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Influence of Drug Solubility and Matrix Structure on Release Rate of Drugs from Wax Matrix Tablets

Ryuzo ISHINO*,[a] and Hisakazu SUNADA[b]

Pharmaceutics Research Laboratory, Tanabe Seiyaku Co., Ltd.,[a] 16–89, Kashima 3-chome, Yodogawa-ku, Osaka 532, Japan and Faculty of Pharmacy, Meijo University,[b] 150, Yagotoyama, Tempaku-ku, Nagoya 468, Japan.

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In order to elucidate individually the influence of drug solubility and the matrix structure on the drug release rate from a wax matrix tablet, the intrinsic dissolution rates of drugs and the release rates of several matrix tablets consisting of various proportions of drug and hydrogenated castor oil were measured for five drugs differing in solubility. From the theoretical modification of Higuchi's equation, the boundary retreat rate of the matrix tablet was expressed with two parameters: one parameter was a constant consisting of three physical quantities (diffusivity, solubility and density), and the other was the tortuosity representing the matrix structure. As the constant term in the modified Higuchi's equation was related to the intrinsic dissolution rate constant for every drug, it was found to be an index of the drug solubility in the matrix system. From this study, therefore, it is clear that the boundary retreat rate constant, namely, the drug release rate constant from the matrix tablet, was in proportion to the solubility and in inverse proportion to the square root of tortuosity. The relation between the tortuosity and the void space (porosity) was well expressed by the proposed equation derived on the basis of the free volume theory (H. Yasuda and C. E. Lamaze, *J. Polymer Sci., Part A-2*, 9, 1537 (1971)). It was found that the tortuosity formed in the matrix tablets varied with the drug species even though the porosity was the same, and also the dependency of tortuosity on porosity varied. Further, it was determined that the dependency of tortuosity on porosity could be controlled by the addition of other materials.

Keywords wax matrix tablet; drug solubility; internal structure; drug release; porosity; tortuosity

Introduction

Concerning the mechanism of drug release from a granular matrix system, Higuchi was the first to theoretically treat the matrix model and to show that the amount of a drug released per unit surface area was proportional to the square root of the time.[1] His equation implies that the solubility of the drug and the structure of the matrix system in terms porosity and tortuosity can influence the dissolution rate. It was reported that the drug release rate from a matrix tablet varies depending upon many factors, such as the amount and type of the matrix material and additives, crystal size and preparation method.[2] It is considered that these factors should affect either the matrix structure in terms of porosity and tortuosity or the wettability against the dissolution fluid penetrating into the matrix.

The first objective of the present study is to evaluate individually the effect of the solubility of the drug and the matrix structure on the drug release rate. The second objective is to examine the relationship between porosity and tortuosity representing the matrix structure. In the previous paper,[3] it was demonstrated that the void space which was newly created during dissolution could act as the water channel for drug release, although the void space which originally existed between particles could not be utilized as an effective water channel, when isoniazid was released from a wax matrix tablet incorporated into hydrogenated castor oil exhibiting adhesion wetting. We applied the modified Higuchi equation, which was proposed in a previous paper, to elucidate a reasonable expression for the effect of solubility and structure on the dissolution rate.

Theoretical Analysis

For a leaching type release mechanism from the planar matrix system, the following diffusion equation was proposed by Higuchi[1]:

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

where Q is the amount of drug released per unit surface area, D is the diffusion coefficient of the drug in the permeation fluid, ε is the porosity of the matrix, τ is the tortuosity of the matrix, A is the concentration of solid drug in the matrix, C_s is the solubility of the drug in the dissolution medium, and t is time.

In this system, the dissolution boundary distance retreating from the surface after t, X_t, is expressed as follows:

$$X_t=\frac{2Q}{2A-\varepsilon C_s} \tag{2}$$

From Eqs. 1 and 2, X_t can be rewritten as:

$$X_t=K_b t^{1/2} \tag{3}$$

and,

$$K_b=2\sqrt{\frac{D\varepsilon C_s}{\tau(2A-\varepsilon C_s)}} \tag{4}$$

where K_b is the boundary retreat rate constant.

