Release from or through a Wax Matrix System. VI.[1] Analysis and Prediction of the Entire Release Process of the Wax Matrix Tablet

Yorinobu YONEZAWA,* Sumio ISHIDA, and Hisakazu SUNADA

Faculty of Pharmacy, Meijo University; Yagotoyama, Tempaku-ku, Nagoya 468–8503, Japan.
Received January 28, 2005; accepted April 25, 2005

Analysis of the entire release process of the wax matrix tablet was examined. Wax matrix tablet was prepared from a physical mixture of drug and wax powder to obtain basic or clear release properties. The release process began to deviate from Higuchi equation when the released amount reached at around the half of the initial drug amount. Simulated release amount increase infinitely when the Higuchi equation was applied. Then, the Higuchi equation was modified to estimate the release process of the wax matrix tablet. The modified Higuchi equation was named as the H-my equation. Release process was well treated by the H-my equation. Release process simulated by the H-my equation fitted well with the measured entire release process. Also, release properties from and through wax matrix well coincident each other. Furthermore, it is possible to predict an optional release process when the amount of matrix and composition of matrix system were defined.

Key words Higuchi equation; modified Higuchi equation; entire release process; optional release process; wax matrix tablet

To control drug release 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] According to Higuchi equation, releases occur infinitely when release process was simulated. Matrix system as a controlled drug release system may be more useful if its entire release process could be analyzed. Therefore, it is necessary to modify the Higuchi equation or derive another equation to estimate the entire release process.

The amount or concentration of drug in the matrix tablet gradually decrease with release time, and release process deviate from the Higuchi equation.[1] So the Higuchi equation should be corrected by using the released amount. The modified Higuchi equation was named as the H-my equation. 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.[5—8] Therefore, applicability or validity of the H-my equation was examined by using the wax matrix tablets prepared from a physical mixture.

Experimental

Materials The samples reported in the previous papers were used.[1,5—9] These were isoniazid JP (INZ, Yukigousei Yakuhin Kogyo Co.) and hydrogenated caster oil (HCO, K_3wax®, mp 84—88 °C, Kawaken Fine Chemical Co.) as a wax powder. The mean diameter of INZ and HCO are 10.6 and 10.3 μm, respectively.

Preparation of Physical Mixture for Wax Matrix Isoniazid and hydrogenated castor oil powder were weighed at a given mixed weight ratio, and were physically mixed together by an automatic mixer (model S 10, Taiyo Kagaku Kogyo Co.) for 10 min.

Preparation of Wax Matrix Tablets The amounts of physical mixture used were 0.300, 0.500, 0.750 and 1.000 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.).

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.) coupled to a flow cell set in a double-beam spectrophotometer (model 200-20, Hitachi Industries 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 the absorbance at 290 nm.[1]

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

Results and Discussion

Release Profile The releases of INZ from wax matrix tablets are shown in Fig. 1.

Application of Higuchi Equation Higuchi proposed a release equation[4] in which the released amount per unit surface area is proportional to square-root time, and expressed as:

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

$$Q=m/S_o=K_H\sqrt{t} \quad (2)$$

where Q is the amount of drug released after time t per unit of exposed area, m is the amount of drug released after time t, S_o is the surface area of the matrix exposed to the fluid, D is the diffusion coefficient of the drug in the permeating fluid, ε is the porosity available as a water channel, τ is the tortuosity of the water channel, A is the initial amount of drug in the matrix per unit volume, and C_s is the solubility of the drug in the permeating fluid. K_H is a summarized release rate constant.

Drug should be released from the effective void space in the matrix, and the void space can be expressed as the porosity ε. Ordinary, the ε value was estimated by the summation of the remaining void space after compression and the space made by the dissolution of soluble component.[5,6] The thickness of the wax matrix tablet (L) was expressed as $L=1.02M_m$ within the examined amount of wax matrix (M_m).[1,5,6] Therefore, ε and A values are mostly defined by the amount of wax matrix and mixed weight ratio of the drug.

