

Release from or through a Wax Matrix System. V.¹⁾ Applicability of the Square-Root Time Law Equation for Release from a Wax Matrix Tablet

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To obtain basic and clear release properties, wax matrix tablets were prepared from a physical mixture of drug and wax powder at a fixed mixing ratio. Properties of release from the single flat-faced surface, curved side surface, and/or whole surface of the wax matrix tablet were examined. Then tortuosity and the applicability of Higuchi's square-root time law equation were examined. The Higuchi equation well analyzed the release processes of different release manners. However, the region fitted to the Higuchi equation differed with the release manner. Tortuosity obtained with release from the single flat-faced surface and curved side surface was comparable with that obtained with the release from a reservoir device tablet, whereas tortuosity obtained with release from the whole surface was larger. As the wax matrix tablets were prepared at a fixed mixing ratio, their internal structures should be similar. Therefore changes in the matrix volume or volume fraction with release were examined, and an extra volume where dissolved drug stray becomes large with release time in the case of release from the whole surface. These factors should be taken into account for evaluation of applicability and release properties. Furthermore, the entire release process should be analyzed using a combination of the square-root time law and other suitable equations in accordance with release manner or condition.

Key words wax matrix tablet; physical mixture; release manner; Higuchi equation; tortuosity

The control of drug release is a topic of much interest. Matrix systems are often used as a method to control drug release. Higuchi mathematically showed the drug release properties of matrix systems,²⁾ and numerous investigations have been carried out since then. According to the Higuchi equation, releases occur infinitely without regard to the amount of soluble component. A point or region where the release process begins to deviate from the Higuchi equation should appear when the amount of soluble component is finite, as is usual with the preparation of a matrix system. A matrix system as a controlled drug-release system may be more useful if its entire release process can be analyzed.

Some troublesome situations such as coverage and thickness of wax should be taken into account when a wax matrix system is prepared using the melt method. Therefore a wax matrix system prepared from a physical mixture of a soluble component and wax powder was chosen to obtain the basic release properties.^{3–5)} Applying the Higuchi equation to release in various manners from the wax matrix tablet, release properties and the applicability of the equation or how release processes deviate from the equation were examined.

Experimental

Materials The samples reported in the previous papers were used.^{3–6)} They were isoniazid JP (INZ, Yukigousei Yakuhin Kogyo Co., Japan) and hydrogenated castor oil (HCO, Kawaken Fine Chemical Co., Japan) as a wax powder. The mean diameter of INZ and HCO was 10.6 and 10.3 μm , respectively.

Preparation of Physical Mixture for Wax Matrix The mixed weight ratio of INZ to HCO powder was fixed at 7:3. The appropriate amounts of INZ and HCO powder were physically mixed using an automatic mixer (type S 10, Taiyo Kagaku Kogyo Co., Japan) for 10 min.^{3–5)}

Preparation of Wax Matrix Tablets The amounts of physical mixture used were 0.30, 0.50, and 1.00 g for tablets 10 mm in diameter. The physical mixture was put into a die and compressed at 124.8 MPa with a flat-faced punch (model Clean Press Correct 12 HUK, Kikusui Co., Ltd., Japan). These were used for measurement of release from the whole surface of tablet and are abbreviated as T₃, T₅, and T₁₀ based on the amount of the wax matrix tablet.

Preparation of Wax Matrix Tablets for Release from Single Flat-Faced Surface The wax matrix tablet of 0.50 g (T₅) was placed at the center of a die of 16 mm and an appropriate amount of HCO powder was added. Then the content was compressed at 62.5 MPa for measurement of release from the single flat-faced surface of tablets. These tablets are abbreviated as F₁₀ based on the release surface and tablet diameter.³⁾

Preparation of Wax Matrix Tablets for Release from Curved Side Surface Using the physical mixture of 0.50 g and an appropriate amount of HCO powder, three-layered tablets 10 mm in diameter were prepared with compression force of 124.8 MPa for measurement of release from the curved side surface of wax matrix tablets. The tablets are abbreviated as C₁₀ based on the release surface and tablet diameter.³⁾

Thickness The thickness of the wax matrix tablets was measured using a digital linear gauge (model DG-933, ONO SOKKI).

