Release from or through a Wax Matrix System. IV.[1] Generalized Expression of the Release Process for a Reservoir Device Tablet

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Generalization of the release process through the wax matrix layer was examined by use of a reservoir device tablet. The wax matrix layer of the reservoir device tablet was prepared from a physical mixture of lactose and hydrogenated castor oil to simplify the release properties. Release through the wax matrix layer showed zero-order kinetics in a steady state after a given lag time, 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 obtained by applying the square root law equation was well connected with the amount of the matrix layer and mixed weight ratio of components in this layer. The second stage was the zero-order release process of drug in the reservoir through the wax matrix layer, because the effective surface area was fixed. The release rate constants were connected with thickness of the matrix layer and permeability coefficient, and the permeability coefficients were connected with the diffusion coefficient of drug and porosity. Hence the release rate constant could be connected with the amount of matrix layer and the mixed weight ratio of components in the matrix layer. It was therefore suggested that the release process could be generalized using the amount of matrix layer and the mixed weight ratio of components in the matrix layer.

Key words physical mixture; wax matrix; reservoir device tablet; release; generalized expression

To control release of a drug is a topic of much interest. The wax matrix system was one method often used to control drug release, and its release properties were mathematically shown by Higuchi.[2—4] Some basic properties of release from and through the wax matrix layer prepared from a physical mixture of water-soluble component and hydrogenated castor oil were obtained in previous papers.[1,5]

When the wax matrix system was prepared from melted granules of water-soluble component and wax, certain factors such as surface coverage and thickness of the melted wax on the surface of the soluble component should be considered. When the wax matrix system is prepared from a physical mixture of soluble component and wax, basic properties of the matrix system can be estimated by simple factors. It was also believed that a reservoir type wax matrix tablet having a fixed surface area may provide more basic release property, and some of the basic release properties obtained were shown in previous papers.[1,5,6]

Here, generalization of the release process through the wax matrix layer was examined using a reservoir device tablet having a matrix layer prepared from a physical mixture of lactose and hydrogenated castor oil. The lag time was analyzed by the Higuchi equation and the actual release process after the lag time was analyzed using the zero-order release kinetic equation.

Experimental

The following descriptions are closely similar to those in previous papers.[1,5]

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. The mean diameters (μm) of INZ, LAC and HCO are 10.6, 9.4 and 10.3, respectively. The true density (g/cm^3) of LAC and HCO are 1.53 and 1.03, 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 by an automatic mixer (model S 10, Taiyo Kagaku Kogyo Co.) for 10 min.

The physical mixture was put into a die 10 mm in diameter. After flattening the surface with a 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, this tablet was placed at the center of the bottom of a die 16 mm in diameter and 600 mg of HCO was added. Then, the contents were compressed at 62.5 MPa.

This system was called the LAC : HCO/INZ system.

Release Test 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 through the wax matrix layer was determined by the absorbance at 290 nm.

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

Results and Discussion

Thickness and Porosity of the Wax Matrix Layer The surface area (S_o cm^2) of the matrix layer was fixed in the preparation process of the reservoir device tablet. By examining the relationship between the amount (M_m) and the thickness (L) of the matrix layer,[5] an equation obtained was expressed as:

$$L\,(\mathrm{cm}) = 1.02\,(\mathrm{cm/g})\,M_m\,(\mathrm{g}) \quad (1)$$

An effective void space available for the release of drug was mainly supplied by water-soluble component in the matrix layer. With dissolution of the water-soluble component, a water channel was formed in the matrix layer and drug was released through it. Hence the effective void space was expressed as porosity.