Besides:

$$\varepsilon=\varepsilon i+\varepsilon d$$
$$\varepsilon d=A/\rho$$

where ε is the porosity, εi is the space remaining between particles after compression, εd is the void space newly created after drug release, and ρ is the true density of the drug.

When hydrogenated castor oil exhibiting adhesional wetting was used as a matrix material, εi could not be utilized as the effective water channel for drug release, and then Eq. 4 could be rewritten as[3]:

$$K_b = 2\sqrt{\frac{D\varepsilon dC_s}{\tau d(2A-\varepsilon dC_s)}}$$

$$K_b = \frac{1}{\sqrt{\tau d}} \cdot \sqrt{\frac{4DC_s}{2\rho - C_s}} \quad (5)$$

Of those parameters, D, C_s and ρ are physical quantities which are closely connected with velocity of dissolution, and τd represents the matrix structure which is connected with the water channel during drug release. When the constant term in Eq. 5. is replaced by constant P, Eq. 7 can be used instead of Eq. 5.

$$P = \sqrt{\frac{4DC_s}{2\rho - C_s}} \quad (6)$$

$$K_b = \frac{P}{\sqrt{\tau d}} \quad (7)$$

This equation implies that the drug release rate from a wax matrix system is controlled by forming the matrix structure, because the drug solute diffuses through a restricted water channel in the matrix system.

Experimental

Materials Nicotinamide (NIA; Yukigosei Yakuhin Kogyo Co.), isoniazid (INZ; Yukigosei Yakuhin Kogyo Co.), caffeine (CAF; Shiratori Seiyaku Co.), theophyllin (THE; Tokyo Organic Chemicals Co.) and aspirin (ASP; Katayama Chemical Co.) were pulverized prior to use. Hydrogenated castor oil (HCO; Kawaken Fine Chemical Co.) and polyethylenglycol (PEG; Sanyo Kasei Kogyo Co.) were used as recieved. All employed materials were of JP grade.

Table I summarizes the properties of the drugs used in this study.

Granulation The melt granulation method was applied. The pulverized drug and HCO powder were together in various proportions. 100 g of the powder blend were melted in a vessel at 95—98 °C under continuous agitating. The homogeneous mass was cooled to room temperature and then pulverized usin a mortar and pestle. The granules obtained were sized by passing through a 20 mesh sieve. Five lots of granules, consisting of drug and wax at ratios of 90:10, 85:15, 80:20, 75:25 and 70:30, were prepared by the same method.

Tableting 500 mg of the drug–HCO granules were compressed by a reciprocating press (Autograph IS-5000, Shimadzu Seisakusho) using a flat-faced punch and die with a diameter of 10 mm. The applied force was 1273 kg/cm^2 and the punch velocity was 10 mm/min. To examine the intrinsic dissolution rate of drugs, tablets consisting of one drug each were compressed, then the lateral and one side of the planar surfaces of each tablet were covered by HCO using the press-coating technique. For drug–HCO–PEG tablets, 500 mg of the powder blend of drug, HCO and PEG were compressed under identical conditions.

Dissolution Test Dissolution tests were conducted according to the paddle method described in JP XII. 900 ml of distilled water thermostated at 37 °C were used as the dissolution fluid, and stirred with a paddle at the rate of 100 rpm. The sinker was applied to prevent flotation of the tablet. The amount of drug released was spectrophotometrically assayed at 280, 310, 300, 296 and 286 nm for NIA, INZ, CAF, THE and ASP, respectively.

Determination of Tablet Properties The weight, diameter and thickness of each tablet were determined using an ordinary balance and gauges. The initial porosity, the remaining void space after compression εi, was calculated from Eq. 8.

$$\varepsilon i = 1 - \frac{Wf_I/\rho_I + Wf_H/\rho_H + Wf_P/\rho_P}{V} \quad (8)$$

where W and V are the weight and the geometrical volume of the tablet, respectively. f is the fraction ratio of a component in the formula, and subscript I, H and P represent INZ, HCO and PEG, respectively.

