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Controlled-release of diclofenac sodium from wax matrix granule

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Abstract

A twin-screw compounding extruder was used to prepare wax matrix granules (WMG) consisting of carnauba wax, diclofenac sodium (DS) as a model drug, and rate-controlling agents such as hydroxypropylcellulose (HPC-SL), methacylic acid copolymer L (Eudragit L-100), and sodium chloride (NaCl). In this preparation, a wax matrix with high mechanical strength was obtained even at temperatures lower than the wax melting point. Dissolution behaviors of DS from WMG were strongly influenced by granule formulation, in which an increase in the content of HPC-SL or Eudragit L-100 brought a significant increase in the dissolution rate. The extent of this enhancing effect in HPC-SL was identical in two different dissolution mediums (pH 6.8 buffer solution and water), but in Eudragit L-100 was more significant in pH 6.8 buffer solution than in water. Only a small increase in the dissolution rate was observed in NaCl-containing WMG. These different behaviors were attributed to the physicochemical properties (i.e. swelling and solubility) of the rate-controlling agent in the dissolution medium. Further, mechanical strengths of the wetted WMG after dissolution studies were > 70 g/mm^2, suggesting that burst release of DS in the gastrointestinal tract would be avoided.

Keywords: Wax matrix granule; Carnauba wax; Diclofenac sodium; Controlled-release; Twin-screw compounding extruder

1. Introduction

In the last two decades, sustained-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance (Merkus, 1986). The matrix system is commonly used for manufacturing sustained-release dosage forms because it makes such manufacturing easy (Cardinal, 1984). In this system, the drug in the form of fine powder and a matrix-forming component are mixed and the mixture is then shaped

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in an appropriate mold. Non-bioerodible polymer and wax are commonly used as matrix-forming components. The use of wax seems to have a particular advantage due to wax's chemical inertness against other materials. A rigid wax matrix can be made by simply heating. Drugs, however, are sometimes unstable under heating, so manufacturing machines and operational conditions have to be carefully specified to obtain wax matrices with the desired properties (Maki et al., 1988). Preparation of matrix systems has been discussed (Bianhini and Vecchio, 1989; El-Egakey et al., 1971; Ghali et al., 1989; Follonier and Doellcer, 1994; McTaggart et al., 1984), but the process is not easy to specify in the case of preparation of high-quality matrices. Furthermore, considering of gastric emptying time of pharmaceuticals, multiple-unit formulation is suitable for sustained-release dosage forms (Bechgaard and Nielsen, 1978), but it is rather difficult to prepare small pellets or granules with the wax matrix system because of the aggregation of granules in the manufacturing process. Wax matrix granule would be valuable as convenient dosage form for controlling drug release if these problems could be solved.

Recently, Nakamichi et al. (Nakamichi et al., 1994) reported that a wax matrix could easily be obtained using a twin-screw compounding extruder. In preparing it, a powder mixture consisting of the drug and wax was continuously fed into the extruder and discharged from the die to form a rigid wax matrix at ambient temperature. Formation occurred even at temperatures lower than the wax melting point because of the high-pressure condition created by two screws in the barrel of the extruder. The use of the twin-screw compounding extruder therefore has several advantages such as ease of manufacturing, short manufacturing time through continuous production, low temperature, ease of sharpening small granules or pellets and the ability to produce quite homogeneous matrices even if filtration between drug and matrix-forming components might be expected due to differences in their densities. These difficulties in the preparation of wax matrix granule are expected to be solved using the twin-screw compounding extruder. No study on this method, however, has been reported.

The objectives of the present study were to prepare wax matrix granules (WMGs) using the twin-screw compounding extruder and to evaluate the control of release of diclofenac sodium (DS) used as model drug for WMG with desired in vivo pharmaceutical properties. These investigations are of importance in the design of WMG. DS is a high potent anti-inflammatory agent with short half-life ($t_{\frac{1}{2}}$ = 1.3 h) (Takahashi et al., 1972; Kozaya et al., 1972). Based on the physical properties (swelling and solubility), hydroxypropylcellulose (HPC-SL), methacylic acid copolymer L (Eudragit L-100) and sodium chloride (NaCl) were selected as rate-controlling agent to regulate the release of DS from WMG.

2. Materials and methods

2.1. Materials

Diclofenac sodium (DS), a model drug, was obtained from Sanwa Chemical Co., Ltd. (Japan). Carnauba wax used as a matrix-forming agent was purchased from Noda Wax Co. (Japan). Hydroxypropylcellulose (HPC-SL) and methacylic acid copolymer L (Eudragit L-100) were supplied by Nippon Soda Co. (Japan) and Rohm Pharma (Germany), respectively. Sodium chloride (Japanese Pharmacopoeia grade), purchased from Tsukishima Yakuhin Ltd. (Japan), was pulverized using a hammer mill (KIII-1, Fuji Paudal Co., Ltd., Japan) before use. All other reagents were of analytical grade.

