Release from or through a Wax Matrix System. I. Basic Release Properties of the Wax Matrix System

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Release properties from a wax matrix tablet was examined. To obtain basic release properties, the wax matrix tablet was prepared from a physical mixture of drug and wax powder (hydrogenated caster oil) at a fixed mixing ratio. Properties of release from the single flat-faced surface or curved side surface of the wax matrix tablet were examined. The applicability of the square-root time law and of Higuchi equations was confirmed. The release rate constant obtained as g/min$^{1/2}$ changed with the release direction. However, the release rate constant obtained as g/cm^2·min$^{1/2}$ was almost the same. Hence it was suggested that the release property was almost the same and the wax matrix structure was uniform independent of release surface or direction at a fixed mixing ratio. However, these equations could not explain the entire release process. The applicability of a semilogarithmic equation was not as good compared with the square-root time law or Higuchi equation. However, it was revealed that the semilogarithmic equation was available to simulate the entire release process, even though the fit was somewhat poor. Hence it was suggested that the semilogarithmic equation was sufficient to describe the release process. The release rate constant was varied with release direction. However, these release rate constants were expressed by a function of the effective surface area and initial amount, independent of the release direction.

Key words wax matrix tablet; release direction; Higuchi equation; semilogarithmic equation

To control drug release is a topic of much interest. Matrix systems were often used as one method to control drug release. Higuchi mathematically showed the drug release properties of matrix systems,[1] and numerous investigations have been carried out since then. Based on the component, matrix systems can be roughly classified into two types, *i.e.*, polymer and wax matrix systems. Drug release from a polymer matrix is likely to be accompanied by dissolution and/or swelling of matrix layer, and the shape and size of the matrix system varies with release time. Thus polymer matrix systems involve complicated conditions. Compared with polymer matrix systems, wax matrix systems are considered to retain the initial form. To control drug release, it is important to maintain some basic properties of the matrix system. Considering the above difference, the release properties of wax matrix systems should be investigated at first.

When a wax matrix system is prepared from melted granules of soluble component and wax, troublesome factors such as surface coverage and thickness of wax on the soluble component must be considered. On the other hand, when a wax matrix system is prepared using a physical mixture of soluble component and wax, basic release properties can be estimated by connecting their basic properties and simple factors.

Therefore, wax matrix tablets were prepared from a physical mixture, and basic release properties were examined by the measurement of release from the single flat surface or curved side surface of the tablets.

Experimental

Materials Isoniazid JP (INZ, Yukigousei Yakuhin Kogyo Co.) was pulverized to about 7 μm prior to use. Hydrogenated caster oil (HCO, Kawaken Fine Chemical Co.) was used as the matrix substance.[2]

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.).

Preparation of Tablets for Release from One Flat Surface The amount of physical mixture was fixed at 0.50 or 1.20 g for tablets 10 or 16 mm in diameter, respectively. The physical mixture was put into a die and compressed at 1273 kg/cm^2 with flat-faced punch (model clean press correct 12 HUK, Kikusui Co., Ltd.). A tablet was placed at the center of a die of 16 or 20 mm and the appropriate amount of HCO powder was added. Then the content was compressed at 637 kg/cm^2.

Preparation of Tablets for Release from Curved Side Surface Using the appropriate amount of HCO and the physical mixture of 0.50 or 1.20 g, three-layered tablets 10 or 16 mm in diameter were prepared with compression force of 1273 kg/cm^2.

Release Test A 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 microtube pump (model MP-3, Tokyo Rikakikai Co., Ltd.) 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.

Based on the release surface and tablet diameter, samples were abbreviated as F_{10}, C_{10}, F_{16}, and C_{16}.

Results and Discussion

Release Profile Release curves of INZ from wax matrix tablets are shown in Fig. 1. First, equations derived for ordinal tablet were applied.[3]

Release from single flat surface was analyzed using the equation:

$$M/M_o = 1 - K_f t \quad (1)$$

Release from the curved side surface was analyzed by using the equation:

$$(M/M_o)^{1/2} = 1 + K_c t \quad (2)$$

where M_o is the initial amount of drug in the tablet, M is the amount of drug remaining in the tablet. K_f or K_c is a rate constant in the respective equations. Applying these equations, it was revealed that they were not useful in dealing with matrix systems. Therefore the release process was treated as described below.

