Design of Controlled Release System with Multi-layers of Powder

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Pellets containing active ingredients were coated with water-insoluble powders, *i.e.* hydrogenated caster oil (Lubliwax (WAX)) and magnesium stearate (Mg-St). The influences of the structural difference of the sustained release layer and curing conditions on the drug release rate were investigated. Sodium valproate (VP-Na) was used as a highly water-soluble model drug. Drug release profiles were influenced by the combination of the WAX layer and the Mg-St layer. Even if the formula of sustained release layers were the same, drug release rate could be affected by the structural difference of the controlled release layer. The Mg-St layer was more effective in prolonging drug release than the WAX layer. Compared with single and double layer types, the triple layer (sandwich) type was most effective in obtaining a long sustained drug release. Heat-treatment retarded drug release mainly by increasing the density of the sustained release layer of the WAX. The Mg-St was effective in protecting the agglomeration between particles during heat-treatment. Optimal heat-treatment conditions were found to exist. Scanning electron microscopy (SEM) analysis indicated that heat-treatment caused the WAX to melt, formed a film-like structure and made the release layer dense. Furthermore, heat-treatment changed the release pattern of VP-Na from sustained release pellets with a multi-layer of powder, leading to zero-order release.

Key words multi-layer; powder coating; heat-treatment; wax; magnesium stearate; sodium valproate

In recent years, multi-particulate systems have gained increasing importance as oral controlled drug delivery forms. These systems present several advantages in comparison to the conventional single units for controlled release, such as more predictable gastric emptying and less local irritation.[1)] Due to their rapid dispersion in the gastrointestinal tract, they maximize drug absorption and minimize potential side effects without lowering drug bioavailability. Multi-particulate systems also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter-subject variability of plasma profiles, which are common with single-unit regimens, are minimized.[2)] In general, pellets are preferable to tablets, because they are not easily influenced by physiological factors (dose dumping) or individual lot differences.[3)] A multi-particulate system using spherical granules as seed cores is one method for controlling drug release. This system was composed of a drug layer and outer sustained release layers. Drug release rate decreases as the thickness of the release controlled layer increases. But it took a long time to make the thick layer. Therefore, to shorten the manufacturing time, powder coating is effective in obtaining a thick layer which decreases the drug release rate. In general, the powder coating layer is very porous compared with the liquid one.[4)]

For making the powder coating layer dense, a combination of Lubliwax (WAX) and magnesium stearate (Mg-St) was adopted, and additional heat-treatment effects on the drug release rate were studied. In general, WAX is used as a matrix agent for sustaining drug release with heat-treatment.[5,6)] In this study, the WAX is used as a layer for sustaining drug release. As the outer Mg-St layer could prevent the melted WAX from aggregating between particles, heat-treatment could be performed for prolonging the release rate. In the case of using WAX as the layer type, the lag-time increased as the WAX layer thickness increased.[7)] For obtaining a zero-order release profile of the drug, we had to mix pellets with different WAX thickness. But zero-order drug release could be performed using a multi-layer with heat-treatment without mixing pellets in this study. Since the solubility of sodium valproate (VP-Na) in water is high and a drug release profile is influenced by only a slight difference in the sustained release layer, we can evaluate the release properties clearly. Therefore, VP-Na was used as a model drug in this study.

Experimental

Materials Spherical sugar granules (Nonpareil, NP-103, Freund Industrial, Tokyo, Japan) were used as seed cores. The diameter of the seed core for this layering process was found to affect the release characteristics of drug from pellets. VP-Na obtained from Dainippon Pharmaceutical Co., Ltd. was used as a highly water-soluble model drug. Magnesium stearate (Mg-St, Taihei Chemical Industrial Co., Ltd.) and hydrogenated caster oil (Lubliwax (WAX), NOF Corporation, mp=86—90 °C) were used as agents for rate controlling. Ethylcellulose 10 (EC 10, Shin-Etsu Chemical Co. Ltd., Japan) was used as a component in a sustained release layer, and its organic solution was also used as a binder. All other materials were of analytical reagent grade.

Preparation of Drug Cores VP-Na powder was layered onto Nonpareil pellets, resulting in 34—47% drug loading, and subsequently the coating was carried out by a CF-Granulator (CF-360, Freund Industrial, Tokyo, Japan). For good reproducibility of the *in vitro* release, uniform particle size distribution is required.[8—10)] Seed cores, whose particle size distributions were definite, were charged into a CF-granulator, and the VP-Na powder was slowly applied to the seed cores by simultaneously spraying a binder solution. Organic solvent was used for making the binder solution (4.55% EC 10 ethanol solution), because the solubility of VP-Na in water is extremely high (about 2 g/ml in purified water at 25 °C). The binder solution was delivered by a peristaltic pump.