Release Test A dissolution apparatus (model NTR-VS, Toyama Sangyo Co., Ltd., Japan) coupled to a flow cell set in a double-beam spectrophotometer (model 200-20, Hitachi Industries Co., Japan) via a microtube pump (model MP-3, Tokyo Rikakikai Co., Ltd., Japan) 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 the absorbance at 290 nm.^{3–5)}

In the release test, the sample was enclosed in a mesh-type sinker to prevent it from floating.

Results and Discussion

Release Profile The release of INZ from wax matrix tablets is shown in Fig. 1.

Application of Square-Root Time Law Equation Higuchi proposed a release equation²⁾ in which the released amount per unit surface area is proportional to the square-root time, and is expressed as:

$$Q = \sqrt{D(\varepsilon/\tau)(2A - \varepsilon C_s)C_s t} \quad (1)$$

$$Q = m/S_0 = K_F \sqrt{t} \quad (2)$$

$$K_F = \sqrt{D(\varepsilon/\tau)(2A - \varepsilon C_s)C_s} \quad (3)$$

where m is the released amount after time t , Q is the amount of drug released after time t per unit exposed area, S_0 is the surface area of the matrix layer exposed to the fluid, D is the

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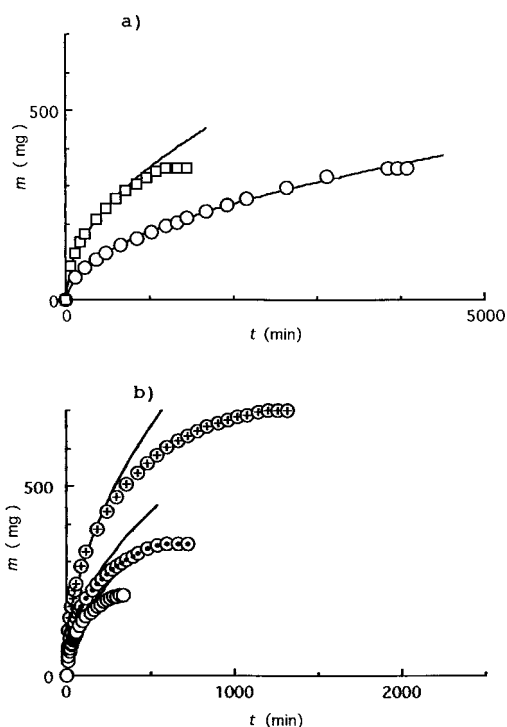


Fig. 1. Release Profile

a) F_{10} and C_{10} : \circ , F_{10} : \square , C_{10} . b) T_3 , T_5 , and T_{10} : \circ , T_3 : \odot , T_5 : \oplus , T_{10} .

diffusion coefficient of the drug in the permeating fluid, A is the total amount of drug per unit volume in the matrix, and C_s is the solubility of the drug in the permeating fluid. ϵ and τ are the available porosity and the tortuosity of the water channel formed in the matrix layer, respectively. K_F is a rate constant included in these factors. Following the equation, $m/S_0 (=Q)$ was plotted against the square-root time, as shown in Fig. 2.

The linear relationship obtained for F_{10} and C_{10} is expressed as:

$$m/S_0 = 0.007500 \text{ (g/cm}^2 \text{ min}^{1/2}) \sqrt{t} \tag{4}$$

On the other hand, the linear relationship obtained for T_3 , T_5 , and T_{10} is expressed as:

$$m/S_0 = 0.006129 \text{ (g/cm}^2 \text{ min}^{1/2}) \sqrt{t} \tag{5}$$

Release in various manners was well summarized by lines. Simulated release curves based on these relationships are shown in Fig. 1 by solid lines. As expected from Fig. 2, simulated values deviated from measured ones after a certain release time.

Tortuosity of the Wax Matrix Changes in the thickness (L) of the matrix tablet with the amount of matrix tablet (M_m) was examined, as shown in Fig. 3. A linear relationship observed is expressed as:

$$L = 1.02M_m \tag{6}$$

The same result was obtained previously.^{4,5} Hence it was thought that compressibility was less affected by the amount within the used region.