2.2. Preparation of wax matrix granules

Formulations of wax matrix granules (WMG) evaluated here are shown in Table 1. WMG was prepared using a twin-screw compounding extruder (KE 30, Kurimoto, Ltd., Japan) a schematic representation of which is shown in Fig. 1. Twin-screw compounding extruder consists of mainly eight portions, the powder supply window, the barrel, the screws, the die, the driving section, the cooling unit, and the control panel (Fig. 1). Compared with single-screw type extruder, it is

Table 1
Formulation of WMG

Ingredient	Formulation (g)															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Diclofenac sodium	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Carnauba wax	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
HPC-SL		10	20	40	50	60	70									
Eudragit L-100								10	20	40	50	60	70			
NaCl														50	60	70

possible to generate high pressure at the kneading and dispersing process by arranging the screw profile such as shape and engagement. Further, twin-screw compounding extruder shows the following advantages: (a) high kneading and dispersing ability can be achieved independently on physico-chemical properties of powders; (b) temperature of processed matters can be controlled correctly; (c) high shearing and kneading forces, and superior extruding capability can be obtained; (d) residing place for raw materials in the barrel is minimum; (e) cleaning of inside is quite simple. Because of these features, powder which may react with the apparatus material should not be used to control the quality of product. Powders consisting of DS, carnauba wax and HPC-SL or Eudragit L-100 or NaCl were well blended in advance and introduced successively into the extruder through the supply window. The barrel was divided into four sections and the temperature in each section could be controlled independently. In the present study, the temperatures employed in the four sections were 30, 50, 70 and 70°C successively from the supply window to the die with a 2-mm diameter hole. Other operational conditions were as follows: manufacturing volume, 1.0 kg; powder supply rate, 55 g/min.; screw rotation speed, 250 revs./min. A long, slender molten wax matrix was discharged continuously from the die through the hole. After cooling at ambient temperature, WMG of approximately 2-mm length and 2-mm diameter (Fig. 2) were obtained by use of a hot cutter.

2.3. Determination of mechanical strength of WMG

Measurement of mechanical strength (Tg, g/mm^2) was conducted in the axial and radial directions with the intact WMGs and the wetted WMGs after dissolution studies. Based on crushing load (Pa, g) determined using a particle hardness tester (Grano, Okada Seiko Co., Japan), Tgs of WMG in the axial and radial directions were estimated according to Eq. (1) (Fell and Newton, 1970) and Eq. (2) (Kuno and Okada, 1982) respectively,

$$Tg = 2\,Pa/\pi\,D\,T \quad (1)$$

$$Tg = Pa/\pi\,(D/2)^2 \quad (2)$$

where D and T are the diameter and the length of WMG, respectively. Tg is the average value of 20 determinations.

2.4. Determination of densities of rate-controlling agents

Densities of rate-controlling agents were determined using an air comparison pycnometer (model 930, Beckmann Instruments Inc., Germany) at 25°C.

2.5. Dissolution of DS from WMG

Dissolution studies were performed according to the paddle method described in Japanese Pharmacopoeia XII, in which water and pH 6.8 phosphate buffer solution maintained at 37 ± 0.5°C

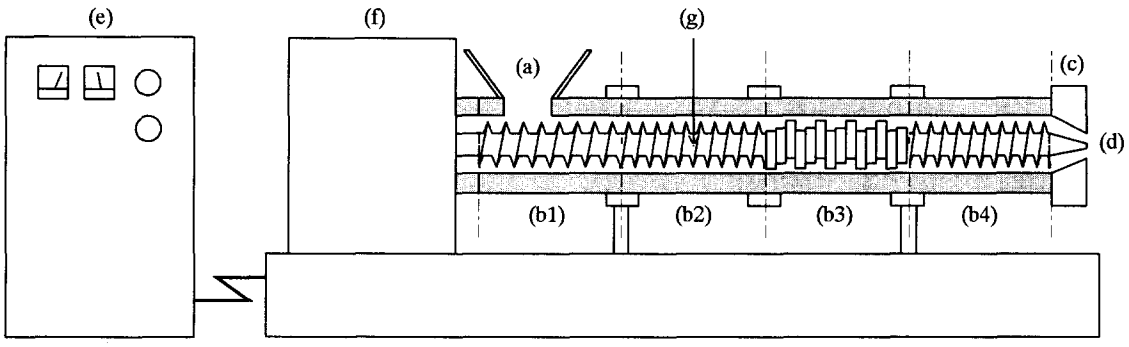

Fig. 1. Schematic representation of a twin-screw compounding extruder. (a) The powder supply window; (b1–4) the barrel; (c) the die with 2-mm diameter hole; (d) the hole; (e) the control panel; (f) the driving section; (g) the screw.