Calculation of Dissolution Parameters Various parameters necessary for analysis of the dissolution behavior were calulated from dissolution data according to Eq. 9,[5]

$$F_t = \mathrm{I} - \frac{V_t}{V_0} = 1 - \frac{q}{r_0^3}(r_0 - K_{Lb}t^{1/2})^2(r_0/q - K_{Cb}t^{1/2}) \quad (9)$$

$$q = r_0/h_0$$

where F_t is the fraction of the released drug at time t; V_0 and V_t are the volume of the unreleased portion at time 0 and t, respectively: r_0, h_0 and q are the initial tablet radius, initial tablet half-thickness, and a ratio factor (usually, $q>1$); and K_{Cb} and K_{Lb} are the boundary retreat rate constants from the compressed and lateral surface, respectively.

Results and Discussion

Influence of Drug Solubility on the Drug Release Rate Equation 7 implies that the release rate of a drug having a given solubility from the HCO matrix tablet is limited as the drug solute can not be diffused except through a restricted pathway in the matrix system. As τd is a term expressing the degree of water channel winding and is an abstract number, it is considered that the constant P must be the parameter representing the drug solubility in a wax matrix system. When the matrix structure is not formed, the drug release rate from the tablet may be regarded as the intrinsic dissolution rate of the drug. Therefore, it was considered that P should relate to the intrinsic dissolution rate. To examine the relation between P and drug solubility, five drugs having different solubilities were compressed and one-planar dissolution tests were conducted. Figure 1 shows the dissolution behavior for the five drugs.

As each drug exhibited the zero order release kinetic in a steady state, the intrinsic dissolution rate constant, K_d, was calculated from the slope of the straight region on the line by the least square method. Figure 2 shows the relation between P and K_d for the five drugs, and the linear relation was found.

Therefore, it was demonstrated that P plays a role as the index of the velocity of dissolution of a drug incorporated into a wax matrix.

TABLE I. Properties of Raw Materials Used in This Study

Items	NIA	INZ	CAF	THE	ASP
Solubility in water (g/ml)[a]	0.973	0.195	0.037	0.011	0.008
Density (g/cm^3)[b]	1.44	1.42	1.44	1.50	1.40
Mean diameter (μm)[c]	6	7	5	6	6
Diffusivity ($\times 10^{-4}$ cm^2/min)[d]	6.5	6.1	4.4	5.0	5.0

a) Determined at 37 °C. *b*) Determined with an air comparison pycnometer. *c*) Calculated from specific surface area. *d*) Calculated by the Wilke–Chang equation.[4]

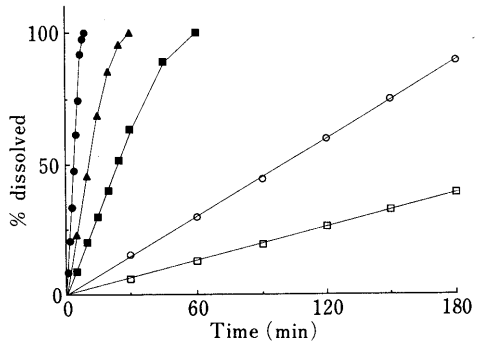

Fig. 1. Intrinsic Dissolution Rate of Five Drugs

Drugs: ●, NIA; ▲, INZ; ■; CAF; ○, THE; □, ASP. These tablets were compressed at 1273 kg/cm^2.

Influence of the Matrix Structure on Drug Release To examine the influence of the matrix structure on the drug release rate, matrix tablets consisting of a drug and HCO in various proportions were compressed for the five drugs, and dissolution tests were conduceted. Figure 3 shows the dissolution profile of each tablet.

The drug release rate decreased with increasing HCO content, and the drug exhibiting greater P was released faster than the smaller one. From all dissolution data shown in Fig. 3, dissolution parameters were calculated by Eq. 9 using the SIMPLEX method.[5] Figure 4 shows the relation between the dissolution parameters and HCO content.

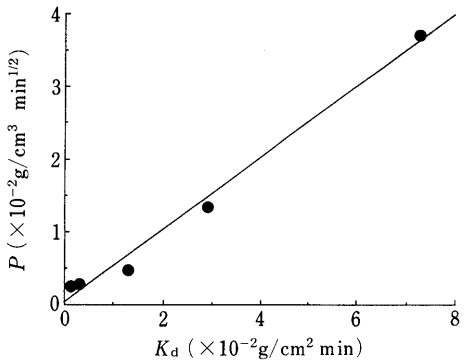

Fig. 2. Relationship between Dissolution Parameter Calculated by Eq. 6 and Intrinsic Dissolution Rate Constant

As is apparent in both figures, the boundary retreat rate constant linearly decreased with the HCO content in all drugs. K_{Cb0} or K_{Lb0}, the boundary retreat rate constant when HCO content was extrapolated to zero, was an index representing the penetration rate constant for the tablet consisting of only drug powder. Figure 5 shows the relationship between K_{Cb0} or K_{Lb0} and P.

