Release from or through a Wax Matrix System. III.[1] Basic Properties of Release through the Wax Matrix Layer

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Release property of reservoir device matrix tablet was examined. Wax matrix layer was prepared from physical mixture of lactose and hydrogenated castor oil to obtain basic release properties. Release process showed zero order kinetics in a steady state after a given lag times, and could be divided into two stages. The first stage was the formation process of water channel by dissolving the soluble component in the wax matrix layer. The lag time was considered to be the time required forming water channel and the time begun to release drug through the wax matrix layer at the same time. The lag time obtained by applying the square root law equation was well connected with the amount of matrix layer and mixed weight fraction of component in matrix layer. The second stage was the zero order release process of drug in the reservoir through the wax matrix layer. The release rate constants were calculated by taking into accounts of the thickness of matrix layer and permeability coefficient, and were well connected with the amount of matrix layer and mixed weight fraction of component. Also it was suggested that the tortuosity of matrix layer could be expressed by a function of the porosity defined by the mixed weight fraction.

Key words physical mixture; wax matrix; reservoir device tablet; release; tortuosity

To control drug release is a topic of much interest. Wax matrix system was often used as one of methods to control drug release, and its release properties were mathematically expressed by Higuchi.[2—4] To control a drug release, it is important to obtain some basic properties of matrix system.

When the matrix layer was prepared from melted granules of soluble component and wax, some factors such as surface coverage and thickness of melted wax on the surface of soluble component should be considered at least. On the other hand, when the wax matrix layer was prepared from a physical mixture of soluble component and wax, basic properties of matrix system can be estimated by connecting simple factors.

It was considered that reservoir type wax matrix tablet having a fixed surface area may provide more basic release property. In the previous paper,[1] a reservoir device wax matrix tablet was prepared from a physical mixture of hydrogenated castor oil and drug (isoniazid) that was the same one in the reservoir. Hence basic release property from and through the wax matrix layer was investigated (abbreviated as INZ : HCO/INZ system). Then tortuosity as a basic property was suggested to be expressed by a function of the porosity.

Here, basic release properties of drug (isoniazid) in the reservoir through the wax matrix layer prepared from the physical mixture of hydrogenated castor oil powder and soluble substance, *i.e.*, lactose were investigated (abbreviated as LAC : HCO/INZ system). As a result, comparable release properties were obtained from both LAC : HCO/INZ and INZ : HCO/INZ systems. Hence it was suggested that the time begin to release the drug in reservoir through wax matrix layer and its release rate constant can be roughly prospected from the amount of matrix layer and mixed weight fraction of component in the matrix layer.

Experimental

Materials Isoniazid JP (INZ, Yukigousei Yakuhin Kogyo Co.) was pulverized prior to use. Lactose (LAC, Meggle D80) was used as the water-soluble ingredient in the matrix layer. Hydrogenated castor oil (HCO, Kawaken Fine Chemical Co.) was used as the matrix substance.[1,5] The mean diameters (μm) of INZ, LAC and HCO are 10.6, 9.4 and 10.3, respectively.

Preparation of Reservoir Device Tablet Reservoir device tablets having a flat wax matrix layer were prepared. Lactose and hydrogenated castor oil powder were weighed at a given mixed weight ratio for the matrix layer, and were physically mixed together using an automatic mixer (model S 10, Taiyo Kagaku Kogyo Co.) for 10 min.

The physical mixture was put into a die having a diameter of 10 mm. After flattening the surface by using the punch, a 50 mg amount of INZ was accumulated on the physical mixture. Then the contents were compressed at 124.8 MPa to make a two-layer tablet. The two-layer tablet was placed at the center of the bottom of a die having a diameter of 16 mm and 600 mg of HCO was added. Then, the contents were compressed at 62.5 MPa. The shape of prepared reservoir device tablet was the same one shown in the previous paper as an outline shape.[1]

This system was expressed as LAC : HCO/INZ system to distinguish from the previous system,[1] *i.e.*, INZ : HCO/INZ system.

Release Test Following the paddle method described in the previous paper,[1] release measurements were carried out in 900 ml distilled water at a paddle rotation speed of 100 rpm at 37 °C. The reservoir device tablet was placed in the dissolution apparatus (model NTR-VS, Toyama Sangyo Co., Ltd.) coupled to a flow cell set in a double-beam spectrophotometer (model 200-20, Hitachi Ind. Co.) *via* a micro tube pump (model MP-3, Tokyo Rikakikai Co., Ltd.), and pen recorder (model 3056, Yokogawa Electric Works, Ltd.). The amount of INZ released from the reservoir device tablet was determined by the absorbance at 290 nm.

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

Results and Discussion

Porosity of the Matrix Layer The water channel was formed by dissolving water-soluble component in matrix layer and drug was released through it.

