Studies on Application of Wax Matrix System for Controlled Drug Release

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In order to examine the function of a wax matrix system as a barrier for the controlled release of oral dosage forms, reservoir devices were prepared and dissolution tests were conducted. The permeability coefficients of isoniazid through wax matrix layers consisting of various proportions of α-lactose monohydrate and hydrogenated castor oil were determined coincidently with the penetration rate constants of water into the wax matrix layers. To elucidate the barrier function relating to control of the drug release rate, dry-coated tablets in which the outer shell was formed with the wax matrix system were prepared. The dissolution behavior of isoniazid from the dry-coated tablets coincided with the simulation result calculated using the obtained permeability coefficient and penetration rate constant.

Keywords wax matrix system; dry-coated tablet; controlled drug release; reservoir device; drug permeability; water penetrability

Introduction

The matrix tablet which incorporates the active ingredient in an inert material matrix has been well known to act as an effective sustained release medicament.[1] After release of the active or water soluble ingredients in the matrix system, the matrix system becomes porous without disintegrating.[2] This porous structure is thought to be similar to that of the insoluble polymer membrane generally used as a barrier for control of drug release rate.[3] Thus, it appears that the matrix system could be applied to control the drug release rate in the same way as the polymer membrane, but only a few papers have focused on the ability of the matrix system to control drug release.[4] The advantages of applying the matrix system as a barrier to controlling drug release, as opposed to the polymer membrane, are thought to be as follows: the thickness of the barrier layer can be adjusted more easily than the spray coating of polymer, and it is possible to incorporate the desired drug into the barrier layer.

The objectives of the present study were to determine the drug permeability and the water penetrability of the wax matrix system, and to apply the wax matrix system as a barrier in a controlled release dosage form.

In this paper, the reservoir device shown in Fig. 1 was prepared for the determination of drug permeability and water penetrability of the wax matrix system, and dissolution tests were conducted. To elucidate the function of the wax matrix as a barrier to control the drug release rate, a dry-coated tablet in which the outer shell was formed with the wax matrix system was prepared (shown in Fig. 2) to conform with the composition reported by Fryklof *et al.*[4a]

Theoretical Analysis The drug release rate from the reservoir device in the steady-state was expressed as:

$$\frac{dM}{dt}=\frac{PA(C1-C2)}{L} \quad (1)$$

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, $C1$ and $C2$ are the concentration in the reservoir and outer fluid, respectively, and L is the thickness of the wax matrix layer.

The drug permeability, P, was defined as:

$$P=\frac{DK\varepsilon}{\tau} \quad (2)$$

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

In the case of the reservoir device using a hydrogenated castor oil (HCO) matrix system shown in Fig. 1, the drug solute permeated through the restricted water channel in the matrix layer which was newly created following release of the soluble ingredient.[5] As the water channel in the wax matrix layer fills with the dissolution fluid, the distribution coefficient, K is unity. In this experimental condition, the dissolution fluid is maintained under the sink condition, thus $C1-C2 \fallingdotseq C1$ in Eq. 1. Therefore, Eq. 1 and Eq. 2 could be rewritten as Eq. 3 and Eq. 4, respectively.

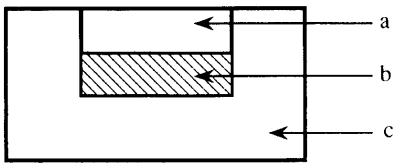

Fig. 1. Schematic Representation of Reservoir Device

a, dissolution surface formed from matrix layer consisting of α-lactose monohydrate (LAC) and hydrogenated castor oil (HCO); b, drug reservoir (isoniazid (INZ) layer); c, water non-permeable layer consisting of HCO.

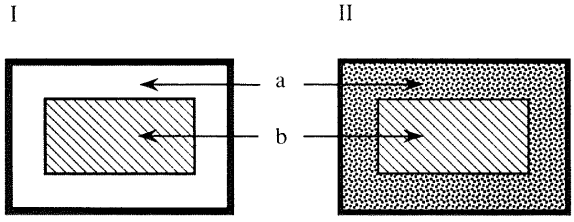

Fig. 2. Schematic Representation of Dry-Coated Tablet

a, outer shell formed from wax matrix system; b, core tablet consisting of INZ; I, wax matrix system incorporating no INZ; II, wax matrix system incorporating INZ.