Following the equation, the released amount per unit surface area m/S_o ($=Q$) is plotted against the square-root time as shown in Fig. 2 as an example.

* To whom correspondence should be addressed. e-mail: yzw@ccmfs.meijo-u.ac.jp

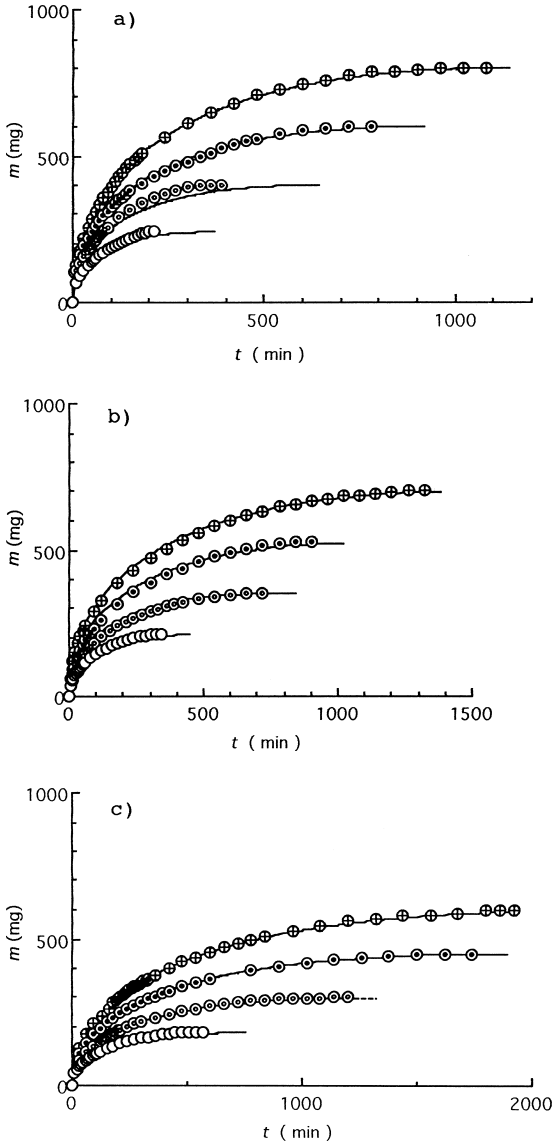

Fig. 1. Release and Simulation Curves for Wax Matrix Tablet

—, simulated by using the H-my equation. Mixed weight ratio ($X_{INZ}:X_{HCO}$): a), 8 : 2; b), 7 : 3; c), 6 : 4. Amount of matrix tablet (mg): ○, 300; ◎, 500; ⦿, 750; ⊕, 1000.

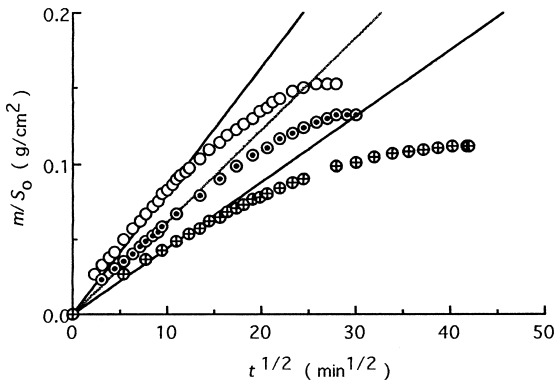

Fig. 2. Higuchi Plots for Wax Matrix Tablet of 750 mg

Mixed weight ratio ($X_{INZ}:X_{HCO}$); ○, 8 : 2; ⦿, 7 : 3; ⊕, 6 : 4.

The release process began to deviate from the Higuchi equation at a certain region. Applicability of the square-root time law equation was examined by using the ratio of released amount to the initial amount of drug (M_o) expressed as m/M_o, and it was revealed that the release process began to deviate from the equation around $m/M_o \fallingdotseq M_o/2$.[1] Therefore, the equation can not analyze the entire release process.