Concerning to the water channel, the porosity could be calculated as follows:

$$\varepsilon_c = 1 - \{(M_m X_{LAC}/\rho_{LAC}) + (M_m X_{HCO}/\rho_{HCO})\}/V \quad (1)$$

$$\varepsilon_{LAC} = M_m X_{LAC}/V\rho_{LAC} = M_o/V\rho_{LAC} \quad (2)$$

$$\varepsilon = \varepsilon_c + \varepsilon_{LAC} = 1 - (M_m/V\rho_{HCO})X_{HCO} \quad (3)$$

where ε_c is the initial porosity, *i.e.*, the remaining void space after compression. M_m and M_o are the amount of matrix layer

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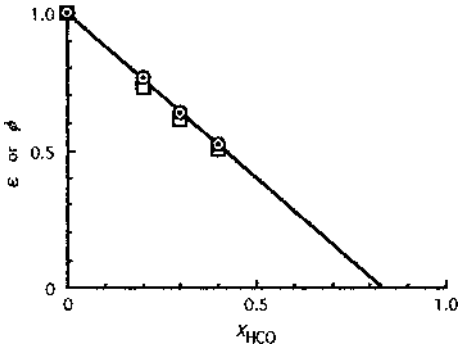

Fig. 1. Relationship between the Mixed Weight Ratio of HCO (X_{HCO}) and the Porosity (ε) or Volume Fraction (ϕ) Available for Release

⊙, ε; □, ϕ.

and the amount of water-soluble component in matrix layer, respectively. V is the geometrical volume of matrix layer. X and ρ are the mixed weight ratio and the true density of the component, respectively. $\rho_{LAC}=1.53$ g/cm^3, and $\rho_{HCO}=1.03$ g/cm^3. ε_{LAC} is the porosity arose from the dissolution of LAC in the matrix layer. ε is the total porosity, *i.e.*, the total void space available for release.

After calculating the porosity by using Eqs. 1 and 2, the relationship between X_{HCO} and ε or the volume fraction of LAC (ϕ) was examined as Fig. 1. A fairly good linear relationship expressed by following equation was obtained.

$$\varepsilon=1.0-1.197X_{HCO} \quad (4)$$

The coefficient in the X_{HCO} term was about 1.20, and was expected from Eq. 3. Since the ε_c value is relatively small compared with the ε_{LAC} value, the ϕ value in the matrix layer prepared by high compression force was close to the ε value. So almost the same relationship between X_{HCO} and ϕ was obtained.

Release Profiles through Matrix Layer Release profiles of INZ from reservoir device tablet having a matrix layer consisted of LAC and HCO were shown in Fig. 2. Release of INZ through the wax matrix layer showed zero order kinetics after a given lag time, and the release process could be divided into two stages. It was considered that the first stage is the formation process of water channel by dissolving the water-soluble component, *i.e.*, LAC in the wax matrix layer and the second stage is the release process through the wax matrix layer.

Properties of the First Stage in Release Process The lag time was appeared as a result of water penetration and dissolution of LAC, and was the time required to form the water channel in the matrix layer. The penetration distance in the wax matrix layer from the release surface after time t is expressed as a function of square root time t. Then, it was considered that the penetration distance is equal to the thickness of wax matrix layer (L) at the lag time (T_F). Here, the lag time was defined as the intersection of the time axis and line of zero order release. The L value should be defined by the amount of matrix layer (M_m). By plotting L against M_m, a fairly good linear relationship was obtained independent of the mixed weight fraction, and was expressed as L (cm)$=1.02M_m$ (g). The initial amount of LAC (M_{LAC}) as the water-soluble component should exist in L. According to Higuchi equation[2—4] and the previous paper,[1] released amount was

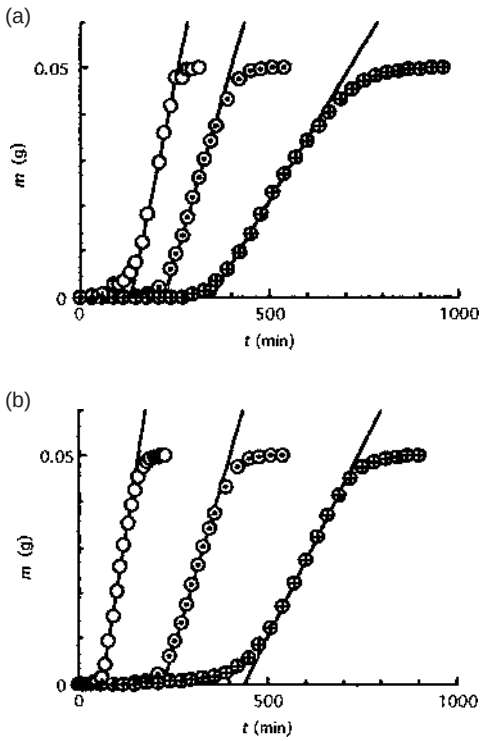

Fig. 2. Release Profiles

(a) Amount of drug in reservoir: 100 mg. Mixed weight ratio in matrix layer (LAC/HCO): ○, 8/2; ⊙, 7/3; ⊕, 6/4. (b) Mixed weight ratio in matrix layer: LAC/HCO=7/3. Amount of matrix layer (mg): ○, 50; ⊙, 100; ⊕, 150.