were selected as the dissolution medium and paddle rotation speeds were 50, 100, and 200 revs./min. Ten millilitres of the dissolution medium were withdrawn at predetermined intervals and filtrated (F72, Toyama Industry Co., Japan). The volume of the dissolution medium was kept at 500 ml by adding fresh medium at the same temperature. Drug concentrations in the dissolution medium were assayed spectrophotometrically at 277 nm (UV-240 spectrophotometer, Shimadzu Corporation, Japan).

2.6. Microscopic observation

WMGs were observed by scanning electron microscopy (SEM) (JSM-T200, Jeol Ltd., Japan).

3. Results and discussion

3.1. Preparation of wax matrix granules (WMG)

Powders of each formulation shown in Table 1 were introduced into the supply window of the extruder and extruded toward the die through a barrel consisting of four sections. These sections are called the first, second, third and fourth from the supply window successively toward the die. During the preparation process, the powders were again mixed and exposed to high pressure between two screws in the barrel, but carnauba wax did not melt in the first and second sections of the barrel, maintained at temperatures of 30 and 50°C, respectively. The screws in these two sections mainly mix the powders and extrude it toward the third and fourth sections. In the third section, carnauba wax was confirmed to be melted (the screws have a special structure enabling them to generate higher pressure here than in the other sections). Due to the extruded powder and screws, this high pressure could be maintained in the fourth section, in which the temperature was held at 70°C. As a result of high pressure and this relatively high temperature, carnauba wax was kept in a molten state although the normal melting point of the wax is around 83°C. No method for estimating the actual pressure in the barrel is currently available. The temperature of 70°C was necessary to prevent the solidification and blockage of the discharge of molten wax matrix at the die when a long and slender molten wax matrix was continuously squeezed from the die through the hole. The wax matrix was cut into about 2-mm diameter, 2-mm long monolithic WMGs by a hot cutter after solidifying at ambient temperature. The cutter can be attached to the die to make WMG preparation much easier, particularly in large-volume production.

3.2. Mechanical strength of WMG

The performance of sustained-release dosage form in the gastrointestinal tract is considerably influenced by anatomical and physicological constraints such as gastric emptying time, chemical and enzymatic degradation, and gastrointestinal motility. In particular, an effect of gastrointestinal

