients blended into the wax matrix system on the drug dissolution rate, allowing the matrix to serve as an additional barrier for a controlled release system. A reservoir device[5] was prepared as a model device and dissolution tests were carried out. The effect of the drug solubility on the drug dissolution rate was also investigated.

Theoretical Analysis Drug dissolution from the reservoir device in a steady state, using a wax matrix layer as a barrier in controlled release, occurs by diffusion of a saturated drug solution into the dissolution fluid at the wax matrix layer. Regarding this phenomena as a sort of membrane permeation, Fick's law can be applied and expressed as the drug dissolution rate from the reservoir device in a steady state as in Eq. 1.

$$\frac{dM}{dt}=\frac{PA(C_{in}-C_{out})}{L} \quad (1)$$

where dM/dt is the flux of solute across the wax matrix layer, P is the permeability coefficient of the wax matrix layer, A is the matrix area, C_{in} and C_{out} are the concentration in the reservoir and outer fluid, respectively, and L is the thickness of the wax matrix layer. The dissolution test condition surrounding the tablet is maintained at a sink condition. So, $C_{in}-C_{out}\fallingdotseq C_{in}$ in Eq. 1. Therefore, Eq. 1 can be rewritten as Eq. 2.

$$\frac{dM}{dt}=\frac{PAC_{in}}{L} \quad (2)$$

The drug permeability P, is defined by Eq. 3.

$$P=\frac{D\varepsilon}{\tau} \quad (3)$$

where D is the diffusivity coefficient of the solute in the wax matrix layer, ε is the void space in the wax matrix layer acting as the channel for solute diffusion, and τ is the tortuosity related to the porosity.

Experimental

Materials Table I summarizes the properties of the materials used in this study. Isoniazid (INZ, Yukigosei Yakuhin Kogyo Co.), nicotinamide (NIA, Yukigosei Yakuhin Kogyo Co.), and caffeine (CAF, Shiratori Seiyaku Co.) were pulverized to about 7 μm prior to use. Hydrogenated castor oil (HCO, Kawaken Fine Chemical Co.) was used as the matrix substance. Lactose (Lac_D, D.M.V. 200 mesh; Lac_M, Meggle D80) was used as the water-soluble ingredient.

Granulation The wax matrix granules were prepared by melt granulation. Lactose and HCO powders were mixed together in a ratio of 80 : 20. The powders were mixed and melted in a vessel at 95—98 °C under continuous agitation. The homogeneous mass was cooled to room

TABLE I. Properties of Materials Used in This Study[4c)]

Parameters	NIA	INZ	CAF	HCO
Solubility in water (g/ml)[a)]	0.973	0.195	0.037	Insoluble
Density (g/cm^3)[b)]	1.44	1.42	1.44	1.03
Mean diameter (μm)[c)]	6	7	5	28
Diffusivity ($\times 10^{-4}$ cm^2/min)[d)]	6.5	6.1	4.4	—
Viscosity of saturated solution (mP)[e)]	3.232	0.979	0.719	—

a) Determined at 37 °C. *b*) Determined with an air comparison pycnometer. *c*) Calculated from specific surface area. *d*) Calculated by the Wilke–Chang equation. *e*) Determined by Ubbelohde-type at 37°C.

temperature and then pulverized using a mortar and pestle. The granules obtained were passed throught a 20-gauge mesh.

Tabletting A 50 mg quantity of each powdered drug was put into a die having a diameter of 10 mm (tablet diameter, 1.003 cm), various amounts of wax matrix granules were accumulated on the drug powder, and the contents were compressed at 1273 kg/cm^2. This two-layer tablet was placed at the center of the bottom of a die having a diameter of 16 mm. 1 g of HCO powder was added, and the contents were then compressed at 637 kg/cm^2. All the tabletting experiments were performed using an oil pump press.

Dissolution Test Dissolution tests were performed according to the paddle method described in JP XII. A 900 ml volume of distilled water maintained at 37 °C was used as the dissolution fluid and the fluid was stirred with a paddle at 100 rpm. The amount of drug dissolved from the reservoir device was determined by spectrophotometric assay at 290, 280 and 255 nm for INZ, NIA and CAF, respectively, using an apparatus consisting of a double-beam spectrophotometer (Hitachi 200-20 type), micro tube pump (MP-3 Tokyo Rikakikai Co., Ltd.), and pen recorder (Type 3056 Yokogawa Electric Works, Ltd.).