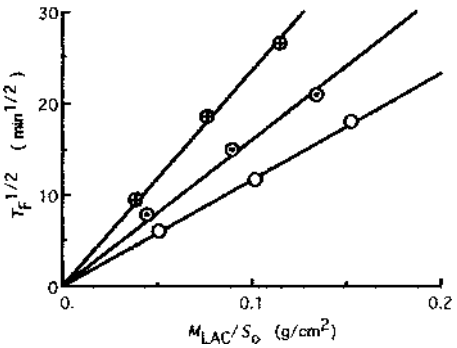

Fig. 3. Relationship between the Square-Root T_F and the Amount of LAC per Unit Surface Area of Matrix Layer (M_{LAC}/S_o)

Mixed weight ratio in matrix layer (LAC/HCO): ○, 8/2; ⊙, 7/3; ⊕, 6/4.

expressed as the amount per unit exposed area (M_{LAC}/S_o). Therefore, the relationship between M_{LAC}/S_o and the square root T_F should be expressed as:

$$M_{LAC}/S_o=M_mX_{LAC}/S_o=K_FT_F^{1/2} \quad (5)$$

where K_F (g/cm^2 min$^{1/2}$) is the penetration rate constant. These relations were shown in Fig. 3. Fairly good linear relationships were appeared, and the K_F value was estimated from the slope of regression line. The K_F value was affected by X_{LAC} as can be seen in Fig. 3. The effective release surface area decrease with the increase of X_{HCO} and/or the decrease of ε. These relationships were examined as shown in Fig. 4. Linear relationships obtained were expressed as:

$$K_F=0.01290-0.02184X_{HCO} \quad (6)$$

$$K_F=0.01286-0.01814(1-\varepsilon) \quad (7)$$

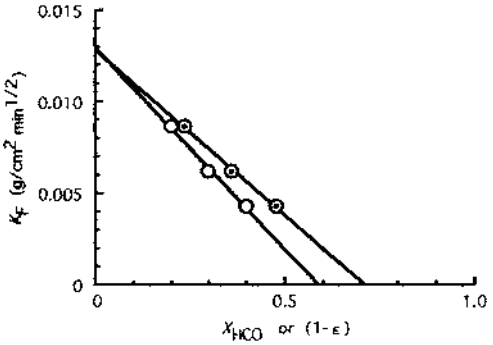

Fig. 4. Relationship between the Penetration Rate Constant (K_F) and X_{HCO} or $1-\varepsilon$
○, X_{HCO}; ⊙, $1-\varepsilon$.

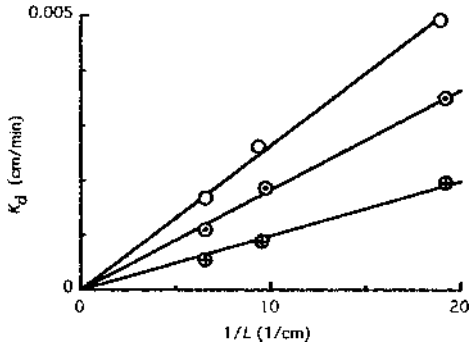

Fig. 5. Relationship between the Release Rate Constant (K_d) and $1/L$
Mixed weight ratio in matrix layer (LAC/HCO): ○, 8/2; ⊙, 7/3; ⊕, 6/4.

These kinds of relationships were observed in the INZ : HCO/INZ system.[1] Therefore the value at the intersection of Y axis was suggested to be defined by the diffusion coefficient, solubility and concentration of LAC in the matrix layer. So it was supposed that the lag time, *i.e.*, the time begin to release drug can be roughly prospected from the amount and composition of matrix layer around examined.

Properties of the Second Stage of Release Process The second release stage appeared after the water channel had been constructed in the matrix layer. Since the effective surface area was fixed, the release process was expressed by a straight line as shown in Fig. 2.

As the release measurements were carried out under a sink condition, the zero order release was expressed as:

$$dm/dt = K_d S_o C_s \tag{8}$$

where dm/dt is the flux of drug across the wax matrix layer, K_d and S_o are the release rate constant at the second stage and surface area of matrix layer exposed to the fluid, respectively. C_s is the solubility. The concentration in outer release fluid is negligible compared with it in the reservoir, *i.e.*, C_s. So the concentration in outer release fluid was omitted in the concentration term. Hence, the K_d values for all the systems were estimated from the slope shown in Fig. 2 as an example.