Drug should be released from or through the effective void space in the wax matrix, and the void space can be given as the total porosity (ϵ). By geometric measurement, ϵ was given by a summation of the initial porosity (ϵ_c) calculated

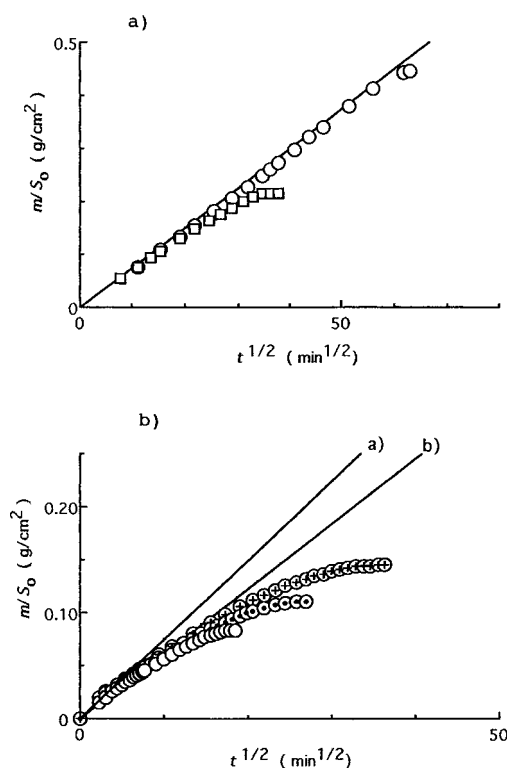


Fig. 2. Higuchi Plot

a) F_{10} and C_{10} : \circ , F_{10} : \square , C_{10} . b) T_3 , T_5 , and T_{10} : \circ , T_3 : \odot , T_5 : \oplus , T_{10} . Line a), F_{10} and C_{10} ; line b), T_3 , T_5 , and T_{10} .

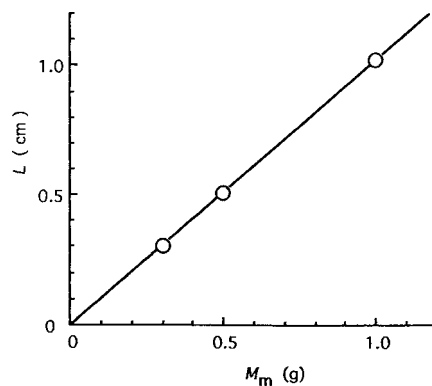


Fig. 3. Relationship between the Thickness (L) and the Amount of Wax Matrix Tablet (M_m)

from the remaining void space after compression and the porosity (ϵ_d) arose from the dissolution of soluble component in the wax matrix. The ϵ_c value is relatively small compared with the ϵ_d value. The A and ϵ values obtained were about 0.875 g/cm^3 and 0.636 , respectively. The values of D and C_s were $0.00061 \text{ (cm}^2/\text{min)}$ and 0.195 (g/ml) , respectively.⁶ Hence the tortuosity obtained for F_{10} and C_{10} was 2.19 , and the value is very close to that (2.50) of the reservoir device tablet.^{4,5} On the other hand, the tortuosity obtained for T_3 , T_5 , and T_{10} was around 3.27 .

The difference in the tortuosity was thought to be due to the release manner. The dissolution and release manner was imaged as shown in Fig. 4. In Fig. 4, v_c is the volume formed by release toward the curved side surface like C_{10} (C-type release), and v_f is the volume formed by release toward the