If a linear relation was found in Fig. 5, it would mean that the matrix structure concerning the drug release is not affected by the drug species. As is apparent in the figure, however, a linear relation was not found, which means that the configuration of the water channel formed in the matrix tablet differs with the drug species.

Relationship between εd and τd in Wax Matrix Tablet In an HCO matrix system, the void space newly created after drug release acts as the water channel, and the con-

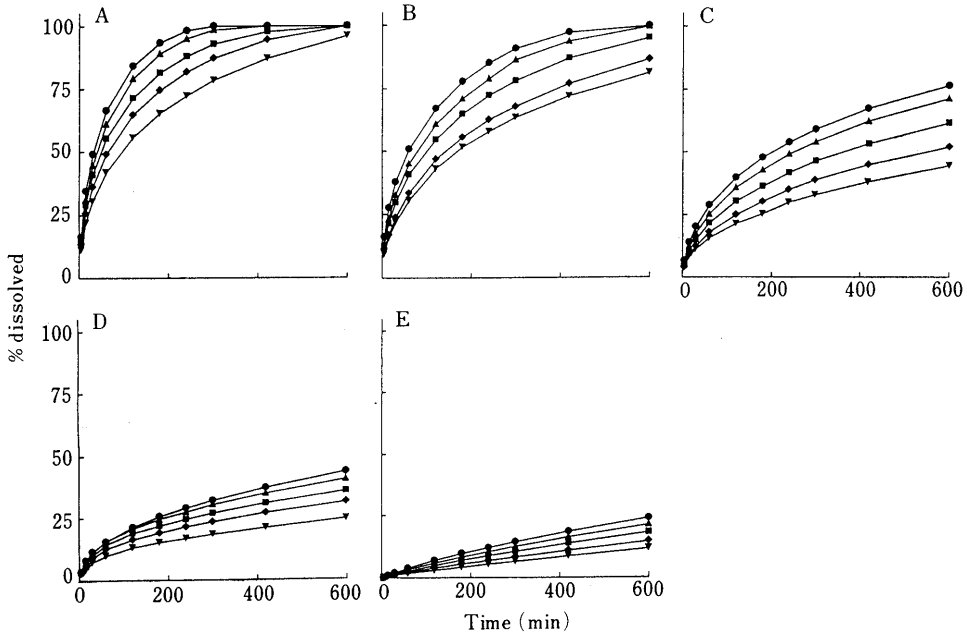

Fig. 3. Drug Release Profiles from HCO Matrix Tablets

Drugs: A, NIA; B, INZ; C, CAF; D, THE; E, ASP. Drug–HCO ratios: ●, 90:10; ▲, 85:15, ■, 80:20; ◆, 75:25; ▼, 70:30. These tablets were prepared at various drug–HCO ratios compressed at 1273 kg/cm^2.

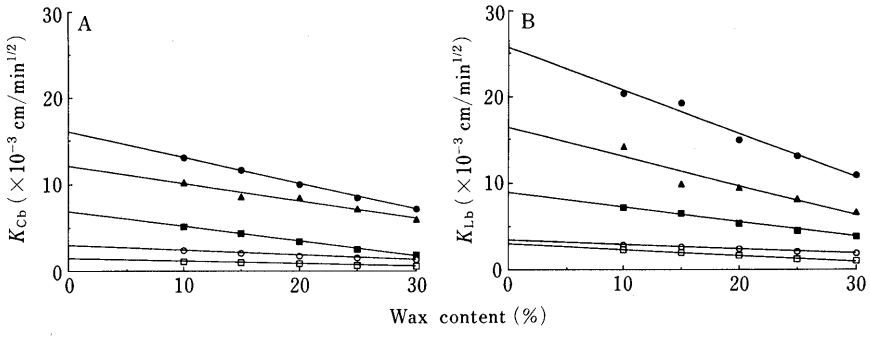

Fig. 4. Relationship between HCO Content and Boundary Retreat Rate Constant Calculated by Eq. 9

A, K_{Cb}; B, K_{Lb}. Drugs: ●, NIA; ▲, INZ; ■, CAF; ○, THE; □, ASP. These tablets were prepared at various drug–HCO ratios compressed at 1273 kg/cm^2.