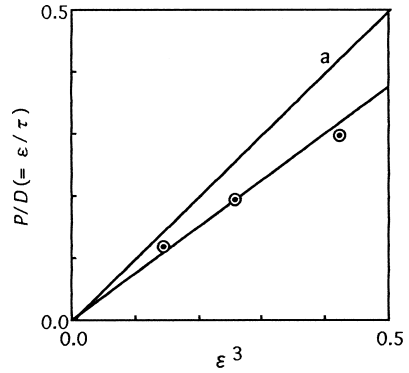

Fig. 3. Relationship between ε^3 and P/D Estimated by Higuchi Equation

Line a, $P/D=\varepsilon^3$.

Using the penetration coefficient P ($=D(\varepsilon/\tau)$), Eq. 1 was expressed as[1,5]:

$$Q=\sqrt{P(2A-\varepsilon C_s)C_s t} \tag{3}$$

The P value was calculated from K_H, and the relationship between P/D and ε^3 was show in Fig. 3. A good linearity was observed at the initial release process, and following relationship was obtained.

$$P/D=0.750\varepsilon^3 \tag{4}$$

In the ideal matrix, matrix structure should be uniform three-dimensionally for given porosity, and the matrix ought to have own tortuosity in accordance with the structure.[5—8] In this case, following relationship was obtained when it was examined with reservoir device tablet.[5,6]

$$P/D=\varepsilon^3 \tag{5}$$

and

$$\tau=\varepsilon^{-2} \tag{6}$$

Thus the same matrix showed different properties. It was supposed that the amount of drug decrease with release time, and the release process gradually deviate from the Higuchi equation.[1] Also the deviation brought the property expressed by Eq. 4.

Modification of Higuchi Equation An equation available the entire release process was derived. The remaining amount of drug in the matrix gradually decrease, and is insufficient to satisfy a derivation condition of Higuchi equation. Hence, Higuchi equation was modified by taking into account of the released amount.

For the common case of $\varepsilon C_s \ll A$ in the initial state,[3] relationship expressed by Eq. 1 simplifies to

$$Q=\sqrt{2PAC_s}\sqrt{t} \tag{7}$$

and

$$dQ/dt=\sqrt{PAC_s/2t} \tag{8}$$

so

$$dm/dt = S_o\sqrt{PAC_s/2t} \quad (9)$$

The concentration of drug in the matrix is expressed as:

$$A = M_o/V_m \quad (10)$$

here, M_o is the initial amount of drug in the matrix and V_m is the matrix volume. The concentration of drug in the matrix can not keep the initial constant value throughout the release process, and the concentration in the matrix is corrected by subtracting the release amount as follows.

$$A - m/V_m = (M_o - m)/V_m \quad (11)$$

Then, Eq. 9 was rewritten as

$$dm/dt = S_o\sqrt{P(M_o - m)C_s/2V_m t} \quad (12)$$

When the amount remaining in the matrix M $(=M_o - m)$ was used, Eq. 12 could be expressed as

$$-dM/dt = S_o\sqrt{PMC_s/2V_m t} \quad (13)$$

or

$$-M^{-1/2}dM = S_o\sqrt{PC_s/2V_m}\, t^{-1/2}dt \quad (14)$$

Integrating Eq. 14 and rearrangement, the following equation is obtained.

$$\sqrt{M/M_o} = 1 - S_o\sqrt{PC_s t/2V_m M_o} \quad (15)$$

Following Eq. 15, the release process shown in Fig. 1 were treated and $\sqrt{M/M_o}$ *versus* $S_o\sqrt{t/V_m M_o}$ plot are shown in Fig. 4. Hence, the release process should be simulated as:

$$m = M_o[1 - \{1 - \sqrt{PC_s/2}\, S_o\sqrt{t/V_m M_o}\}^2] \quad (16)$$

It appeared fairly good linearity, and the slope was estimated. The release processes are simulated by use of the slope and Eq. 16. The simulated release process was shown by a solid in Fig. 1.