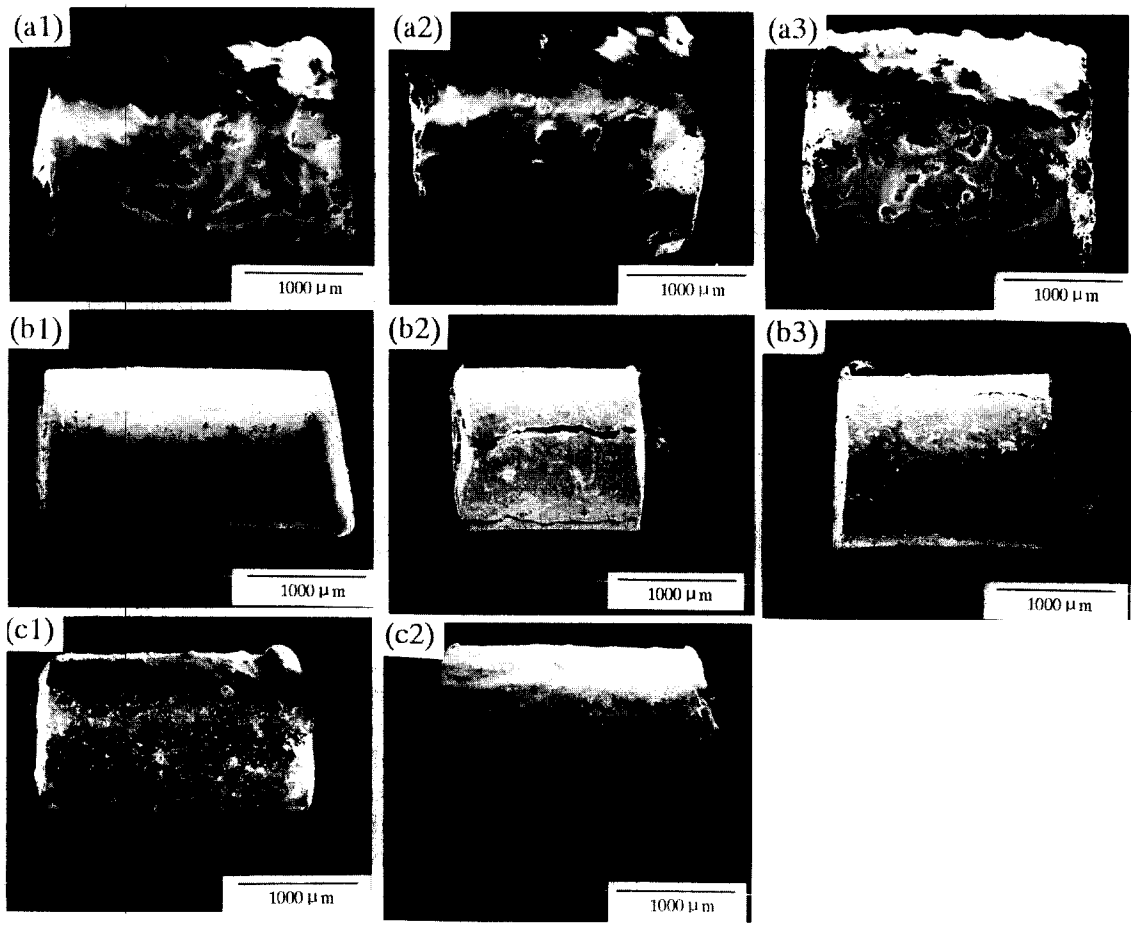

Fig. 2. Scanning electron micrographs of wax matrix granules (WMGs) containing HPC-SL, Eudragit L-100, NaCl before and after the dissolution studies. (a1) HPC-SL-containing WMG before the dissolution study. (a2) HPC-SL-containing WMG after the dissolution study in water. (a3) HPC-SL containing WMG after the dissolution study in pH 6.8 buffer solution. (b1) Eudragit L-100 containing WMG before the dissolution study. (b2) Eudragit L-100 containing WMG after the dissolution study in water. (b3) Eudragit L-100 containing WMG after the dissolution study in pH 6.8 buffer solution. (c1) NaCl containing WMG before the dissolution study. (c2) NaCl containing WMG after the dissolution study in water.

motility on the dosage form should be carefully evaluated because mechanical damage will lead to unexpected burst release of drug. Ogura (Ogura, 1989) suggested that the mechanical strength of wetted granules should be > 10 g as crushing load to maintain its original shape in the gastrointestinal tract. This means that granules with strength of < 10 g would be damaged due to gastrointestinal motility. The determination of the mechanical strength of the dosage form and the effect of the stirring condition on the release rate of the drug in dissolution test allow us to estimate such influence in in vivo.

Results of mechanical strength tests of WMG in both axial and radial directions are summarized in Table 2, showing that Tg of intact WMG in the radial direction was around 400–600 g/mm^2 and that the addition of a rate-controlling agent had no influence within the experimental range. This suggests that the amount of rate-controlling agent in the intact WMG (38.9% (w/w) at maximum content) was not enough to affect mechanical

Table 2
Mechanical strength of WMG

Formulation	w/w%	Radial direction			Axial direction	
		Before dissolution study (g/mm^2)	After dissolution study (g/mm^2)		Before dissolution study (g/mm^2)	After dissolution study (g/mm^2) in pH 6.8 buffer
			In water	In pH 6.8 buffer		
No added	0.0	537.7 ± 30.5	602.1 ± 34.2	635.9 ± 30.7	1261.5 ± 74.3	1441.0 ± 74.3
HPC-SL	15.4	486.7 ± 23.7	373.4 ± 16.9	357.0 ± 16.4	1230.9 ± 59.4	702.5 ± 49.6
	26.7	536.3 ± 20.7	130.4 ± 5.2	138.7 ± 7.3	1380.0 ± 72.7	267.4 ± 13.9
	38.9	609.4 ± 41.7	73.8 ± 3.2	80.6 ± 3.9	1526.2 ± 66.6	193.5 ± 9.7
EudragitL-100	15.4	428.4 ± 30.1	379.6 ± 41.0	306.4 ± 22.8	930.5 ± 54.0	1029.5 ± 65.5
	26.7	377.0 ± 27.9	264.9 ± 20.5	259.9 ± 21.7	998.9 ± 59.1	826.5 ± 40.2
	38.9	447.5 ± 30.0	76.1 ± 8.1	152.9 ± 11.8	927.2 ± 63.2	270.0 ± 23.3
NaCl	31.3	442.6 ± 19.2	483.5 ± 15.0	510.1 ± 19.8	1051.5 ± 58.3	1096.7 ± 54.9
	35.2	499.2 ± 21.9	509.3 ± 19.2	512.7 ± 20.6	972.1 ± 50.2	1172.0 ± 62.5
	38.9	433.6 ± 23.2	480.0 ± 19.4	520.4 ± 21.3	1029.3 ± 56.5	1172.7 ± 69.5