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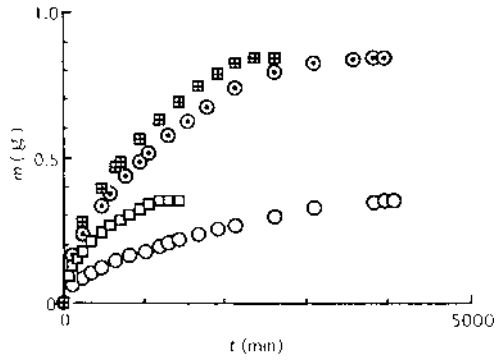

Fig. 1. Drug Release Curves
○, F_{10}; □, C_{10}; ⊙, F_{16}; ⊞, C_{16}.

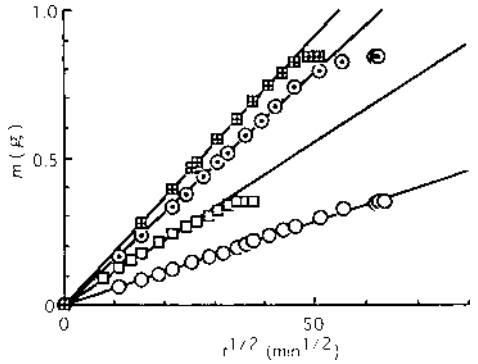

Fig. 2. Square-Root Time Law Equation Plot
○, F_{10}; □, C_{10}; ⊙, F_{16}; ⊞, C_{16}.

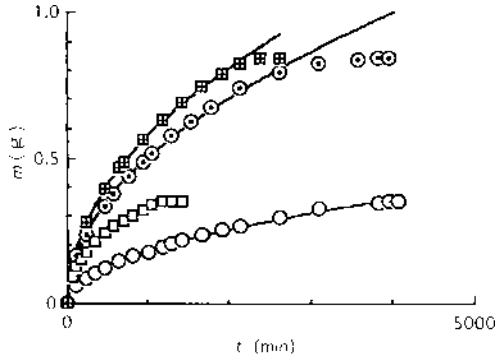

Fig. 3. Release and Simulation Curves
○, F_{10}; □, C_{10}; ⊙, F_{16}; ⊞, C_{16}. —, simulation by the square-root time law equation.

Application of Square-Root Time Law Equation The square-root time law equation was expressed as:

$$m=K_{sqr}\sqrt{t} \tag{3}$$

where m is the released amount, and K_{sqr} is a release rate constant. Treatment using the equation is shown in Fig. 2. Fairly good linear relations were observed, and the K_{sqr} value was obtained by the slope. The validity of estimation was examined by simulation of the release process, as shown in Fig. 3. The values simulated coincided well with those measured up to around 85% of the initial drug amount. The K_{sqr} value (g/min$^{1/2}$) was 0.00567, 0.01106, 0.01575, and 0.01809 for F_{10}, C_{10}, F_{16}, and C_{16}, respectively. Thus the K_{sqr} value of release from the curved surface was larger than that from the flat surface.

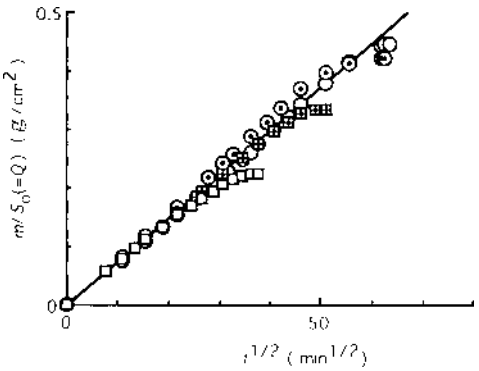

Fig. 4. Higuchi Equation Plot
○, F_{10}; □, C_{10}; ⊙, F_{16}; ⊞, C_{16}.