The initial porosity (ε_c), *i.e.*, the ratio of remaining void space after compression was expressed as:

$$\varepsilon_c = 1 - \{(M_m X_S/\rho_S) + (M_m X_{HCO}/\rho_{HCO})\}/S_o L \quad (2)$$

The porosity (ε_S) arising from dissolution of the water-sol-

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uble component in the matrix layer was expressed as:

$$\varepsilon_S = M_m X_S / S_o L \rho_S = M_o / S_o L \rho_S \quad (3)$$

Then, the total porosity (ε), *i.e.*, the ratio of total void space available for release was given as:

$$\varepsilon_S = \varepsilon_c + \varepsilon_S = 1 - (M_m / S_o L \rho_{HCO}) X_{HCO} \quad (4)$$

where M_m (g) and M_o (g) are the amount of matrix layer and the amount of water-soluble component in the matrix layer, respectively, and X, ρ (g/cm^3) and subscript S are the mixed weight ratio, true density and water-soluble component in the wax matrix layer, respectively. Relationship between the average ε of measured and X_{HCO} examined is shown in Fig. 1. As expected from Eq. 4, a good linear relationship was observed irrespective of the water-soluble component:

$$\varepsilon = 1.0 - 1.20 X_{HCO} \quad (5)$$

Here, the INZ : HCO/INZ system was a reservoir device tablet with the matrix layer prepared from the physical mixture of INZ and HCO.[5] However, the relationship is likely to be affected by the compression property, cases should be checked as they occur.

Release Profile of Reservoir Device Tablet Releases of INZ in the reservoir through the wax matrix layer are shown in Fig. 2 as an example. Release of INZ through this layer showed zero-order kinetics after a given lag time. The lag time and zero-order release rate constant changed in accordance with the amount and composition of matrix layer.

1) Lag Time The lag time appeared to be the time needed for the entire dissolution of water-soluble component in the matrix layer. In other words, the amount of water-soluble component was defined as the time to begin to release a drug in the reservoir. Here, the lag time was defined as the time at the intersection of the time axis and the line of zero-order release.[1] Hence the lag time (T_F min) in this system was expressed by the following equation given by Higuchi.[4]

$$M_S / S_o = M_m X_S / S_o = K_F T_F^{1/2} \quad (6)$$

where K_F (g/cm^2 min$^{1/2}$) is the penetration rate constant of water-soluble component in the matrix layer. Since K_F is expressed as follows according to the Higuchi equation, the value differs from water-soluble component to water-soluble component.

$$K_F = \sqrt{P_F (2A - \varepsilon C_s) C_s} \quad (7)$$

where P_F (cm^2/min) is the penetration coefficient, A (g/cm^3) is the total amount of water-soluble component in the matrix layer per unit volume and C_s (g/cm^3) is the solubility of the water-soluble component in the permeating fluid. As K_F is expressed by a function of ε, and ε is expressed by a function of X_{HCO}, the relationship between X_{HCO} or ε and K_F examined was expressed as:

$$K_F = 0.0129 - 0.0218 X_{HCO} \quad (8)$$

$$K_F = 0.0129 - 0.0181 (1 - \varepsilon) \quad (9)$$

Thus K_F was well connected with X_{HCO} or ε. Rewriting Eq. 6, T_F (min) was expressed as:

$$T_F = (M_m X_S / S_o K_F)^2 \quad (10)$$

Therefore T_F can be evaluated by a function of the amount of matrix layer and mixed weight ratio in the matrix layer.

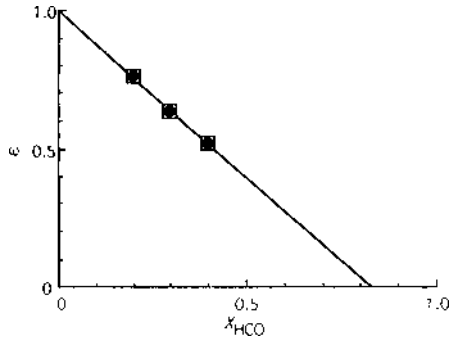

Fig. 1. Relationship between the Mixed Weight Ratio of HCO (X_{HCO}) and the Porosity (ε)

Matrix system: ●, LAC : HCO/INZ; □, INZ : HCO/INZ.

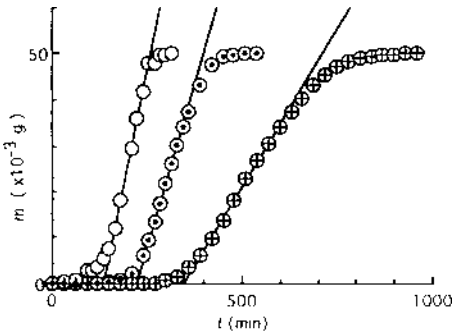

Fig. 2. Release Profiles

Amount of matrix layer: 100 mg. Mixed weight ratio (LAC/HCO): ○, 8/2; ⊙, 7/3; ⊕, 6/4.