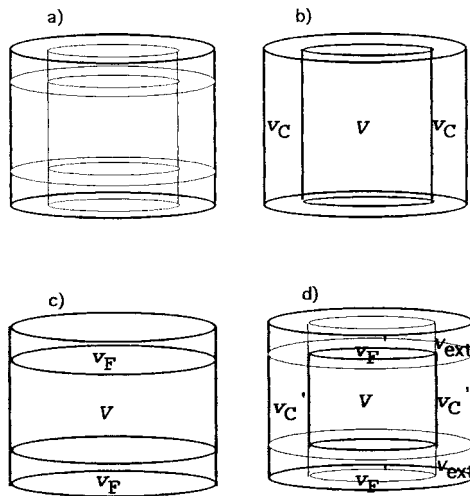


Fig. 4. Illustration of Volumes Formed by Isotropic Dissolution and Release

a) Imaginary division of volume. b) C-type release. c) F-type release. d) Combination of release types.

flat-faced surface like F_{10} (F-type release). Thus the release manner was imaged, in which v'_C is the volume formed by C-type release, v'_F is the volume formed by F-type release, and v_{ext} is the volume remaining after subtraction of v'_C and v'_F from the dissolved volume v for T_3 , T_5 , and T_{10} .

Here it was postulated that the soluble component isotropically dissolves and is released, and the dissolution boundary retracts, as shown in Fig. 4. The release direction was restricted to the direction of the flat-faced or curved side surface for F_{10} or C_{10} , respectively. In those cases the dissolved soluble component came out through the volume v_F or v_C , and the tortuosity was almost the same value in both cases. Therefore the tortuosity might have a similar value when the release direction was restricted to the flat-faced or curved side surfaces. However, when the dissolved soluble component was released through every direction (T_3 , T_5 , and T_{10}), it came out through v_{ext} in addition to v'_F and v'_C . Thus the dissolved component might stray in an extra volume (v_{ext}), and it was assumed that the evaluated tortuosity became large as a result. The matrix structure should be defined by the porosity and is uniform in every direction.³⁾ Therefore it was assumed that the tortuosity differs in accordance with the release manner even if the matrix structures are similar.

Applicability of Square-Root Time Law Equation According to Higuchi,²⁾ drug is released continuously without limitation independent of the drug content in a matrix system. Usually the initial amount of drug M_0 is fixed in the preparation process of a matrix system. Therefore the remaining amount of drug M in the matrix system gradually decreases with release time. When the remaining amount dose not satisfy a derivation condition of the Higuchi equation, the release process should gradually deviate from the equation with the release time. It was assumed that the release process should deviate when the amount of drug in the matrix decreases and reaches the critical remaining amount M_c which can at least fill the matrix layer with the saturated solution. Postulating that the released amount is equal to the dissolved amount in the matrix layer, M_c is equal to $M_0 - m_c$ where m_c is the critical released amount. Then the situation

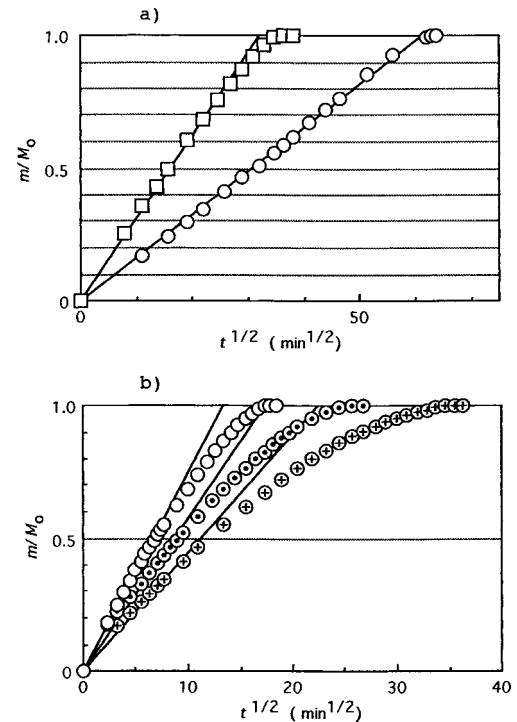


Fig. 5. Ratio of the Released Amount of Drug to the Initial Amount of Drug

a) F_{10} and C_{10} : \circ , F_{10} ; \square , C_{10} . b) T_3 , T_5 , and T_{10} : \circ , T_3 ; \odot , T_5 ; \oplus , T_{10} .