Measurement of Thickness of the Wax Matrix Layer The thickness of the wax matrix layer of each reservoir device used was measured by an image analyzer (Luzex, Nireco), after being air-dried at room temperature after dissolution.

Observation of the Wax Matrix Layer Surface Photomicrographs of the wax matrix layer surface before and after the dissolution test were taken by scanning electron microscope (SEM) (JSM-T20, Nihon Denshi Co.).

Results and Discussion

Influence of Particle Size of Water-Soluble Ingredients in the Wax Matrix Layer After dissolution of water-soluble ingredients in the wax matrix system, the matrix becomes porous without disintegrating. The void spaces of this porous structure, which are formed after elution of the water-soluble ingredients in the wax matrix layer, serve as water channels for drug dissolution. It was considered that the drug dissolution rate could be sustained by controlling the size of the void space and the tortuosity of channels. To examine this hypothesis, the influence of particle size of water-soluble ingredients and variations in dissolution behavior on channel tortuosity were investigated. INZ and Lac_M were used as the drug layer and the water-soluble ingredient, respectively. Lac_M was sieved through a jet sieve (Alpine), using a mesh of 15, 30 or 75 μm. The wax matrix granules were prepared by combining HCO and sieved Lac_M. The physical properties of the tablets are shown in Table II.

The results of dissolution tests are illustrared in Fig. 1. Since the dissolution behavior of INZ from each reservoir device exhibited zero order release kinetics in a steady state after a given lag time, the dissolution rate constant, K_d, representing the flux in Eq. 2, was calculated from the slope of the straight region on the line by the least squares method. It was found that drug dissolution when the larger Lac_M particles were used was relatively fast. We thus

Table II. Physical Properties of Wax Matrix Tablets Used in This Study (1)

Particle size of lactose (μm)	Amount of matrix layer (g)	Thickness of matrix layer (cm)
15—30	0.05	0.051
	0.10	0.096
	0.15	0.141
30—75	0.05	0.054
	0.10	0.098
	0.15	0.147
75—80	0.05	0.050
	0.10	0.100
	0.15	0.142
No sieving (~80)	0.05	0.051
	0.10	0.102
	0.15	0.143

Formulation of wax matrix granules (Lac_M: HCO = 80 : 20).

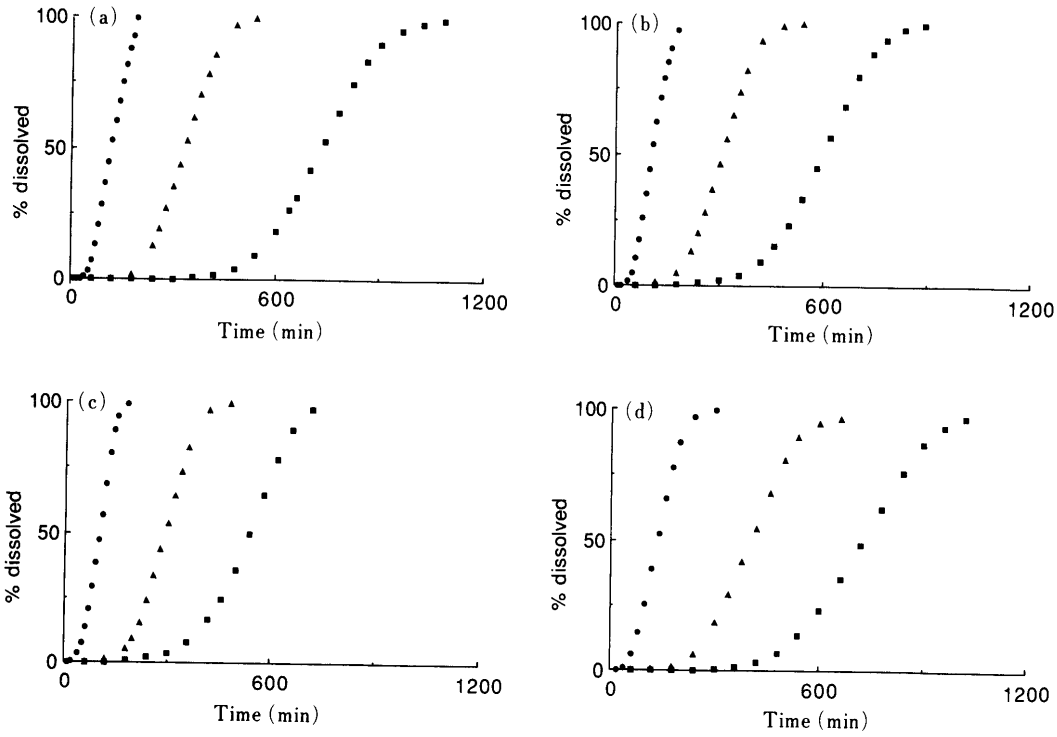

Fig. 1. Dissolution Behavior from a Reservoir Device (1)