Each value represents the mean value ± S.E. (n = 20).

strength. Mechanical strength of WMG after the dissolution study tended to decrease depending on the amount of rate-controlling agent added. This tendency, however, was not observed for the NaCl-containing WMG. This suggests that the amount of rate-controlling agent in the intact WMG (38.9% (w/w) at maximum content) was not enough to affect mechanical strength. Tg of the wetted WMG obtained after our dissolution studies was determined to be at least 70 g/mm^2 in both axial and radial directions in all formulations. These results in Table 2 suggest that WMGs prepared in the study hold enough mechanical strength in the gastrointestinal tract and damage to WMG and resulting burst release of DS would be avoided.

The effects of paddle rotation speed on dissolution rate of DS are summarized in Table 3. No increase or decrease in released DS was observed in the changes of paddle rotation speeds within the experimental range (50–200 revs./min), suggesting that an unexpected burst release of DS in the gastrointestinal tract could be avoided.

3.3. Dissolution behaviors of DS

Appearances of intact WMGs containing different rate-controlling agents are shown in Fig. 2. Surfaces are quite distinct depending on the rate-controlling agent used. Many large unevennesses were observed on the surface of HPC-SL-containing WMGs and the other two types of WMGs show relatively smooth surfaces. This difference can be explained by the morphological characteristics of the rate-controlling agents shown in Fig. 3, since HPC-SL has unfixed, relatively large mass with low density (1.19 ml/g), and Eudragit L-100 and NaCl were fine powders with average Feret diameter of about 26.4 and 23.4 μm, respectively. The average Feret diameter of HPC-SL was 39.2 μm. The rate-controlling agents which do not fuse in WMG

Table 3
Percent of DS released from WMGs containing HPC-SL in 18 h on different paddle rotation speeds

Formulation (w/w%)	Paddle rotation speed		
	50 revs./min	100 revs./min	200 revs./min
15.4	11.8 ± 0.03	11.4 ± 0.03	11.3 ± 0.09
26.7	42.3 ± 0.12	37.7 ± 0.22	41.0 ± 0.12
38.9	77.5 ± 0.58	76.6 ± 0.44	75.4 ± 0.48

Each value represents the mean value ± S.E. (n = 3).

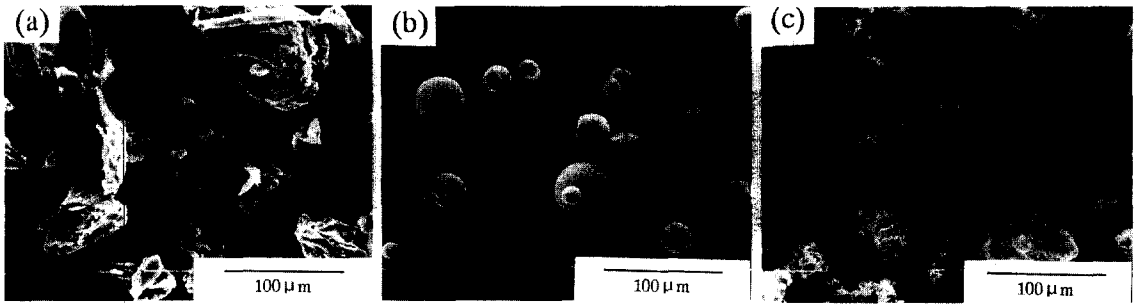

Fig. 3. Scanning electron micrographs of (a) HPC-SL, (b) Eudragit L-100 and (c) NaCl used in the preparation of WMG.

play important role in the evaluation of release rate of DS and in the design of WMG.

In vivo release rate of drug from WMG can be hardly estimated at in vitro condition such as dissolution test, so the preparation of WMG with different release rates is inevitable to optimize the formulation of sustained-release dosage form. From this point of view, the influence of three materials which have different physico-chemical properties were investigated in relation with release rate of DS.

Dissolution studies of DS were carried out in two different dissolution mediums, water and pH 6.8 phosphate buffer solution. HPC-SL is soluble in both mediums but Eudragit L-100 cannot be dissolved in water. Dissolution of DS from NaCl-containing WMG was evaluated only in water. The results obtained are shown in Fig. 4.