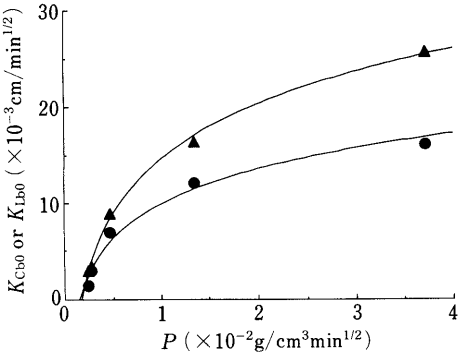

Fig. 5. Relationship between Dissolution Parameter Calculated by Eq. 6 and Extrapolation Value of Boundary Retreat Rate Constant

●, K_{Cb0}; ▲, K_{Lb0}.

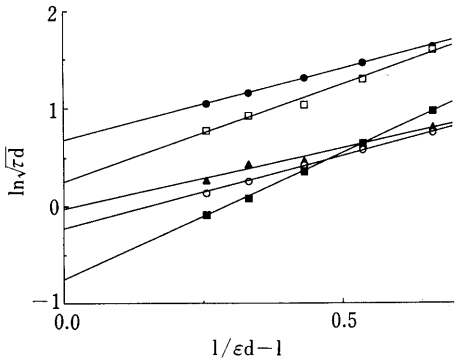

Fig. 6. Relation between Porosity and Tortuosity

Drugs: ●, NIA; ▲, INZ; ■, CAF; ○, THE; □, ASP. Ordinate: $1/\varepsilon d-1$, abscissa: logarithm of square root of τd. These tablets were prepared at various drug–HCO ratios compressed at 1273 kg/cm^2.

figuration of the water channel varied with the drug species, as mentioned above. To determine how τd is affected by the drug species, the relation between εd and τd was examined.

The relationship between swollen polymer membrane and water permeability has been treated theoretically by Yasuda and Lamaze,[6] and the water permeability is expressed as follows:

$$\omega = m\exp\{-\phi(1/H-1)\} \quad (10)$$

where ω is the parameter of water permeability, H is the volume fraction of water in a swollen membrane, and m and ϕ are constants.

When polymer membrane swelling has been done and reaches the steady state, H is regarded as the volume fraction of water channel in the membrane. When this theory is applied to the wax matrix system, ω and H can be replaced by the boundary retreat rate constant and εd, respectively. Equation 10 can then be rewritten as:

$$K_b = m\exp\{-\phi(1/\varepsilon d-1)\} \quad (11)$$

Substituting Eq. 11 into Eq. 7 gives:

$$\sqrt{\tau d} = P/m\exp\{\phi(1/\varepsilon d-1)\} \quad (12)$$

To examine the relation between εd and τd for the five drugs, K_{Cb} values shown in Fig. 4 was used in the analysis, whereupon τd was calculated from K_{Cb} using Eq. 7. Figure 6 shows the relation between the logarithm of square root of τd and $1/\varepsilon d-1$.

Table II. Comparison of Parameters in Eq. 10 among Five Drugs Used in This Study

Drugs	Parameters	
	P/m	ϕ
NIA	1.8	1.50
INZ	1.0	1.20
CAF	0.5	2.88
THE	0.8	1.53
ASP	1.3	1.88

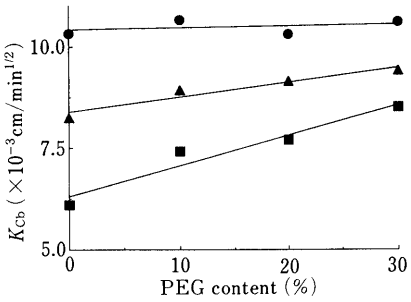

Fig. 7. Relationship between PEG Content and K_{Cb}

HCO content: ●, 10%; ▲, 20%, ■, 30%. These tablets were prepared at various drug–HCO ratios compressed at 1273 kg/cm^2.