Particle size of lactose: (a), 15—30 μm; (b), 30—75 μm; (c), 75—80 μm; (d), no sieving (~80 μm). Weight of matrix layer: ●, 50 mg; ▲, 100 mg; ■, 150 mg.

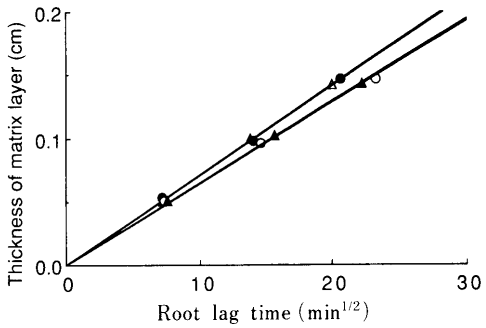

Fig. 2. Relationship between Lag Time and Thickness of Wax Matrix

Particle size of lactose: ○, 15—30 μm; ●, 30—75 μm; △, 75—80 μm; ▲, no sieving (~80 μm).

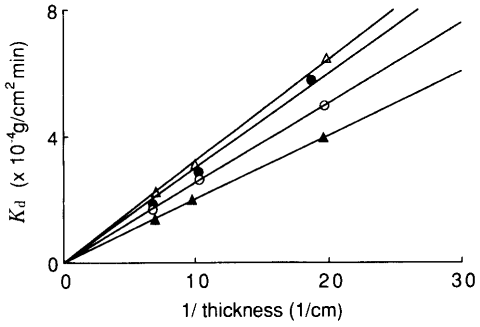

Fig. 3. Relationship between Drug Release Rate Constant in Steady-State and Thickness of Wax Matrix Layer (1)

Particle size of lactose: ○, 15—30 μm; ●, 30—75 μm; △, 75—80 μm; ▲, no sieving (~80 μm).

investigated how the wax matrix layers were affected by the size of Lac_M powders. Since the wax matrix tablets used in this study were a planar dissolution type, the penetration distance from the dissolution surface after time, t, X_t (cm), can be expressed by Eq. 4.

$$X_t = K_p t^{1/2} \tag{4}$$

where K_p is the penetration rate constant.

Under this experimental condition, the penetration distance equals the thickness of the wax matrix layer (L), and the lag time (T_p) represents the total time required for water penetration and drug diffusion through the water channel in the wax matrix layer. Thus, the penetration rate constant, (K_p), which defines the overall the constant for mass transfer through the wax matrix layer, was rewritten as Eq. 5.

$$K_p = \frac{L}{T_p^{1/2}} \tag{5}$$

Figure 2 shows a plot of the thickness of the wax matrix layer as a function of the square root of the lag time. Since a linear relation was found between both parameters, the K_p value was calculated from the slope of the regression line according to Eq. 5. Figure 3 is a plot of K_d against the reciprocal of the thickness of the wax matrix layer. As shown in Fig. 3, a linear relation was found for each case, and the P value was calculated from the slope of each line using the least squares method, in accordance with Eq. 2. The K_p and P values obtained are summarized in Table III.

The penetrability of the dissolution fluid through the wax matrix layer and the permeability of INZ were increased by using the wax matrix granules consisting of larger water-soluble ingredient particles, even if the difference in penetrability was slight. Thus, if the wax matrix layer consists of larger Lac_M particles, the channels formed after the dissolution of Lac_M could be better distributed, leading to a decrease in tortuosity. It was thus considered that the drug dissolution rate could be increased.

In order to calculate the actual tortuosity and investigate how tortuosity in the wax matrix layer is affected by differences in particle size of the ingredient, a 500 mg quantity of the wax matrix granules was placed in a die having a diameter of 10 mm and then compressed at 1273 kg/cm^2 (diameter, 1.003 cm; thickness, 0.474 cm).