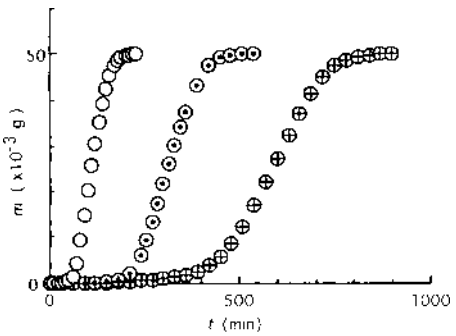

Fig. 3. Release Profiles

Mixed weight ratio: LAC/HCO=7/3. Amount of matrix layer (mg): ○, 50; ⊙, 100; ⊕, 150.

2) Account of the Thickness of the Matrix Layer An example of the release of a drug in the reservoir through the wax matrix is shown in Fig. 3. The actual release process can be expressed by a zero-order kinetic equation, because the exposed surface area was fixed in the preparation process. As measurement was carried out under a sink condition, amount released (m g) was expressed as:

$$m = K_d S_o C_s t \quad (11)$$

where K_d (cm/min) is the release rate constant. K_d is expressed using the permeability coefficient (P_S cm^2/min) and thickness of the matrix layer (L cm) as follows.

$$K_d = P_S / L \quad (12)$$

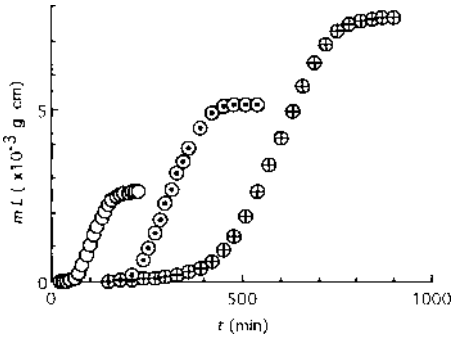

Fig. 4. Release Profiles Taken into Account of the Thickness (L) of Matrix Layer

Mixed weight ratio: LAC/HCO=7/3. Amount of matrix layer (mg): ○, 50; ⊙, 100; ⊕, 150.

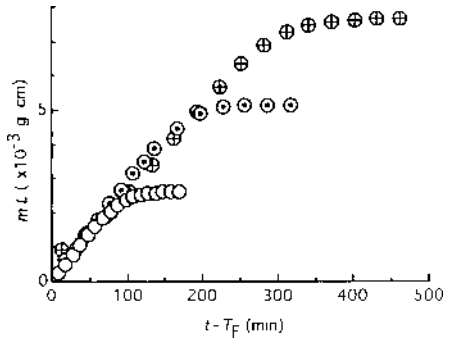

Fig. 5. Release Profiles Taken into Account of the Thickness (L) of Matrix Layer and Lag Time (T_F)

Mixed weight ratio: LAC/HCO=7/3. Amount of matrix layer (mg): ○, 50; ⊙, 100; ⊕, 150.

Hence Eq. 11 could be rewritten as

$$mL=P_S S_o C_s t \tag{13}$$

Following Eq. 13, Fig. 3 was rearranged as Fig. 4. Here, some data were omitted to clarify the figure.

3) Account of the Lag Time The lag time (T_F) was taken into account in Eq. 13 to adjust the starting time of release as follows:

$$mL=P_S S_o C_s (t-T_F) \tag{14}$$

Following Eq. 14, Fig. 4 was rearranged as Fig. 5. Thus the release process of different amounts of matrix layer at a fixed composition (Fig. 3) can be shown as a simple form (Fig. 5) by rewriting Eq. 11 as Eq. 14.

Following Eq. 14, the release of a drug through a wax matrix layer of different composition is shown in Fig. 6. Each release process through the wax matrix layer of a different composition can be shown in simple form.

