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

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In order to examine basic properties of release from and through wax matrix layer, reservoir device matrix tablet was prepared from a physical mixture of hydrogenated caster oil and drug that was the same one in the reservoir. Release process could be divided into two stages. The first stage was the formation process of water channel by dissolving the drug in the wax matrix layer, and dissolved drug was released from the matrix layer following the square-root-of-time law equation. Hence, the drug penetration coefficient and tortuosity in the matrix layer were estimated. The second stage was the zero order release process of drug in the reservoir through the wax matrix layer. The release rate constant was calculated from the slope of line. Hence, the drug permeability coefficient and tortuosity were estimated. Fundamentally, tortuosity can not be expressed by some meaningful factors, and is obtained as an experimental result. By preparing wax matrix system from a physical mixture other than melted granule method, it was suggested that the matrix structure was uniform three-dimensionally. As a result, tortuosity could be expressed by a function of porosity, because unrecognized factors such as the surface coverage and thickness of melted wax on the soluble component should not be involved.

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 shown by Higuchi.[2] To control a drug release, it is important to obtain some basic properties of matrix system.

When the matrix system 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 system was prepared from a physical mixture of soluble component and wax, basic properties of matrix system can be estimated by connecting simple factors.

In the previous paper,[1] release property of wax matrix tablet prepared from a physical mixture was examined, and it was suggested that the structure of matrix was uniform three-dimensionally.

Here, it was considered that reservoir type tablet having a fixed surface area may provide more basic release property. Then, a reservoir device wax matrix tablet was prepared from a physical mixture of hydrogenated caster oil and drug that was the same one in the reservoir. Hence basic release property from and through the wax matrix layer was investigated.

Experimental

Materials The samples reported in the previous paper were used.[1,3] These were isoniazid JP (INZ, Yukigousei Yakuhin Kogyo Co.) and hydrogenated caster oil (HCO, Kawaken Fine Chemical Co.). The mean diameter of INZ and HCO are 10.6 and 10.3 μm, respectively.

Preparation of Reservoir Device Tablet Reservoir device tablets having a flat wax matrix layer were prepared. Isoniazid and hydrogenated caster oil were weighed at a given mixed weight ratio of the amount of 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 a 50 mg amount of INZ was accumulated on the physical mixture, the contents were compressed at 1273 kg/cm^2 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 637 kg/cm^2. Prepared reservoir device tablets were abbreviated as $R_{8/2}$, $R_{7/3}$ and $R_{6/4}$ based on the composition of matrix layer. An outline shape of the reservoir device tablet is shown in Fig. 1.

Release Test Release test was carried out following the method described in the previous paper.[1] 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., Led.), and pen recorder (model 3056, Yokogawa Electric Works, Ltd.) was used. Release measurement was carried out in 900 ml of distilled water at a paddle rotation speed of 100 rpm at 37 °C. The released amount was determined by absorbance at 290 nm.

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

Results and Discussion

Thickness of the Matrix Layer Relationship between the amount of matrix layer (M_m) and the thickness of matrix layer (L) was shown in Fig. 2.

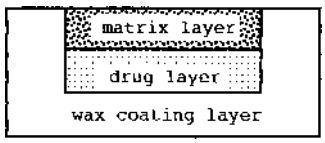

Fig. 1. An Outline Shape of the Reservoir Device Tablet

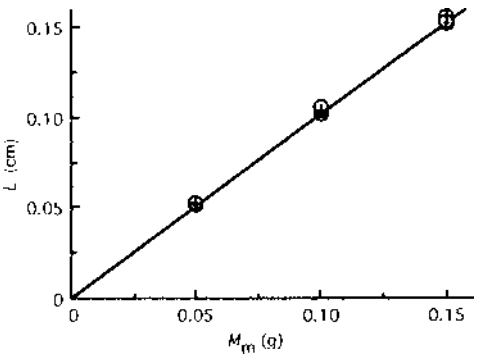

Fig. 2. Relationship between the Amount (M_m) and the Thickness (L) of Matrix Layer

Reservoir device tablet: ○, $R_{8/2}$; ⊙, $R_{7/3}$; ⊕, $R_{6/4}$.

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A fairly good linear relation was appeared independent of the mixed weight ratio in the matrix layer, and was expressed as:

$$L=1.020M_m \quad (1)$$

Then, it was suggested that the compressibility was less affected by the composition within examined.