It was determined that Eq. 12 could be applied to express the relation between εd and τd, because a linear relation was found for every drug. τd values differed with the drug species, even though εd was the same, and the dependency of τd on εd, ϕ, differed as well.

The P/m and ϕ values calculated from Eq. 12 are listed in Table II. P/m represents τd value at εd equal to 1. In this case P/m must be equal to 1 theoretically, although a situation where τd equals 1 can not occur except in a tablet consisting of the drug only. In this study, as P/m was extrapolated from the data obtained for the matrix tablet, it was thought to express the intrinsic value for the matrix tablet. Therefore, it was considered that P/m express the degree of connectivity of drug particles acting as the dissolution pathway. The degree of connectivity of the dissolution pathway in the matrix tablet is in the order, NIA < ASP < INZ < THE < CAF.

ϕ represents the dependency of τd on εd. The degree of dependency is in the order, INZ < NIA < THE < ASP < CAF.

As these parameters depended on the drug species, the drug release rate from the matrix tablets consisting of drug and HCO could not be controlled arbitrarily. Therefore, for the purpose of controlling the dissolution rate, the addition of another material was thought to be effective. To examine the effect of the addition of another material on the configuration of the water channel, INZ–HCO–PEG matrix tablet (where $P/m=1$) in which a part of the amount of INZ was replaced with PEG was prepared. The reasons why PEG was chosen are that PEG is soluble in water and disperses all over the matrix tablet, and because is does not dissolve in HCO.

In order to determine the influence of the PEG content on the water permeability of INZ–HCO–PEG matrix tablet, K_{Cb} was plotted against the PEG content in Fig. 7.

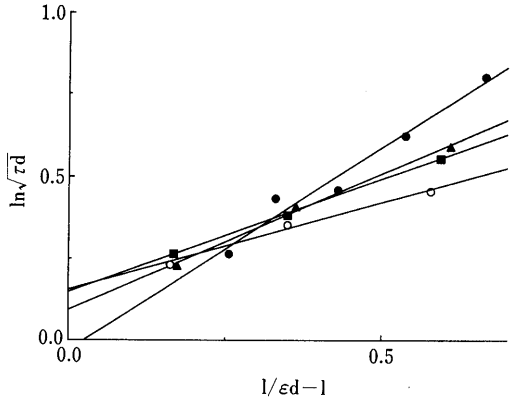

Fig. 8. Relationship between Porosity and Tortuosity

PEG content: ●, 0%; ▲, 10%; ■, 20%; ○, 30%. Ordinate: $1/\varepsilon d-1$, abscissa: logarithm of square root of τd. These tablets were prepared at various drug–HCO ratios compressed at 1273 kg/cm^2.

TABLE III. Influence of PEG Content on Parameters in Eq. 10

PEG content (%)	Parameters	
	P/m	ϕ
0	1.0	1.20
10	1.1	0.83
20	1.2	0.68
30	1.2	0.53

When the matrix tablet contained a small amount of HCO, *i.e.*, when the matrix tablet contained a large amount of drug, K_{Cb} was significantly increased with increasing PEG content. To examine the influence of PEG on the configuration of the dissolution pathway, the results showed in Fig. 7 were analyzed in the same way as for Fig. 6.

As is apparent in Fig. 8, a linear relation was found in all cases. The calculated values of P/m and ϕ are listed in Table III. P/m values were almost 1 in spite of a variation in PEG content. It was found that the addition of PEG does not affect the connectivity of the water channel. On the other hand, ϕ was decreased with increasing PEG content, *i.e.*, the dependency of τd on εd decreased with increasing PEG content.

Conclusion

The results of this investigation showed that: 1) The parameter obtained from a modified Higuchi's equation related the intrinsic dissolution rate constant of the drugs and was found to be an index of the drug solubility in the matrix system; 2) the drug release rate from the matrix tablet was in proportion to the solubility and was in inverse proportion to the tortuosity; 3) the relation between the porosity and tortuosity was well expressed by the proposed equation derived on the basis of the free volume theory; and 4) the dependency of τd on εd could be controlled by the addition of another material.

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