could be approximately expressed as:

$$\{(M_0 - m_c)/M_0\} V_m A = C_s \varepsilon V_m \quad (7)$$

Therefore the ratio of m_c to M_0 is expressed as:

$$m_c/M_0 = (A - \varepsilon C_s)/A \quad (8)$$

The critical release ratio m_c/M_0 can be defined by the mixed weight ratios in the matrix system, because $\varepsilon = 1 - 1.20X_{HCO}^{4,5)}$ and $A = M_0/LS_0 = M_m(1 - X_{HCO})/LS_0$. Then the m_c/M_0 value was evaluated as 0.858. Thus the release process to fit the Higuchi equation until the released amount reaches around m_c . Using the ratios m/M_0 , the aspects are shown in Fig. 5.

1) The Case of F_{10} and C_{10} : In the case of F_{10} , m/M_0 fit the line more than 0.858. On the other hand, m/M_0 deviated from the line before 0.858 in the case of C_{10} . Considering the release direction, the ratio of dissolved area to released area is almost constant for F_{10} , whereas the ratio for C_{10} decreases with the release time and the dissolved drug should be released toward the radiating direction. This might be why m/M_0 began to deviate from the line before the expected point in the case of C_{10} . However, the fit region was roughly postulated by the calculation. Two equations are needed to analyze the entire release process regardless of the release manner or direction.³⁾

2) The Case of T_3 , T_5 , and T_{10} : When the dissolved soluble component is released in every direction as T_3 , T_5 , and T_{10} , M_c should be calculated by considering v_{ext} in addition to v'_F and v'_C (Fig. 4). Each volume requires $(1 - 0.858)M_0$ to be fulfilled with the saturated solution at a certain release time. Then M_c may be around $3(1 - 0.858)M_0 = 0.45M_0$ based on a simple mathematical consideration.

From a different point of view, the dissolving amount in the matrix layer supplied by M is sufficient to satisfy a

derivation condition of the Higuchi equation in the initial time. But it gradually decreases with the decrease in M . When M decreases to less than $0.5M_0$, the matrix layer of v ($=v'_F+v'_C+v_{ext}$) cannot be supplied with a dissolving amount sufficient to maintain steady-state release properties. The dissolving or released amount in the matrix layer becomes lower. As a whole, the limitation of m_c/M_0 to fit the Higuchi equation was thought to be around 0.5.

The initial matrix volume (V_m) decreases to the volume (V) when undissolved soluble component remains. Postulating isotropic dissolution in the wax matrix layer, V_m and V are expressed as follows:

$$V_m = \pi d^2 L / 4 \tag{9}$$

$$V = \pi f^3 d^2 L / 4 \tag{10}$$

where d is the initial diameter and L is the initial thickness of the wax matrix tablet. f is the coefficient brought from isotropic conditions, and d and L decrease to fd and fL , respectively. The dissolved volume (v), volume toward the flat-faced surface (v'_F) and volume toward the curved side surface (v'_C) are expressed as follows:

$$v = V_m - V = (\pi d^2 L / 4)(1 - f^3) \tag{11}$$

$$v'_F = (\pi f^2 d^2 / 4)(1 - f)L = (\pi d^2 L / 4)f^2(1 - f) \tag{12}$$

$$v'_C = (\pi d^2 / 4)fL - (\pi f^2 d^2 / 4)fL = (\pi d^2 L / 4)(f - f^3) \tag{13}$$

Hence the extra volume (v_{ext}) is given as:

$$v_{ext} = v - (v'_F + v'_C) = (\pi d^2 L / 4)(1 - f - f^2 + f^3) \tag{14}$$

The volume fraction of v to V_m is given as:

$$v / V_m (= m / M_0) = (1 - f^3) \tag{15}$$

Therefore the coefficient f can be calculated as:

$$f = (1 - v / V_m)^{1/3} \tag{16}$$

Using the f value, the volume fractions at the dissolved volume v are expressed as:

$$v'_F / V_m = f^2(1 - f) \tag{17}$$

$$v'_C / V_m = (f - f^3) \tag{18}$$

$$v_{ext} / V_m = (1 - f - f^2 + f^3) \tag{19}$$

Changes in the volume fraction with release are shown in Fig. 6.