Porosity of the Matrix Layer Drug should be released from or through the effective void space in the wax matrix layer, and the void space can be expressed as the porosity (ε). The ε value was estimated by the remaining void space after compression and the dissolution of soluble component as follows:

$$\varepsilon_c=1-\{(M_mX_{INZ}/\rho_{INZ})+(M_mX_{HCO}/\rho_{HCO})\}/S_oL \quad (2)$$

$$\varepsilon_{INZ}=M_mX_{INZ}/S_oL\rho_{INZ} \quad (3)$$

$$\varepsilon=\varepsilon_c+\varepsilon_{INZ} \quad (4)$$

where ε_c is the initial porosity calculated from the remaining void space after compression, S_o is the surface area of matrix layer, X and ρ are the mixed weight fraction and true density of the component, respectively. $\rho_{INZ}=1.42$ g/cm^3, and $\rho_{HCO}=1.03$ g/cm^3. ε_{INZ} is the porosity arose from the dissolution of INZ in the matrix layer. Then, ε is expressed by Eq. 4.

After calculating the porosity as mean value, the relationship between X_{HCO} and ε was examined as Fig. 3. A linear relationship was appeared, and was expressed as:

$$\varepsilon=1-1.198X_{HCO} \quad (5)$$

On the other hand, by combining Eqs. 2 and 3, Eq. 4 could be expressed as:

$$\varepsilon=\varepsilon_c+\varepsilon_{INZ}=1-(M_m/S_oL\rho_{HCO})X_{HCO} \quad (4)'$$

The value of $M_m/S_oL\rho_{HCO}$ is 1.212, and was very close to the value appeared in Eq. 5. This relationship can be expected from Fig. 2 where the M_m/L value is a constant within the mixed weight ratio examined in this study (Eq. 1).

The volume fraction of INZ (ϕ) was given as:

$$\phi=(X_{INZ}/\rho_{INZ})/\{(X_{INZ}/\rho_{INZ})+(X_{HCO}/\rho_{HCO})\} \quad (6)$$

Hence the relationship between X_{HCO} and ϕ was examined as Fig. 3, too. The linear relationship obtained was expressed as:

$$\phi=1-1.218X_{HCO} \quad (7)$$

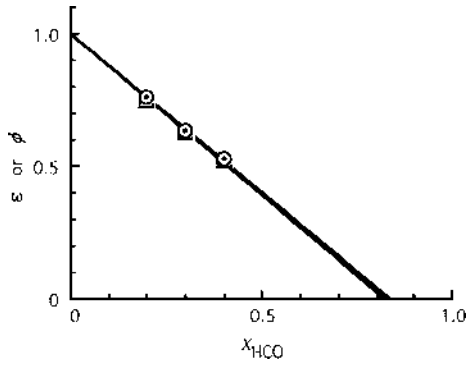

Fig. 3. Relationship between the Mixed Weight Fraction of HCO (X_{HCO}) and the Porosity (ε) or Volume Fraction (ϕ) Available for Release

⊙, ε; □, ϕ.

Generally, the ε_c value is relatively small compared with the ε_{INZ} value, and it was considered that the ε value greatly depends on the mixed weight fraction. So, it may be reasonable that the ϕ value was close to the ε value when the tablet was made by high compression force.

Release Profile of Reservoir Device Tablet Following Higuchi equation,[2] release of INZ from reservoir device tablet was shown in Fig. 4. Observing the applicability, it was thought that release process could be divided into two stages. The first stage followed Higuchi equation, and the second stage deviated from the equation.

Properties of the First Stage in Release Process The first stage showed a linear relationship (Fig. 4), and the released amount per unit surface area ($m/S_o=Q$) should be expressed as follows:

$$m/S_o=K_F\sqrt{t} \quad (8)$$

where K_F is the release rate constant at the first stage, and the K_F values were estimated from the slopes. Release and its simulation curves using Eq. 8 were shown in Fig. 5 as an example. Following the previous paper,[1] the release process was analyzed by using a semilogarithmic equation, and the resultant simulation curve was shown in Fig. 5 at the same time. It was revealed that the semilogarithmic equation could not simulate the entire release process. Higuchi equation, of course, could not simulate the entire process. But, Higuchi equation was thought to be useful to obtain basic properties of release from or through the matrix layer. The other release measurements were treated by the same manners.