Addition of HPC-SL or Eudragit L-100 to WMG formulation caused a significant increase in the dissolution rate depending on the amounts added (Fig. 4a–d), although only 2% of DS was released from WMG without any rate-controlling agent in 24 h. For example, the amount of DS released in water in 24 h increased respectively from 2 to 5.0, 13.7, 46.3, 63.3, 78.0, and 84.7% by adding 8.3, 15.4, 26.7 31.3, 35.2, and 38.9% (w/w) HPC-SL into WMG formulations. The extent of this enhancing effect of HPC-SL was almost the same in both dissolution mediums, and no lagtime in dissolution was observed. On the other hand, the enhancing effect of Eudragit L-100 was more pronounced in pH 6.8 phosphate buffer solution, in which amounts of DS released for 24 h were 1.3–1.8 times higher than in water (Fig. 4c,d). Furthermore, the lagtime was observed in the dissolution of DS in water and not in pH 6.8 phosphate buffer solution. In the case of NaCl-containing WMG, only a small increase (about 10%) independent of the additional amount was obtained in 24 h. After dissolution studies in water and pH 6.8 phosphate buffer solution, cracks and pores were observed on the surface of HPC-SL-containing WMG, as shown in Fig. 2a2,a3. In the case of Eudragit L-100-containing WMG as shown in Fig. 2b2,b3, large cracks were observed in WMGs obtained from two dissolution mediums, although small pores were seen only in WMG obtained from pH 6.8 phosphate buffer solution. NaCl-containing WMG (Fig. 2c2) had only small pores and no cracks. This suggests that DS was released through the pore observed on the surface of WMG, and development of the crack could effectively created new surface inside of WMG leading to enhance release of DS.

The mechanism of these dissolution behaviors can be described based on the microscopic observations of WMGs and the physicochemical properties (i.e. swelling and solubility) of the rate-controlling agent, as illustrated in Fig. 5. HPC-SL can be simultaneously dissolved and swelled in both dissolution mediums, so a quick and high release rate without any lagtime was obtained. However, since Eudragit L-100 is insoluble in water, a distinct dissolution enhancement could not be obtained until a structural change in WMG, such as the cracks seen in Fig. 2, was caused by the swelling of Eudragit L-100. We considered that the lagtime observed in water is the time required for the penetration of water into