The volume fraction v_{ext} / V_m changes rapidly compared with other values. To clarify their contribution, the volume fractions to the dissolved volume v are calculated as:

$$v'_F / v = f^2(1 - f) / (1 - f^3) \tag{20}$$

$$v'_C / v = (f - f^3) / (1 - f^3) \tag{21}$$

$$v_{ext} / v = (1 - f - f^2 + f^3) / (1 - f^3) \tag{22}$$

Changes in the volume fractions with release are shown in Fig. 7.

As can be seen in Fig. 7, the volume fraction v_{ext} where the dissolved component may stray begins to become large abruptly when v / V_m reaches around 0.5, whereas v'_F , v'_C , or $v'_F + v'_C$ becomes small abruptly in that region.

Supposing that the above description of a simple mathematical consideration and changes in the geometrically cal-

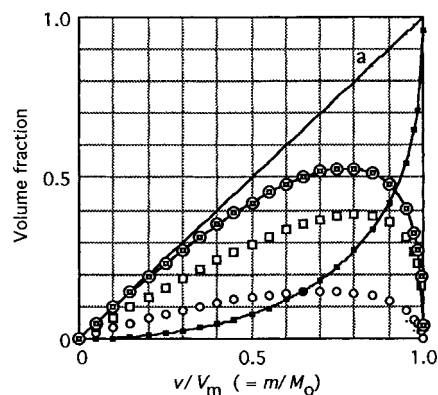


Fig. 6. Change in the Volume Fractions with Release
a, v/V_m ; \square , v'_F/V_m ; \circ , v'_C/V_m ; \odot , $(v'_F+v'_C)/V_m$; \blacksquare , v_{ext}/V_m .

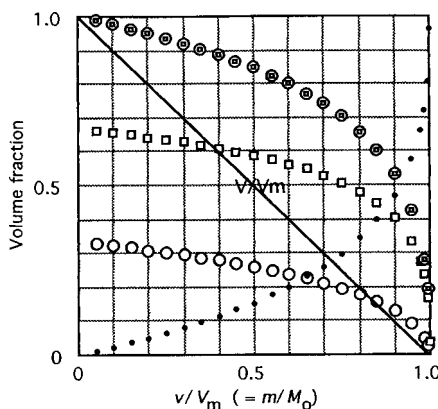


Fig. 7. Change in the Volume Fraction with Release
 \square , v'_F/v ; \circ , v'_C/v ; \odot , $(v'_F+v'_C)/v$; \blacksquare , v_{ext}/v .

culated volume fraction hold true, the release process is expected to deviate from the Higuchi equation when the dissolved or released amount reaches around half of the initial amount. Thus it is considered that at least two release equations are needed to analyze the entire release process, and the connecting point of the equations could be roughly set at $v / V_m = m / M_0 = 0.5$.

Conclusions

Wax matrix tablets were prepared from a physical mixture of drug and wax powder. Release from the tablets occurred in various manners of release, and was analyzed using the Higuchi equation. The applicability of the Higuchi equation was confirmed for various release manners. However, the region fitting the equation differed in accordance with the release manner or direction. The fitting region was broadest when release occurred from the flat-faced surface, whereas it was narrowest when release occurred from the whole surface. Tortuosity of the wax matrix tablets obtained with the release from the flat-faced surface and curved side surface of the tablet was similar to that previously obtained with release from a reservoir device tablet. On the other hand, tortuosity obtained with the release from the whole surface of the tablet was slightly larger than that from the flat-faced and curved side surfaces.

The structures of the wax matrices should be similar to each other, because they were prepared at a fixed mixing

ratio. Examining a simple mathematical calculation and changes in the geometrically calculated volume fraction, the volume (called the extra volume) where the dissolved drug stray became large abruptly with release when release occurred from the whole surface of the tablet. Then it was assumed that the extra volume made the fitting region narrowest and the tortuosity larger for release from the whole surface of the wax matrix tablet. Thus the evaluated release properties differ with the release manner even if the structures of the wax matrix systems were similar.

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