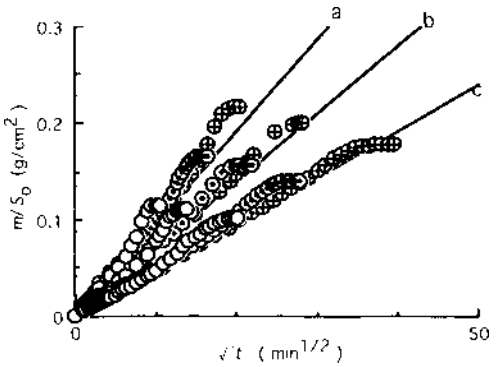

Fig. 4. Higuchi Plot

Reservoir device tablet: a, $R_{8/2}$; b, $R_{7/3}$; c, $R_{6/4}$. Amount of matrix layer (mg): ○, 50; ⊙, 100; ⊕, 150.

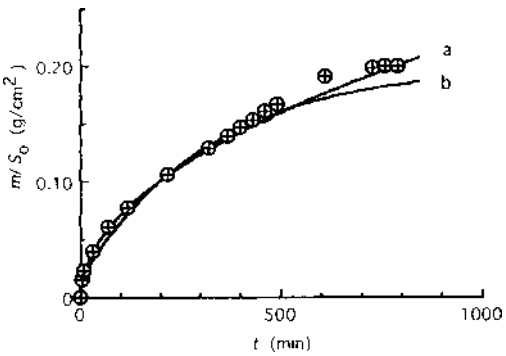

Fig. 5. Release and Simulation Curves for $R_{7/3}$ (150 mg)

a) Simulation using Higuchi equation, b) simulation using a semilogarithmic equation.

According to Higuchi,[2] the released amount from the matrix layer was expressed by the square-root-time law as:

$$Q=\sqrt{P_F(2A-\varepsilon C_S)C_S t} \quad (9)$$

where Q is the amount of drug released after time t per unit exposed area, P_F is the penetration coefficient, A is the total amount of drug in the matrix layer per unit volume and C_S is the solubility of the drug in the permeating fluid. Therefore, K_F is expressed as:

$$K_F=\sqrt{P_F(2A-\varepsilon C_S)C_S} \quad (10)$$

Here, the distribution coefficient was not taken into account, because the drug does not dissolve in the wax but in the water channel. The value of S_o is equal to 0.785 cm^2, C_S is equal to 0.195 g/cm^3, and $A=M_{INZ}/S_oL$ (g/cm^3). Hence the P_F value could be calculated. Also, P_F was expressed as follows:

$$P_F=D(\varepsilon/\tau_F) \quad (11)$$

where D is the diffusion coefficient of the drug in the permeating fluid, and is 6.1×10^{-4} cm^2/min.[1] τ_F is the tortuosity of the water channel estimated in the first stage. Rewriting Eq. 11, P_F can be expressed as a function of the ε/τ_F value.

$$P_F/D=\varepsilon/\tau_F \quad (12)$$

It was considered that the effective release channel should affect the P_F value, and the effective release channel should be affected by the void space, *i.e.*, porosity. When the ε value is equal to 1, the P_F/D value should be equal to 1. Therefore the relationship between ε and P_F/D was examined by plotting the logarithm P_F/D *versus* logarithm ε, and a linear relationship observed was expressed as:

$$\log(P_F/D)=-0.0100+2.978\log\varepsilon \quad (13)$$

$$P_F/D=0.977\varepsilon^{2.978} \quad (14)$$

Hence Eq. 14 could be rewritten as an approximate equation:

$$P_F/D=\varepsilon^3 \quad (15)$$

When the sample was made by high compression force, the ϕ value was close to the ε value as described above. Therefore applicability of the volume fraction for the porosity was examined. So the relationship between P_F/D and ε or ϕ was shown in Fig. 6. The relationship appeared was expressed as:

$$P_F/D=0.999\varepsilon^3 \quad (16)$$

$$P_F/D=1.000\phi^3 \quad (17)$$

This relationship could be easily expected from Fig. 3. The equation suggested that the release was affected by the porosity in every direction, *i.e.*, three dimensionally. Therefore it was thought that the structure of matrix layer should be uniform in every direction. This kind of affecting manner of porosity could be acceptable by the consideration of geometrical structure of matrix layer prepared from a physical mixture. Then, it was suggested that the P_F value could be given and the release process could be roughly expected before experiment for a given matrix system.