Applicability of Eq. 16 is fairly good for the entire release process while the release amount simulated by Higuchi equation increase infinitely.[1,7] Here, the modified Higuchi equation was named as the H-my equation. According to the H-my equation, the penetration coefficient can be calculated from the slope $(=\sqrt{PC_s/2})$ shown in Fig. 4, and the relationship between P/D and ε^3 is show in Fig. 5. A good linearity was observed, and it was revealed that P/D value is approximately equal to ε^3. Hence, release properties from or through wax matrix well coincident each other. Thus the same matrix showed the same properties by applying the H-my equation.

Previously Higuchi equation was treated as $C_s \ll A$ in the initial state. Here, the ratio of εC_s to $2A$ was examined, because εC_s is smaller than C_s. The thickness L and porosity ε were given by the amount of matrix M_m and mixed weight ratio, respectively.[5,6]

$$L = 1.02M_m \quad (17)$$

$$\varepsilon = 1 - 1.20X_{Hco} \quad (18)$$

and

$$2A = 2M_m X_{INZ}/1.02M_m S_F = 2X_{INZ}/1.02S_F \quad (19)$$

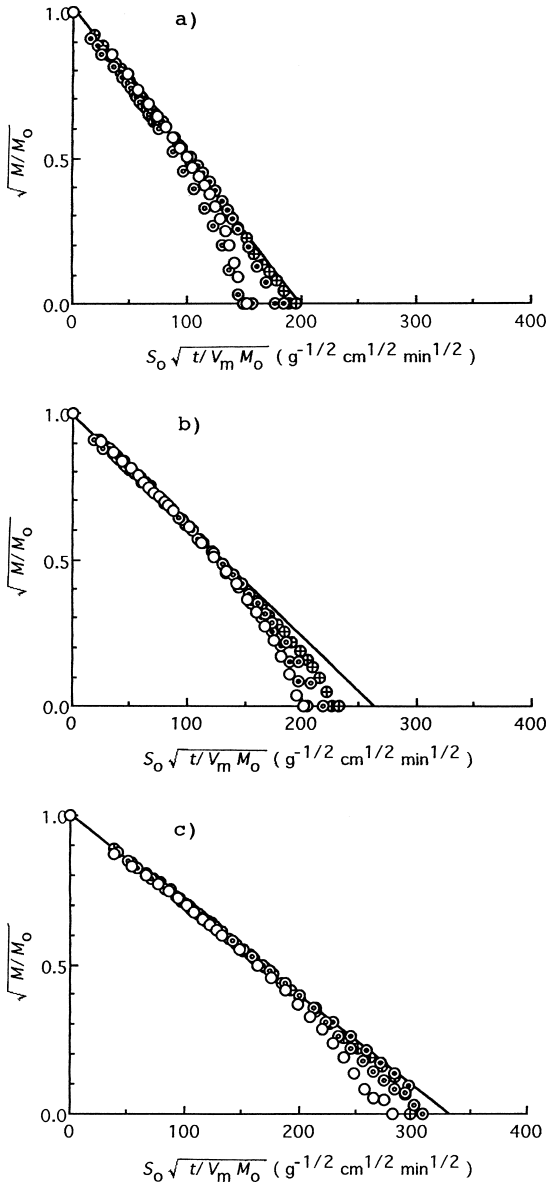

Fig. 4. The H-my Equation Plot

Mixed weight ratio (X_{INZ} : X_{HCO}): a), 8 : 2; b), 7 : 3; c), 6 : 4. Amount of matrix tablet (mg): ○, 300; ◎, 500; ⦿, 750; ⊕, 1000.