TABLE III. Penetration Constant of Water into Wax Matrix Layer, Permeability of INZ through Wax Matrix Layer and Tortuosity of Wax Matrix Layer

Particle size of lactose (μm)	K_p (x 10^{-3} cm/min$^{1/2}$)	P (x 10^{-4} cm^2/min)	τ
15—30	6.417	1.292	4.370
30—75	7.097	1.537	3.494
75—80	7.145	1.650	2.937
No. sieving (~80)	6.480	1.033	2.736

Using this tablet, ε_i, ε_d, and ε, were calculated from Eqs. 6, 7, and 8, respectively, and then SEM photomicrographs of the compressed surface of the wax matrix before and after the dissolution test were observed and the water channels for drug dissolution were identified (Fig. 4).

$$\varepsilon_i = 1 - \frac{Wf_L/\rho_L + Wf_H/\rho_H}{V} \tag{6}$$

$$\varepsilon_d = A/\rho_L \tag{7}$$

$$\varepsilon_t = \varepsilon_i + \varepsilon_d \tag{8}$$

where ε_i is initial porosity, the remaining void space after compression. W and V are the weight and the geometrical volume of the tablet, respectively. f is the fraction ratio of a component in the formulation, and subscripts L and H respresent Lac_M and HCO, respectively. ρ is the true density of the materials ($\rho_L = 1.53$ g/cm^3). ε_d is the void space newly created after Lac_M dissolution. A is the concentration of solid Lac_M in the wax matrix ($A = 1.067$ g/cm^3). ε_t is the total porosity of the wax matrix after Lac_M dissolution ($\varepsilon_i = 0.043$, $\varepsilon_d = 0.697$, $\varepsilon_t = 0.740$).

Using the ε_t value calculated from the above equation, the tortuosity, τ, was calculated from Eq. 3, and the result of these calculations are shown in Table III with K_p and P. Irrespective of particle size of the water-soluble ingredient, the porosity of the wax matrix layer was generally constant, but if the particle was small, the tortuosity was increased. From SEM photomicrographs before the dissolution test (Fig. 4a), the surface of the wax matrix system was smooth and could be regarded as homogeneous. After the dissolution test, however, the wax matrix system maintained the tablet form without disintegrating, becoming a porous structure following the