The tortuosity (τ_F) was calculated by Eq. 11. Combining Eqs. 12 and 15, τ_F should be given as a function of $1/\varepsilon^2$ or $1/\phi^2$, and this relationship was examined as Fig. 7. A good

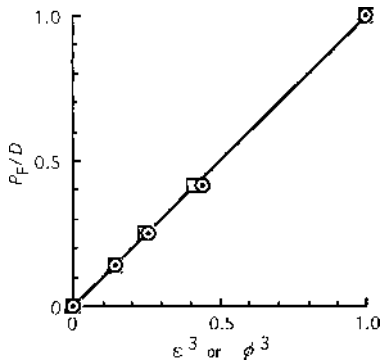

Fig. 6. Relationship between ε^3 or ϕ^3 and P_F/D
⊙, ε^3; □, ϕ^3.

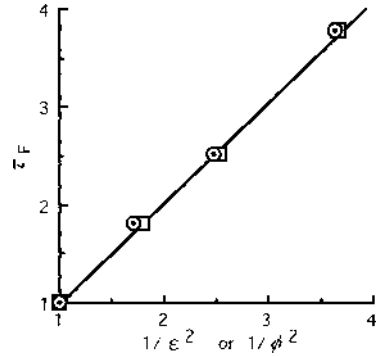

Fig. 7. Relationship between $1/\varepsilon^2$ or $1/\phi^2$ and τ_F
⊙, $1/\varepsilon^2$; □, $1/\phi^2$.

linear relationship expressed as followed was obtained.

$$\tau_F=1.041(1/\varepsilon^2) \quad (18)$$

$$\tau_F==1.034(1/\phi^2) \quad (19)$$

Hence, the P_F value depended on the porosity that defined the three-dimensional matrix structure. According to Higuchi equation, the P_F value should be affected by the porosity and tortuosity. Then, it was suggested that the value of tortuosity was given by $1/\varepsilon^2$ or $1/\phi^2$ when sample was prepared from a physical mixture by high compression force.

It is desirable that the release properties could be expressed by a simple equation or regulation for a practical use as a controlled release formulation. Hence the release rate constant at the first stage, *i.e.*, K_F was examined as Fig. 8. A relationship observed was expressed as:

$$K_F=0.01437-0.02409X_{HCO} \quad (20)$$

The relationship could be rewritten as:

$$K_F=0.01437(1-1.676X_{HCO}) \quad (21)$$

Combining Eqs. 10 and 15, K_F could be expressed as:

$$K_F=\sqrt{D\varepsilon^3(2A-\varepsilon C_S)C_S} \quad (22)$$

In accordance with Eq. 22, Eq. 21 could be rewritten as:

$$K_F=\sqrt{0.0002065(1-1.676X_{HCO})^2} \quad (23)$$

The ε value was expressed as a function of X_{HCO} by Eq. 5. Therefore relationship between $(2A-\varepsilon C_S)C_S$ and X_{HCO} was examined as Fig. 9. Observed linearity was expressed as:

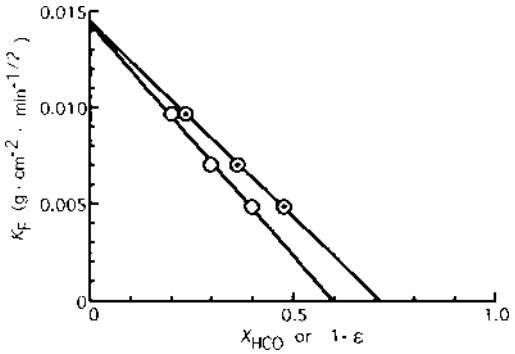

Fig. 8. Relationship between X_{HCO} or $1-\varepsilon$ and K_F
○, X_{HCO}; ⊙, $1-\varepsilon$.