The K_d values varied in accordance with the mixed weight fraction and amount or thickness of matrix layer. By using the thickness of matrix layer, the permeability coefficient (P) could be connected with K_d as follows:

$$K_d = P/L \tag{9}$$

Following Eq. 9, the K_d values were plotted against the $1/L$ values as shown in Fig. 5. A good linearity was appeared, and the P value was estimated from the slope of each line. The P value varied in accordance with the mixed weight fraction of component in the matrix layer independent of the amount of matrix layer. Thus the P value depended on the changes of matrix structure.

The permeability coefficient (P) and diffusivity (D) was correlated with the properties of matrix structure as follows:

$$P = D(\varepsilon/\tau) \tag{10}$$

here, τ is the tortuosity in matrix layer. The diffusion coefficient of INZ (D_{INZ}) is equal to 0.00061 cm^2/min.[1] In Eq. 10, the distribution coefficient was not taken into account, because the drug does not dissolve in the wax but in the water

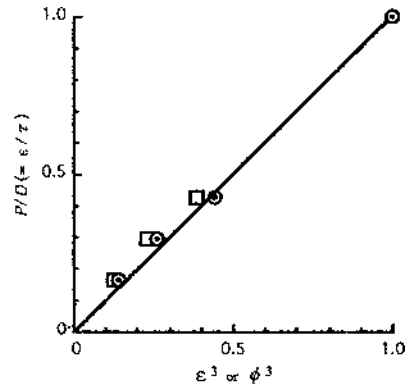

Fig. 6. Relationship between P/D and ε^3 or ϕ^3
⊙, ε^3; □, ϕ^3; ——, slope = 1.

channel. According to Eq. 10, the P/D value should be equal to 1 when the ε value is equal to 1, since τ is equal to 1 at that time. So the relationship was examined as shown in Fig. 6. The linear relationship observed was approximately expressed as:

$$P/D = \varepsilon^3 \tag{11}$$

Hence the K_d value could be roughly defined as:

$$K_d = D\varepsilon^3/L \tag{12}$$

Here the ε and L values were given by a function of the amount and composition of matrix layer. Therefore the second release process could be predicted when an amount and composition of matrix layer were given.

Tortuosity The tortuosity in the matrix layer can be evaluated from Eqs. 10 and 11 within examined. Thus the value could be expressed by using the porosity as a property of the matrix structure.

Relationships between P/D and ε^3 for the release from (the first release stage of INZ : HCO/INZ system)[1] and through (the second release stage of LAC : HCO/INZ system) matrix layer were shown in Fig. 7. A linear relationship was appeared, and the P/D value might be approximately equal to ε^3. Thus the matrix structure was considered to be uniform three dimensionally. This result coincided with that obtained from the examination of relationship between the release direction and the release property.[6]

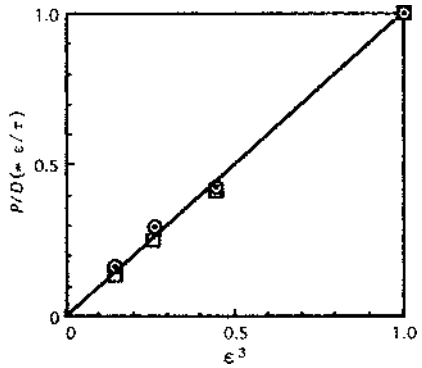

Fig. 7. Relationship between P/D and ε^3
◉, LAC : HCO/INZ system; □, INZ : HCO/INZ system; ——, $P/D=\varepsilon^3$.

Conclusions

Release of isoniazid from reservoir device tablet having matrix layer prepared from physical mixture of lactose and hydrogenated castor oil powder was examined. Release of INZ occurred after a certain lag time, and the release process was considered by dividing into two stages.

The first stage was the formation process of water channel. The penetration rate constant obtained was expressed by a simple function of the mixed weight fraction of component in the matrix layer. Hence, the lag time was given by a function of the amount and composition of matrix layer.

The second stage was the zero-order release process of drug in the reservoir through the matrix layer. The release rate constant was a function of the permeability coefficient and thickness of matrix layer those were well connected with the porosity and amount of matrix layer, respectively. Also the porosity was given by a function of mixed weight fraction. So it was revealed that the release rate constant could be prospected from the amount and composition of matrix layer.

The tortuosity in matrix layer was approximately expressed by a function of the porosity. The relationship was confirmed from the properties of release from and through matrix layer.

Hence, it was suggested that the release profile for the reservoir device tablet could be roughly forecast when the amount and composition of matrix layer were given.

References

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