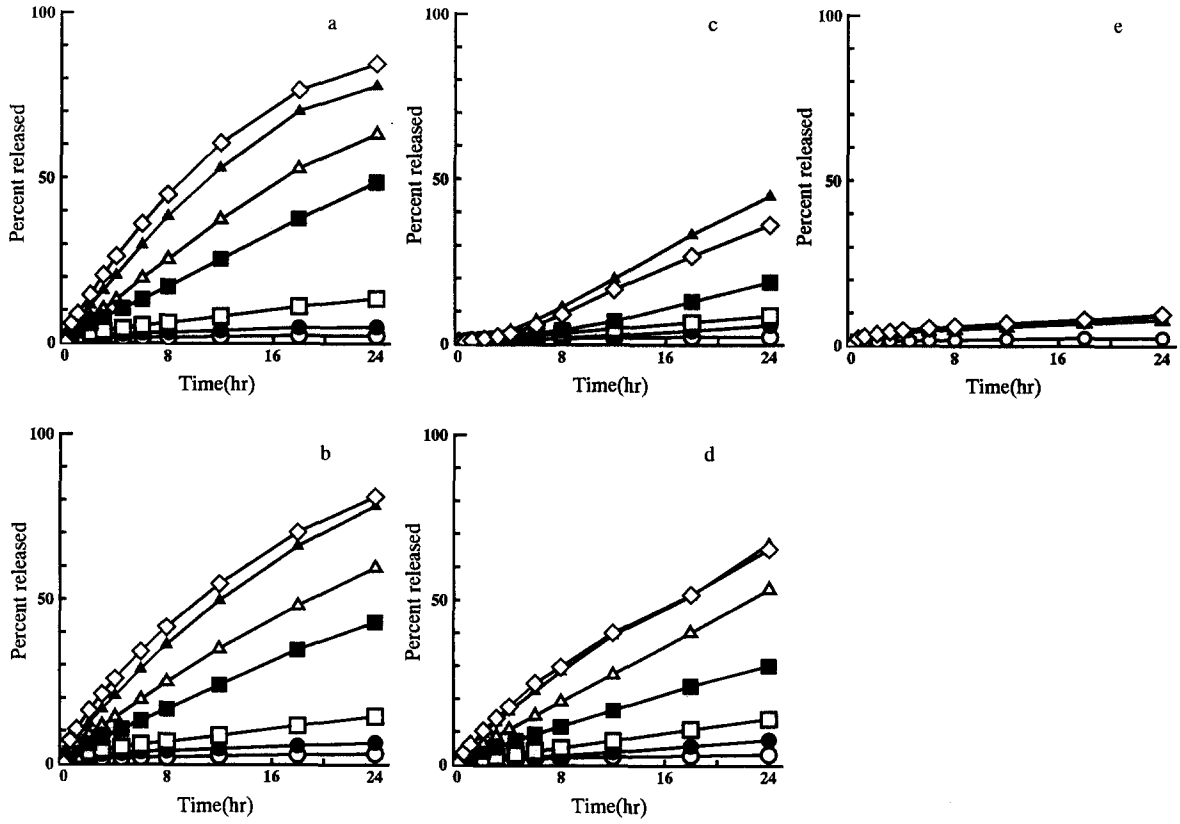

Fig. 4. Dissolution profiles of DS from various wax matrix granules (WMGs) containing (○) 0, (●) 8.3, (□) 15.4, (■) 26.7, (△) 31.3, (▲) 35.2 and (◇) 38.9% (w/w) of rate-controlling agent. (a) HPC-SL-containing WMG in water. (b) HPC-SL-containing WMG in pH 6.8 buffer solution. (c) Eudragit L-100-containing WMG in water. (d) Eudragit L-100-containing WMG in pH 6.8 buffer solution. (e) NaCl-containing WMG in water. Each point represents the mean value of three determinations.

the WMG and the occurrence of structural change by the swelling of Eudragit L-100. On the other hand, Eudragit L-100 was soluble and swellable in pH 6.8 phosphate buffer solution so a quick and high release rate was obtained as observed in HPC-SL-containing WMG. Development of cracks and pores is considered to be closely related to the dissolution behaviors of DS from WMG. These results in the dissolution study indicates that control of DS release rate from WMG could be easily achieved by adding rate-controlling agent employed in the study. Further, swelling and solubility of rate-controlling agent are closely associated with not only release rate but also mechanism of DS release from WMG.

The relationship between logarithms of the percent of DS released in 24 h and the volume ratio (%) of HPC-SL or Eudragit L-100 to wax (Fig. 6a,b) indicate that there were good linear relationships with correlation coefficients > 0.978. Such physical finding is not clear at present, however, it is reasonable to speculate here that the design of WMG with desired release profile is easily estimated based on the volume ratio of rate-controlling agent to wax. In these figures, the slope of the line calculated by the least-square method is considered to be an index of the enhancing effect of each rate-controlling agent. The volume ratio used in the plot was estimated from the determination of density, in which densities of HPC-SL and Eudragit L-100 were determined to be 1.19 and 1.48 g/ml, respectively. In pH 6.8 buffer solution, HPC-SL and Eudragit L-100 gave almost the same slopes (0.0403). This result was