Application of the Higuchi Equation Higuchi proposed a release equation[1c] in which the released amount per unit surface area is proportional to square-root time, and expressed as:

$$Q=\sqrt{D(\varepsilon/\tau)(2A-\varepsilon C_S)C_S t} \tag{4}$$

$$Q=m/S_o=K_H\sqrt{t} \tag{5}$$

where Q is the amount of drug released after time t per unit of exposed area, S_o is the surface area of the matrix layer exposed to the fluid, D is the diffusion coefficient of the drug in the permeating fluid, ε is the available porosity, τ is the tortuosity of the water channel, A is the total amount of drug in the matrix per unit volume, and C_S is the solubility of the drug in the permeating fluid. Following the equation, m/S_o ($=Q$) was plotted against the square-root time, as shown in Fig. 4.

The Q-values were close to each other, and these release processes were expressed by a linear relationship. The slope of Q (g/cm^2) *versus* square-root time was about 0.0075 g/cm$^2\cdot$min$^{1/2}$. Compressibility was thought to be almost the same, and the A and ε values were mostly defined by the mixed weight ratio. The A and ε values were about 0.86 g/cm^3 and 0.64, respectively. Also, release rate depends on release area. Therefore the result was considered to be acceptable, and it may be concluded that the wax matrix structure was uniform in every direction, and the release property was almost the same, independent of release surface or direction at a fixed mixing ratio.

Application of Semilogarithmic Equation The square-root time law and Higuchi equations could not simulate the entire release process, as shown in Fig. 3. Considering the first-order model, a semilogarithmic equation was applied.

$$\ln(M/M_o)=-K_{Ln}t \tag{6}$$

where K_{Ln} is an apparent release rate constant. Following the equation, $\ln(M/M_o)$ *versus* t plot is shown in Fig. 5. In this case, the linearity of the semilogarithmic equation was not as good compared with that of the square-root time law or Higuchi equation. However, each release process was simulated by using the apparent release rate constant, *i.e.*, K_{Ln}, to examine whether the equation could trace the outline of release process. Simulation curves are shown with measured release curves in Fig. 6.

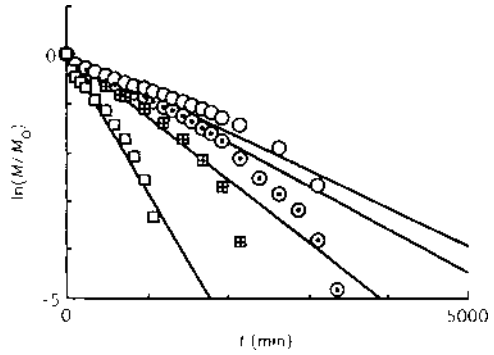

Fig. 5. Semilogarithmic Equation Plot
○, F_{10}; □, C_{10}; ⊙, F_{16}; ⊞, C_{16}.

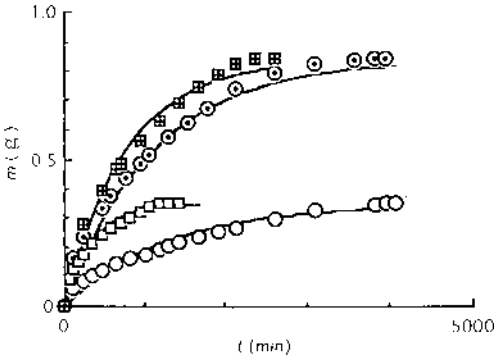

Fig. 6. Release and Simulation Curves
○, F_{10}; □, C_{10}; ⊙, F_{16}; ⊞, C_{16}. —, simulation by the semilogarithmic equation.

Simulated values coincided fairly well with those measured. Hence it was thought that the deviation in linear relationship in Fig. 5 resulted from mathematical treatments. The K_{Ln} values obtained were 0.000796, 0.0028185, 0.00089145, and 0.0012832 (1/min) for F_{10}, C_{10}, F_{16}, and C_{16}, respectively. Thus the K_{Ln} value for a flat-faced surface was smaller than that for a curved side surface.