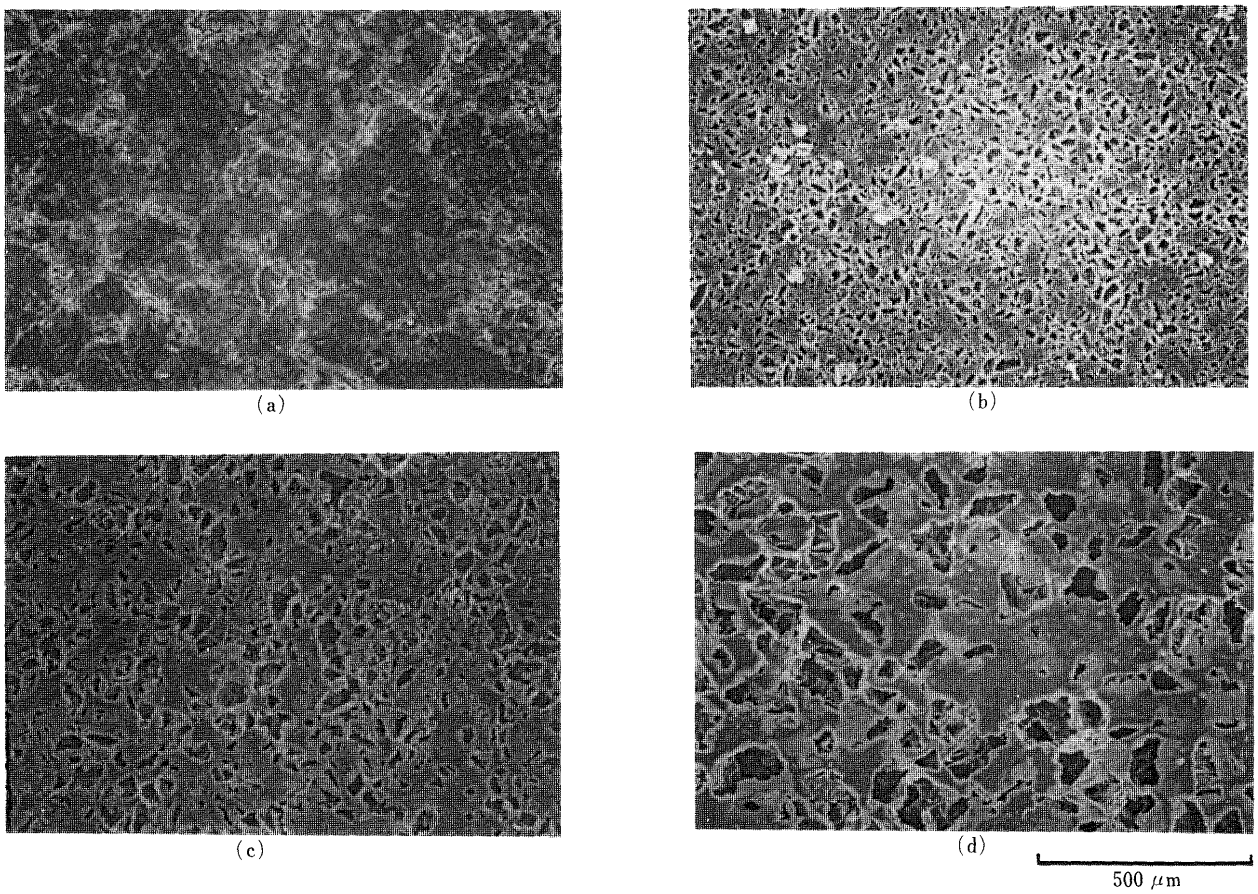

Fig. 4. Scanning Electron Microscope (SEM) Photomicrographs of Wax Matrix System on Compressed Surface Before and After Dissolution Test
(a) before dissolution test, (b) after dissolution test (15—30 μm), (c) after dissolution test (30—75 μm), (d) after dissolution test (75—80 μm).

dissolution of Lac_M in the wax matrix layer (Fig. 4b—d). It is clear from the SEM findings that a large number of small channels formed after the dissolution of Lac_M, if the smaller Lac_M particles were used as water-soluble ingredients. Thus, the diffusion pathway of the wax matrix layer could be extended and the tortuosity could be increased, thereby improving the function of the wax matrix as a barrier for controlling drug dissolution.

Influence of Solubility on the Drug Permeability of the Wax Matrix System Three types of drugs (INZ, NIA, CAF) differing in solubility were used as the model drugs to investigate the influence of drug solubility on the permeability of the wax matrix layer. The physical properties of the tablets used in this study are listed in Table IV. Reservoir devices for each drug were prepared in three preparations varying according to the amount of the wax matrix layer consisting of Lac_D and HCO (80 : 20) at three levels (50, 100, 150 mg).

The results of the dissolution tests of each tablet are shown in Fig. 5. Similar to the preceding study, the drug dissolution rate constant, K_d, was calculated from the slope of the straight region on the line by the least squares method. Figure 6 is a plot of K_d against the reciprocal of the matrix thickness, and the P value was calculated from the slope of each line by the least squares method in accordance with Eq. 2. It was supposed that the drug dissolution rate could be increased by using a drug with higher solubility when making the drug reservoir. In this study, however, the drug dissolution rate of NIA, which has the highest solubility, was similar to that of INZ, and the P value was expected to be low. Since the P value of the wax matrix layer is theoretically constant, regardless of drug type, it is assumed that the viscosity of a saturated drug solution formed in the drug reservoir may affect the release rate according to the Einstein equation (Eq. 9).

$$D=\frac{kT}{6\pi\eta r} \tag{9}$$

where D is the diffusivity coefficient, k is Boltzmann's constant, T is the absolute temperature, η is the viscosity

TABLE IV. Physical Properties of Wax Matrix Tablets Used in This Study (2)

Drug	Amount of matrix (g)	Thickness of matrix layer (cm)
NIA	0.05	0.054
	0.10	0.108
	0.15	0.150
INZ	0.05	0.049
	0.10	0.089
	0.15	0.137
CAF	0.05	0.052
	0.10	0.099
	0.15	0.144

Formulation of wax matrix granules (Lac_D: HCO = 80 : 20).