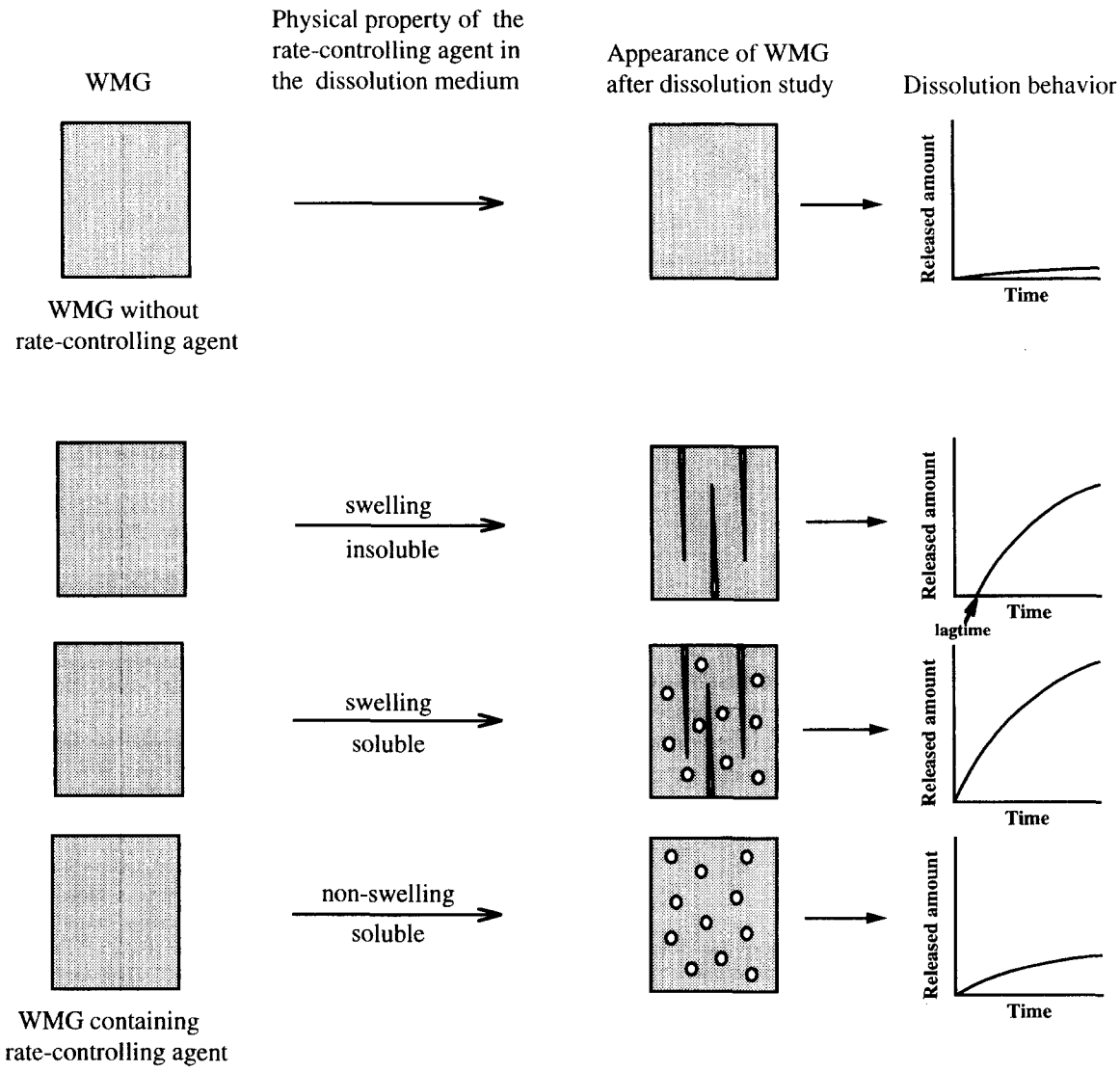

Fig. 5. Possible mechanism of dissolution profiles of DS from wax matrix granule (WMG).

ascribed to their soluble and swellable properties in the dissolution medium. The slope of Eudragit L-100 obtained in water (Fig. 6a) was smaller than that in HPC-SL, but the difference was not significant. The lack of the enhancing effect attributable to the dissolution of Eudragit L-100 may be the reason for this difference. Provided that the rate-controlling agent is insoluble in the dissolution medium, swelling capability should be closely related to the increase in the dissolution rate of the drug. The present study suggested that the swelling property of the rate-controlling agent contributed more significantly to dissolution of DS than did dissolution property, since both the amount and particle size of the rate-controlling agent on the surface of WMGs would not be enough to increasing the contribution of dissolution to the enhancing effect. NaCl is soluble in both dissolution mediums but its swelling was ignored, so DS could be released only though the

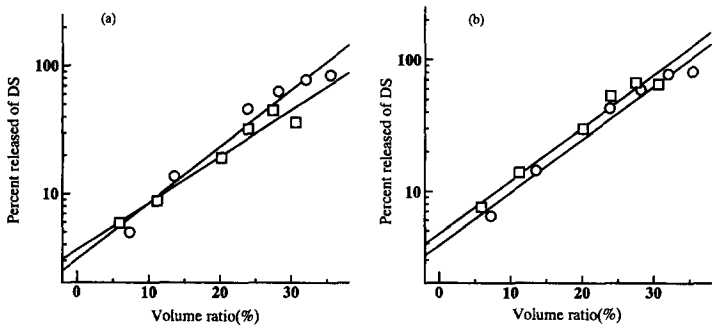

Fig. 6. Relationship between the logarithms of percent of DS released and volume ratio (%) of (○) HPC-SL or (□) Eudragit L-100 in (a) water and (b) pH 6.8 buffer solution.

volume generated by the dissolution of NaCl from WMG. As stated above, the enhancing effect of NaCl was in very small. As an example in which the swelling of low substituted hydroxypropylcellulose (L-HPC) was used as driving force to cause drug release from granule, Ueda et al. (Ueda et al., 1994a,b) reported the times explosion system (TES).

On the preparation of WMG using twin-screw compounding extruder, the above results suggest that WMGs with desired release profiles can be produced easily by selecting proper rate-controlling agents on the basis of physicochemical properties such as swelling and solubility.

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