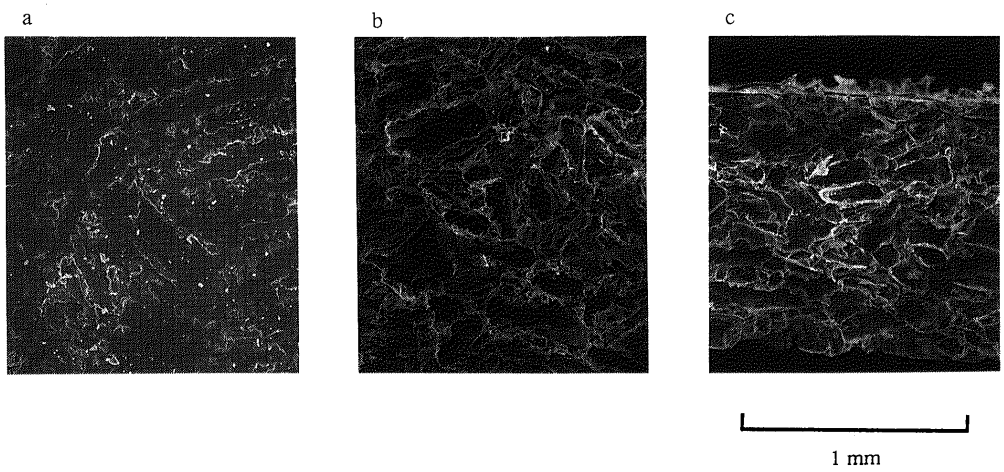

Fig. 3. Scanning Electron Microscope (SEM) Photomicrographs of Wax Matrix System before and after Dissolution Test
a, compressed surface before dissolution test; b, compressed surface after dissolution test; c, lateral surface after dissolution test.

$$\frac{dM}{dt}=\frac{PAC1}{L} \quad (3)$$

$$P=\frac{D\varepsilon}{\tau} \quad (4)$$

Experimental

Materials Isoniazid JP (INZ) was obtained from Yukigousei Yakuhin Kogyo Co., and pulverized to about 7 μm prior to use. HCO was obtained from Kawaken Fine Chemical Co. (K_3wax®, mp 84—88 °C), α-lactose monohydrate (LAC) was obtained from D.M.V., (200 mesh), and used as received.

Granulation The melt granulation method was applied. LAC and HCO powder were mixed together in various proportions. A 100 g quantity of powder blend was melted in a vessel at 95—98 °C under continuous agitation. The homogeneous mass was cooled to room temperature and then pulverized using a mortar and pestle. The granules obtained were sized by passing them through a 20 mesh sieve. Three lots of granules consisting of LAC and HCO at ratios of 90 : 10, 80 : 20 and 70 : 30, were prepared by the same procedure. The granules used for the outer shell of the dry-coated tablet were also prepared by the same procedure.

Tabletting All the tabletting experiments were performed using a reciprocating press (Autograph IS-5000, Shimadzu Seisakusho) with a flat faced punch and die. The preparation of the reservoir device was as follows. A 50 mg quantity of INZ powder was put into a die having a diameter of 10 mm, and the various amounts of the granules were accumulated on the INZ powder and the contents were compressed at 1273 kg/cm^2 and a punch velocity of 10 mm/min. 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 600 kg/cm^2.

The dry-coated tablet was prepared using the press coating technique. A 100 mg quantity of INZ powder for the core tablet was placed in a die having a diameter of 8 mm, and was compressed at 400 kg/cm^2. A 150 mg quantity of the granules was placed in a die having a diameter of 10 mm, then the core tablet was placed in the center of the granules. The remaining 150 mg of granules were then poured into the die, and the contents were compressed at 600 kg/cm^2.

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. The fluid was stirred with a paddle at 100 rpm. The solubility of INZ is 0.195 g/ml in water at 37 °C, then all of the dissolution test is conducted under the sink condition. In the case of the dry-coated tablet, a sinker was applied to prevent flotation of the tablet. In the case of the reservoir device, a plate glass was applied to the wax coated planar surface of each sample to prevent flotation, and it was placed at the bottom of the vessel so as to keep the dissolution surface upward. The amount of drug release was spectrophotometrically assayed at 280 nm.

Microscopy Measurement The thickness of the matrix layer of each reservoir device was measured using an image analyzer (Luzex 500, Nireco Co.). Photomicrographs of the matrix before and after the dissolution test were taken by SEM (JSM-T20, Nihon Denshi Co.).