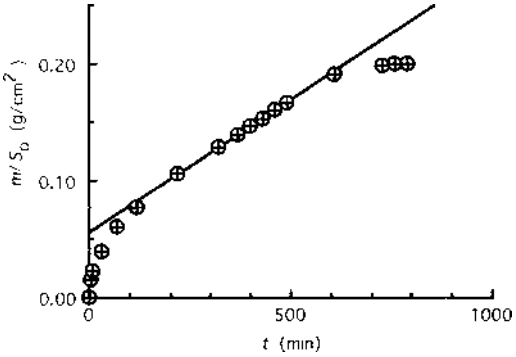

Fig. 10. The Second Release Process
Reservoir device tablet: $R_{7/3}$. Amount of matrix layer: 150 mg.

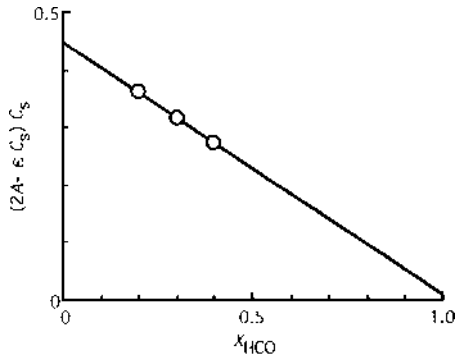

Fig. 9. Relationship between X_{HCO} and $(2A-\varepsilon C_S)C_S$

$$(2A-\varepsilon C_S)C_S=0.4491-0.4418X_{HCO}$$
$$=0.4491(1-0.9837X_{HCO}) \quad (24)$$

When $X_{HCO}=0$, ε is equal to 1. As A is equal to $M_m X_{INZ}/S_o L$, A at $X_{INZ}=1$ is given by $1/1.020S_o$ when Eq. 1 was applied. Then the value of $(2A-C_S)C_S$ was calculated as:

$$(2A-C_S)C_S=\{2\times(1/1.02\times0.785)-0.195\}\times0.195$$
$$=0.4490 \quad (25)$$

So $(2A-\varepsilon C_S)C_S$ within examined could be expressed by an approximated form as:

$$(2A-\varepsilon C_S)C_S=(2A-C_S)C_S(1-X_{HCO}) \quad (26)$$

Also, the value of $D(2A-C_S)C_S$ calculated was equal to 0.0002739. Combining Eqs. 5, 24 and 26, following equation was obtained.

$$D\varepsilon^3(2A-\varepsilon C_S)C_S=0.0002739(1-X_{HCO})(1-1.20X_{HCO})^3 \quad (27)$$

Comparing Eq. 23 with Eq. 27, coefficient of 0.0002065 was about 25% smaller than the $D(2A-C_S)C_S$ value, and the function expressed by X_{HCO} was quite different.

On the other hand, following equation was obtained in Fig. 8.

$$K_F=0.014427-0.02025(1-\varepsilon) \quad (28)$$

Combining Eqs. 5 and 28, following equations were obtained.

$$K_F=0.01442-0.02425X_{HCO} \quad (29)$$

$$K_F=0.01442(1-1.681X_{HCO}) \quad (30)$$

These equations were comparable to Eqs. 20 and 21, respectively. Thus the K_F value was deduced by the measured mean value of ε. Therefore it was considered that the K_F value could be given as a simple function of mixed weight ratio.

Deviation in the value of coefficient could be arose from experimental error or lack of some factors those should be taken into account. Function expressed by X_{HCO} should be solved by experimental treatment (Fig. 3) or mathematical approximation, even though it could not be done in the present time.

In addition to above consideration, it was somewhat strange that $D(2A-\varepsilon C_S)C_S$ was expressed as $D(2A-C_S)C_S$ when $X_{HCO}=0$ and/or $\varepsilon=1$. In this case, $D(2A-\varepsilon C_S)C_S$ should be expressed as $2DAC_S$ at $\varepsilon=1$, because whole drug in the layer dissolves thoroughly. But, it was thought to be difficult to examine the validity in the present time.