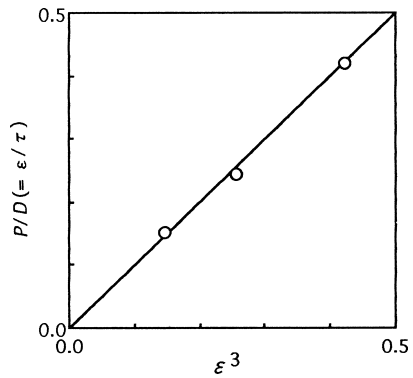

Fig. 5. Relationship between ε^3 and P/D Estimated by the H-my Equation

$$\varepsilon C_s = \{1 - 1.20(1 - X_{INZ})\}C_s < X_{INZ}C_s \quad (20)$$

here X_{Hco} is the mixed weight ratio of HCO, X_{INZ} is the mixed weight ratio of isoniazid and S_F is the single flat-face surface

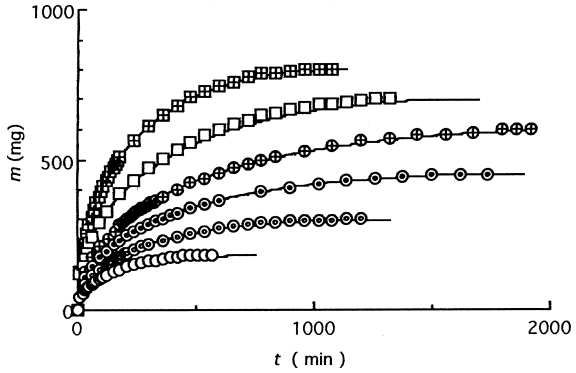

Fig. 6. Release and Simulation Curves for Prediction of Optional Release Process by the H-my Equation

Amount of matrix (mg) and mixed weight ratio ($X_{INZ}:X_{HCO}$): ⊞, 1000, 8 : 2; □, 1000, 7 : 3; ⊕, 1000, 6 : 4; ⦿, 750, 6 : 4; ◎, 500, 6 : 4; ○, 300, 6 : 4.

area (0.785 cm^2), respectively. The ε value is a little smaller than X_{INZ}. The ratio $\varepsilon C_s/2A$ is expressed as:

$$\varepsilon C_s/2A < 1.02 S_F C_s/2 = 0.078 \quad (21)$$

So it was reasonable to treat as $\varepsilon C_s \ll A$.

Prediction of the Entire Release Process for Wax Matrix Tablet by the H-my Equation The release and simulated processes are summarized in Fig. 6. The simulated release processes well coincide with measured release process within examined region. As p value could be estimated by using ε value, the optional release process could be predicted by the H-my equation when the amount of matrix and mixed weight ratio of component are defined. In the other word, release process could be designed. Also it was supposed that the available region could be expanded by farther examination.

Conclusions

Wax matrix tablet was prepared from a physical mixture of drug and wax powder to obtain basic release properties. Applicability of Higuchi equation and analytical method available for the entire release process of wax matrix tablet were examined. The release process began to deviate from Higuchi equation when the released amount reached at around the half of the initial drug amount. Higuchi equation can not analyze or simulate the entire release process of wax matrix tablet. Using the release amount, Higuchi equation was modified. It was revealed that the modified Higuchi equation named as the H-my equation is useful to analyze or simulate the entire release process of wax matrix tablet. So it is possible to predict an optional entire release process when the amount of matrix and composition were defined.

References

1) Yonezawa Y., Ishida S., Sunada H., *Chem. Pharm. Bull.*, **51**, 904—908 (2003).
2) Higuchi T., *J. Soc. Cosmetic Chemists*, **11**, 85—97 (1960).
3) Higuchi T., *J. Pharm. Sci.*, **50**, 874—875 (1961).
4) Higuchi T., *J. Pharm. Sci.*, **52**, 1145—1149 (1963).
5) Yonezawa Y., Ishida S., Suzuki S., Sunada H., *Chem. Pharm. Bull.*, **50**, 220—224 (2002).
6) Yonezawa Y., Ishida S., Suzuki S., Sunada H., *Chem. Pharm. Bull.*, **50**, 814—817 (2002).
7) Yonezawa Y., Ishida S., Sunada H., *Chem. Pharm. Bull.*, **49**, 1448—1451 (2001).
8) Yonezawa Y., Ishida S., Suzuki S., Sunada H., *Chem. Pharm. Bull.*, **50**, 1219—1222 (2002).
9) Ishino R., Sunada H., *Chem. Pharm. Bull.*, **41**, 196—200 (1993).