Results and Discussion

Permeability and Penetrability of the Wax Matrix System The scanning electron photomicrographs in Fig. 3 show the surface of the LAC–HCO matrix system before and after the dissolution test.

Before the dissolution test, the surface of the wax matrix system was smooth and could be regarded as homogeneous. On the other hand, after the dissolution test the wax matrix system maintained the tablet form without disintegrating, and became a porous structure following release of LAC in the wax matrix. This porous structure was throught to be the same as that of water insoluble polymer membranes used to create a barrier for controlled drug release.

To determine the drug permeability coefficient of the wax matrix system, the reservoir devices shown in Fig. 1 were prepared and dissolution tests were conducted. The release rate was examined as a function of the thickness of the wax matrix layer and the HCO content in the matrix layer. The results of the dissolution tests were shown in Fig. 4.

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 release rate constant, K_d representing the flux in Eq. 3 was calculated from the slope of the straight region on the line by the least squares method. To obtain the drug permeability coefficients of the wax matrix layers varying in the ratio of LAC to HCO, the relation between the reciprocal of the matrix thickness and K_d was investigated. As shown in Fig. 5, a linear relation was found for each ratio of LAC to HCO.

The permeability coefficients of INZ through the wax matrix layer were calculated from the K_d value and the thickness of the wax matrix layer using Eq. 3 by the least squares method.

Water penetration in a planar matrix system is known to obey the boundary retreat mechanism. So, in this matrix layer the penetration distance from the dissolution surface after time $t(X_t)$ is expressed as[6]:

$$X_t=K_p t^{1/2} \quad (5)$$

where K_p is the penetration rate constant. Under this

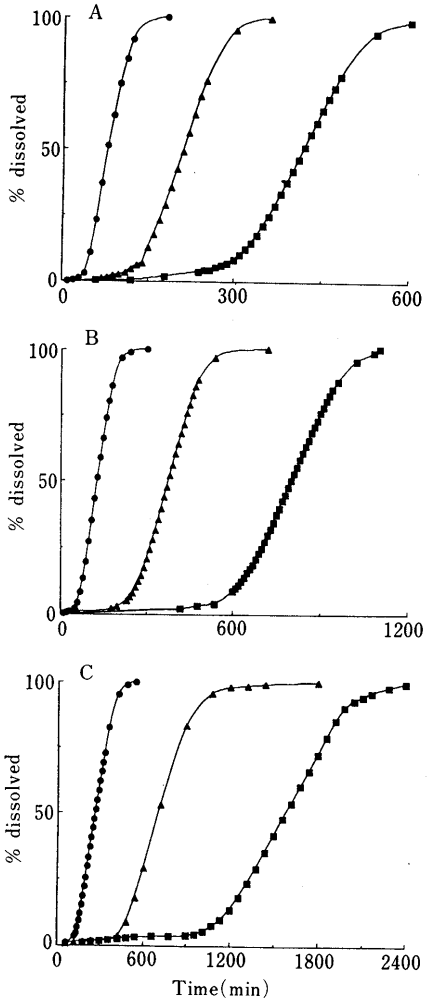

Fig. 4. Dissolution Behavior of INZ from Reservoir Device

LAC:HCO ratio; A: 90:10, B: 80:20, C: 70:30. Weight of wax matrix layer: ●, 50 mg; ▲, 100 mg; ■, 150 mg.

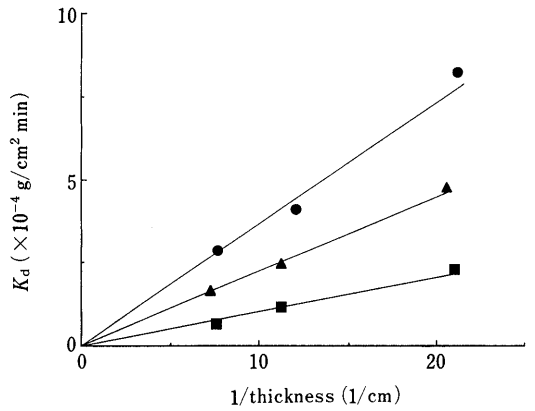

Fig. 5. Relationship between Dissolution Rate Constant in Steady-State and Reciprocal Thickness of Wax Matrix Layer

LAC:HCO ratio; ●: 90:10, ▲: 80:20, ■: 70:30.