Generally, dissolution or release rate depends on the effective surface area. Since the release rates were almost the same in Fig. 4, estimation of the release rate constant using the M/M_o value should be affected by the initial amount. Therefore the influence of the effective surface area (εS_o) and initial amount on the K_{Ln} value was examined, as shown in Fig. 7.

A fairly good relationship appeared between the K_{Ln} and $\varepsilon S_o/M_o$ values, and was expressed as:

$$K_{Ln}=-0.0013392+0.0014325(\varepsilon S_o/M_o) \quad (7)$$

$$K_{Ln}=0.001432(\varepsilon S_o/M_o-0.935) \quad (8)$$

however, the meaning of the value of 0.935 is not clear at the present time. At the same time, a fairly good relationship appeared between the square-root K_{Ln} value and the $\varepsilon S_o/M_o$ values and was expressed as:

$$K_{Ln}^{1/2}=0.018767(\varepsilon S_o/M_o) \quad (9)$$

$$K_{Ln}^{1/2}\ (1/\text{min}^{1/2})=K\ (\text{g/cm}^2\cdot\text{min}^{1/2})\ (\varepsilon S_o/M_o) \quad (10)$$

or

$$K_{Ln}=0.00035220(\varepsilon S_o/M_o)^2 \quad (11)$$

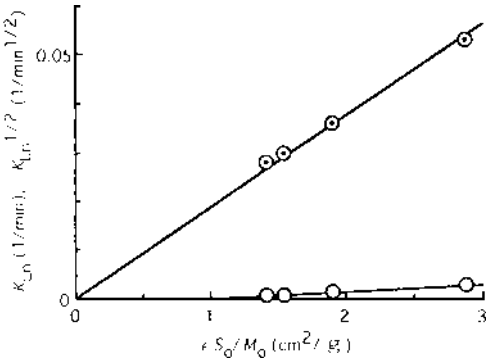

Fig. 7. Influence of the Effective Surface Area and Initial Amount on the Release Rate Constant
○, K_{Ln}; ⊙, $K_{Ln}^{1/2}$.

$$K_{Ln}\ (1/\text{min})=K^2\ (\text{g}^2/\text{cm}^4\cdot\text{min})\ (\varepsilon S_o/M_o)^2 \quad (12)$$

where K is a proportional constant. It was considered that good linearity appeared in the square-root K_{Ln} corresponding with the Higuchi equation. This linear relationship also suggested that the wax matrix structure was uniform in every direction, and the release property was almost the same independent of release direction, coinciding with the results shown in Fig. 4. As K_{Ln} could be expressed by Eq. 12, K may include physical properties such as solubility, diffusion coefficient, and thickness.

Conclusions

After applying various equations, the applicability of the square-root time law and Higuchi equations, properties of release from a single flat-face surface or curved side surface from matrix tablets were confirmed. The release rate constant obtained as $g/min^{1/2}$ changed with size and release direction. However, the release rate constant obtained as $g/cm^2\cdot min^{1/2}$, *i.e.*, release from the unit surface area, was almost the same for each. Hence it was suggested that the release property was almost the same independent of release surface or direction at a fixed mixing ratio. However, these equations could not simulate the entire release process.

When a semilogarithmic equation was applied, linearity was not as good compared with the square-root time law or Higuchi equation. However, the semilogarithmic equation could simulate the entire release process, even though the fit was somewhat poor. Thus it is suggested that the semilogarithmic equation is sufficient to treat the release process. Release rate constants estimated varied with release surface or direction. However, these release rate constants were given by a function of a proportional constant, *i.e.*, the effective surface area and initial amount independent of the release direction. Therefore it is suggested that the wax matrix structure was uniform in every direction and the release property was almost the same, independent of release direction.

These release tests were carried out with relatively small amounts of drug compared with its solubility, and the semilogarithmic equation was revealed to be useful. Generally, the dissolution equation differs in accordance with the amount of drug. Thus the appropriate equation to analyze or simulate the release process may differ based on the amount of drug and/or matrix system.

References

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