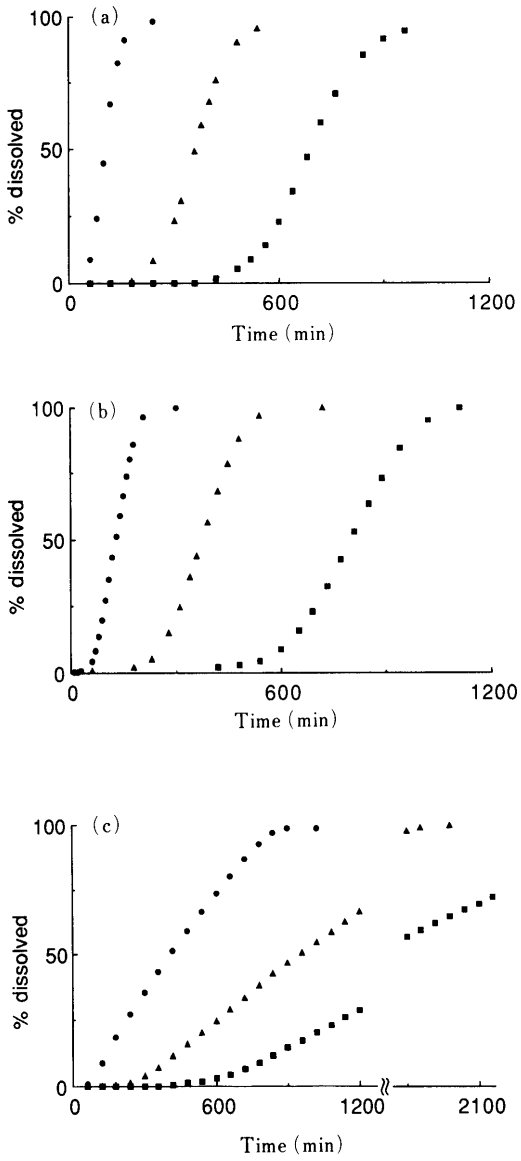

Fig. 5. Dissolution Behaivor from Reservoir Device (2)

Drug layer: (a), NIA; (b), INZ; (c), CAF. Weight of matrix layer: ●, 50 mg; ▲, 100 mg; ■, 150 mg.

of the solution and r is the molecular radius.

The viscosity of saturated solutions of each drug were measured by an Ubbelohde-type viscometer at 37 °C (Table I). The permeability coefficient, P, is shown in Table V. The viscosity of INZ and CAF closely agreed, as did the P value. The P value of NIA, which was estimated to be small, and the viscosity were higher than both INZ and CAF. The difference of viscosity between NIA and others was in agreement with that of P. Thus, the results indicate that the viscosity of a saturated drug solution, which is formed during drug dissolution, affects diffusion at the controlled release barrier.

Conclusion

From the results of this study, the following conclusions were reached. 1) Drug permeability and water penetrability at the wax matrix layer were affected by particle size of the lactose formulated in the wax matrix layer. If smaller

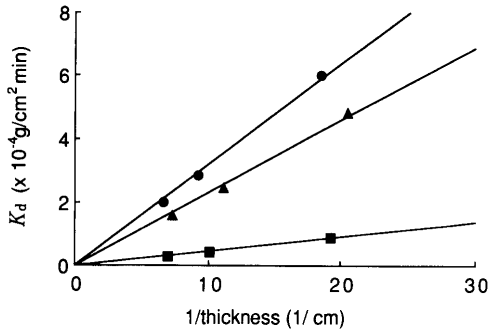

Fig. 6. Relationship between Drug Release Rate Constant in Steady-State and Thickness of Wax Matrix Layer (2)

Drug layer: ●, NIA; ▲, INZ; ■, CAF.

Table V. Permeability of Drug through Wax Matrix Layer

Drug	P ($\times 10^{-4}$ cm^2/min)
NIA	0.328
INZ	1.177
CAF	1.209

lactose particles were used, both drug permeability and water penetrability decreased. 2) Porosity in the wax matrix layer remained unchanged despite the particle size of lactose, but tortuosity increased in inverse proportion to the particle size. Thus, it was found that the use of larger lactose particles resulted in a small number of large channels, while use of smaller lactose particles resulted in a greater number of small channels. 3) The permeability coefficient of the wax matrix layer differed depending on the kind of drug used to form the drug reservoir, which was attributed to differences in the solubility and viscosity of the saturated drug solution formed in the drug reservoir.

Thus, when using the wax matrix system as a factor for controlled drug release, it is suggested that more precise controlled release is possible by considering not only the thickness of the wax matrix layer and the quantity of water-soluble ingredients, but also particle size, drug solubility and the viscosity of the saturated drug solution.

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