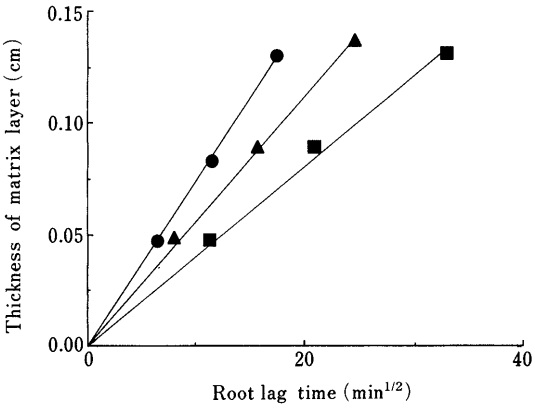

Fig. 6. Relation between Lag Time and Thickness of Wax Matrix Layer

LAC:HCO ratio; ●: 90:10, ▲: 80:20, ■: 70:30.

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 rate constant for mass transfer through the wax matrix layer was rewritten as:

$$K_p = L/T_p^{1/2} \quad (6)$$

Figure 6 is a plot of the thickness of the wax matrix layer against 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. 6. The P and K_p values obtained are summarized in Table I. Both the P and K_p values decrease with increasing HCO content in the matrix system.

Application of the Wax Matrix System to Control Drug Release The basic study described above demonstrated that the wax matrix system could act similar to insoluble polymer membranes which are generally used to control drug release. To confirm this function of the wax matrix system in a practical dosage form, a dry-coated tablet in which the outer shell was formed with the wax matrix system was prepared and dissolution tests were conducted. The formulations of the dry-coated tablets are summarized in Table II.

Table I. Permeability of INZ through Wax Matrix Layer andPenetration Constant of Water into Wax Matrix Layer

LAC:HCO	P ($\times 10^{-6}$ cm^2/s)	K_p ($\times 10^{-3}$ cm/min$^{1/2}$)
90:10	3.23	7.52
80:20	1.65	5.90
70:30	0.90	3.83

Table II. Formulation of INZ Dry-Coated Tablets Used in This Study

	Ingredient	Formulations (mg/tablet)	
		F-1	F-2
Core tablet	INZ	100	100
Outer shell	INZ	—	60
	LAC	240	210
	HCO	60	30

The results of the three dissolution tests for each formulation are shown in Fig. 7.

In the case of the wax matrix system incorporating no drug (Fig. 7A), the dissolution behavior of INZ from each tablet exhibited a zero order release kinetic after a given

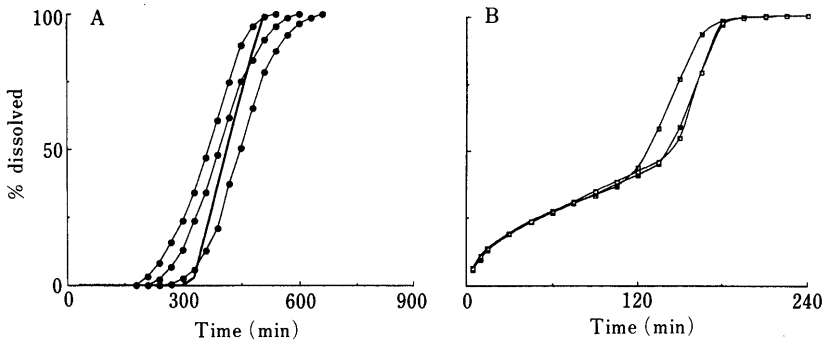

Fig. 7. Dissolution Behavior of INZ from Dry-Coated Tablet

A, wax matrix system incorporated no INZ: ●, observed results; —, simulation result. B, wax matrix system incorporated INZ.

lag time. The drug release rates coincided with each other, and agreed with the simulation result calculated using the obtained P and K_p values, though a variation between lag times was found. The reason for this variation was thought to be connected with the position of core tablet in dry-coated tablet because the lag time varied about 60 min by varying the thickness of the outer shell of 0.1 mm. The calculation was performed at a thickness of the outer shell of 1.0 mm, which was the same as the observed value.

In the case of the wax matrix system incorporating drug (Fig. 7B), the dissolution behavior of INZ from each tablet exhibited a zero order release kinetic after drug release from the matrix layer. Thus, the wax matrix layer could maintain its ability to control drug release. In addition, it was considered that repetitive drug release dosage forms might be prepared by applying the wax matrix system as the outer shell of a dry-coated tablet.

From the present studies, it was confirmed that the wax matrix system could be utilized as an effective barrier for controlled drug release.

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