Properties of the Second Stage in Release Process The release profile was shown in Fig. 10 as an example, and the second release process was shown by the solid line. The formation process of water channel in the matrix layer was expressed by Higuchi equation. Then drug in the reservoir comes out through the channel, and the process showed a zero-order release as was expressed by a solid line. The zero-order-release linear relationship was expressed as followed:

$$m/S_o=a+K_S t \quad (31)$$

here K_S is an apparent release rate constant and a is a coefficient. Dissolved drug in the reservoir comes out through the wax matrix layer. The concentration in the reservoir was equal to solubility. On the other hand, the concentration in the solution was very low enough to consider being sink condition. Therefore Eq. 31 could be rewritten as:

$$m/S_o=a+K_d C_S t \quad (32)$$

where K_d is the release rate constant in the second stage, and was connected with the permeability coefficient (P_S) as follows:

$$K_d=P_S/L \quad (33)$$

The relationship was examined as shown in Fig. 11. Relatively good linear relationships were observed except $R_{8/2}$. As a reason, it was considered that release occurred continuously from and through the matrix layer having insufficient matrix structure compared with the other matrix layers.

The P_S value was obtained as the slope of straight line.

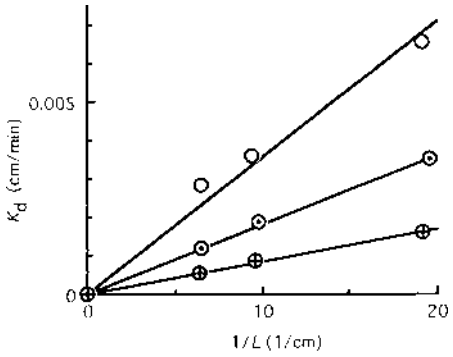

Fig. 11. Estimation of Permeation Coefficient
Reservoir device tablet: ○, $R_{8/2}$; ⊙, $R_{7/3}$; ⊙, $R_{6/4}$.

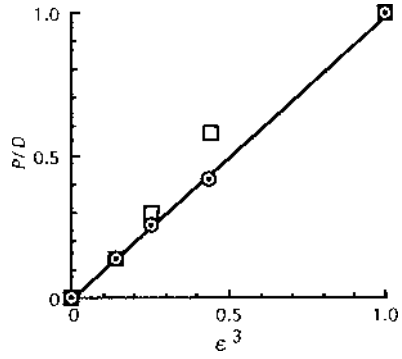

Fig. 12. Relationship between ε^3 and P/D
⊙, P_F/D; □, P_S/D.

Then, relationship between P_S/D and ε^3 was examined as shown in Fig. 12. Here, values obtained in the first stage were shown for a comparison. Even though the P_S/D value for $R_{8/2}$ deviated from the line as expected from above description, they were likely to be connected with the porosity.

Tortuosity of the Matrix Layer Fundamentally, tortuosity can not be expressed by some meaningful factors, and is obtained as an experimental result. When the matrix was prepared with melted wax, tortuosity estimated was extremely large.[4] In this case, it was considered that melted wax spread on the surface of soluble component and structure of matrix became complicate. Hence porosity and factors such as the surface coverage and thickness of melted wax should be taken into account at the same time, and effects of these factors could not be deduced easily. Thus, large tortuosity might be attributed to complicated matrix system that involved unrecognized factors.

When a matrix layer was prepared by compression of a physical mixture, porosity available for release was roughly defined by the compressibility of the mixture and volume fraction of water-soluble component. Hence properties of the matrix layer could be roughly understandable. In the ideal matrix layer, structure should be uniform three-dimensionally for a given porosity, and the matrix layer ought to have own tortuosity in accordance with the structure. In this paper, it was suggested that tortuosity could be expressed by a function of porosity within examined.

The first release process was release from forming water channel, and the second release process was release from established water channel. Difference in tortuosity between the first and second release process was thought to be arisen from difference in property of water channel.

Conclusion

Reservoir device matrix tablet was prepared from a physical mixture of hydrogenated caster oil and drug that was the same one in the reservoir. Then basic properties of release from and through wax matrix layer were examined. Here some complicated factors such as the surface coverage and thickness of wax layer should not be taken into account. Release process could be divided into two stages.

The first stage was the formation process of water channel by dissolving the drug in the wax matrix layer, and the process was explained by the square-root-of-time law equation. The second stage was the zero order release process of drug in the reservoir through the wax matrix layer. Hence, a basic property, *i.e.*, the tortuosity was examined.

The tortuosity in the matrix layer could be expressed by a function of porosity, because unrecognized factors such as the surface coverage and thickness of melted wax on the soluble component should not be involved.

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