4) Account of the Porosity The permeability coefficient was expressed as:

$$P_S=D(\varepsilon/\tau) \tag{15}$$

where D (cm^2/min) is the diffusion coefficient of drug and τ is the tortuosity in the matrix layer. It was suggested that the matrix layer is three dimensionally uniform.[6] Also, by plotting $\log(P_S/D)$ against $\log \varepsilon$, it was confirmed in previous papers[1,5] that P_S (cm^2/min) and D (cm^2/min) were approximately connected with ε as follows:

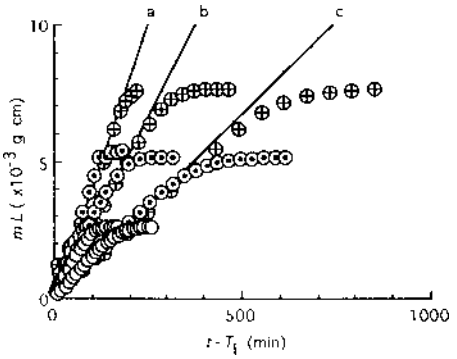

Fig. 6. Release Profiles Taken into Account of the Thickness (L) of Matrix Layer and Lag Time (T_F)

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

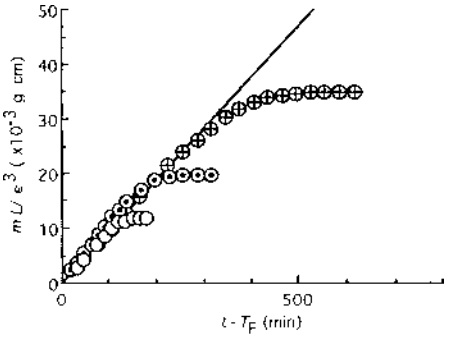

Fig. 7. Release Profiles Taken into Account of the Thickness (L) of Matrix Layer, Lag Time (T_F) and Porosity (ε)

Amount of matrix layer: 100 mg. Mixed weight ratio (LAC/HCO): ○, 8/2; ⊙, 7/3; ⊕, 6/4.

$$P_S/D=\varepsilon^3 \tag{16}$$

So, Eq. 14 could be rewritten as:

$$mL/\varepsilon^3=DS_o C_s (t-T_F) \tag{17}$$

Hence release through the matrix layer of different composition is shown in Fig. 7. By applying Eq. 14, release through the matrix layer of a different amount of this layer at a fixed composition was expressed by a simple form (Fig. 6). By applying Eq. 17, release through a matrix layer of a different composition at a fixed amount of that layer was expressed by a simple form (Fig. 7). Therefore, the release process through the matrix layer of a different amount and composition of that layer can be expressed by Eq. 17 as a generalized equation.

Generalized Expression of the Release Process Considering the properties of the matrix layer, the release process taking into account the thickness, lag time and porosity is expressed by Eq. 17.

As described above, the lag time (T_F min) and release rate constant (K_d cm/min) could be defined by the thickness (L) and porosity (ε), and these features could be defined by the amount and composition of the matrix layer. Therefore, when the amount (M_m) and composition (X_{HCO} or X_S) of the matrix layer were given as a preparation formulation, the lag time, *i.e.*, the starting point of release and the actual release process could be roughly predicted by Eqs. 10 and 17, respectively.

Conclusions

The generalized expression for release from a wax matrix system was examined. Release of drug from reservoir device tablet having a matrix layer prepared from a physical mixture of lactose and hydrogenated castor oil powder was carried out. Release of the drug occurred after a certain lag time, and the process was divided into two stages.

The first stage was the formation process of a water channel. The penetration rate constant obtained was expressed by a simple function of the mixed weight ratio of components in the matrix layer. Hence, the lag time was given by a function of the amount and composition of the 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 the matrix layer. Furthermore, these were well connected with the porosity given as a function of the amount and composition of that layer. So it was revealed that the release rate constant could be predicted from the amount and composition of the matrix layer.

It was therefore suggested that the release profile could be roughly expressed by a generalized equation when the amount and composition of the matrix layer in a reservoir device matrix tablet were given.

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