Preparation of Sustained Release Pellets Drug-loaded pellets were coated with different coating levels of water-insoluble powders (*i.e.* WAX and Mg-St). The composition of pellets (Tables 1, 2) and the parameters for the powder-layering process are listed in Table 3. The formula indicated by M, W and S in Table 2 means a Mixed layer of the WAX and the Mg-St, a WAX layer and a Mg-St layer, respectively. For example, WSWS means that the pellet is composed of 4 layers, that is, 1st is WAX (W), 2nd is Mg-St (S), 3rd is WAX (W) and 4th (outer layer) is Mg-St (S). The formula MS-1 means that the pellet is composed of 2 layers and the 1st layer is the mixture layer (M) of WAX and Mg-St with the ratio of 65/32 and 2nd layer is Mg-St (S).

The water-insoluble powder was slowly applied to the drug core by simul-

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taneous spraying of a binder solution. A binder solution (4.55% EC 10 ethanol solution) was prepared by dissolving EC 10 in ethanol with magnetic stirring, because the VP-Na was very sensitive to humidity. The binder solution was continuously sprayed on the moving drug cores using a peristaltic pump. Powder addition was started at the same time the binder solution spraying started. At fixed intervals, fixed weights of the powder composition were layered onto the drug cores. Resultant sustained release pellets were dried in an oven at 40 °C for 20 h prior to heat-treatment.

***In Vitro* Release Testing** Release testing was carried out by the Japanese Pharmacopoeia (JP XIV) rotating basket method (50 rpm.; purified water 900 ml; 37 °C). Purified water was used as a dissolution medium. The concentration of VP-Na was measured using an electric conductivity meter (Digital conduct meter, Model, CM-15A, DKK-TOA Corporation, Japan). MDT[11] (mean dissolution time) was used as an index of the drug release rate, and these values were calculated using the computer program "MULTI".

Heat-Treatment Heat-treatment was performed using a CF-granulator under a rotating bottom plate (Table 4). Heat-treatment effects (temperature and time) were investigated using pellets composed of 6 sustained release layers (Table 1, formula No. 4). After powder coating, the resulting pellets were cured at 70, 75 or 85 °C for 2—30 min by a CF-Granulator to prolong the release rate.

Microscopy of Pellets The surface morphology of several pellets was observed with an optical microscope (OLYMPUS (VANOX), Tokyo, Japan). Cross-sections of coated pellets with or without heat-treatment were examined by scanning electron microscopy (SEM, JSM-T20, JEOL, Ltd., Japan).

Results and Discussion

A CF-Granulator[12] was an appropriate machine for powder coating. Keeping the balance between the feeding rate of the layering powder and the binder solution is very important for powder coating using a CF-Granulator. The feeding rate of powder and binder was optimized in order to prevent agglomeration and powder loss. Particle size distributions of the coated pellets prepared in this study were sharp (mean diameters were about 1400 μm).

Morphology of Several Coating Process Pellets Microscopic evaluation of pellets was performed. Figure 1 shows optical photographs of pellets produced at each stage of the coating process. Figure 1(A) shows a photograph of the seed cores. On the surface of the seed cores, VP-Na was coated (B) (drug cores). On the surface of drug cores, the WAX and the Mg-St were coated (Table 1, formula No. 3) (C). According to visual observations, the surfaces of pellets are all smooth, indicating that the balance of powder feeding and the binder addition were in good conditions in this study.

Effect of the Loading Weight of Water-Insoluble Powders on Release Profiles The effect of varying coating levels of the WAX and the Mg-St on release profiles is shown in Figs. 2 and 3, respectively. Table 1 shows the formula of these pellets (formula No. 1 and No. 2). It is known that the drug release rate is considerably influenced by the coating level of the water-insoluble powder.[13] According to the release profiles of Fig. 2 (WAX) and Fig. 3 (Mg-St), the Mg-St was more effective in prolonging the release rate of a drug from coated-pellets than WAX. But, in both cases, high loadings of water-insoluble powders were required to achieve long-sustained release.

Effect of Heat-Treatment Conditions on Drug Release There are several curing techniques, *i.e.* heat, UV irradiation and chemical reaction using catalysts.[14] In general, curing reduces the rate of drug release and results in stable drug release profiles.[15] In this study, heat-treatment was performed using a CF-granulator under a rotating bottom plate under the conditions shown in Table 4.

(1) Effect of Heat-Treatment Temperature and Time on the Drug Release Rate: Figure 4 shows the dissolution profiles of VP-Na from VP-Na sustained release pellets (formula No.4 (Table 1)) which were heat-treated with various heat-treatment temperatures and times. As heat-treatment temperature increased, the drug release rate decreased. Heat-treatment for 10 min is sufficient for obtaining a stable release layer. Further heat-treatment at 70 and 75 °C did not affect the drug release rate.

However, in the case of pellets heat-treated for 30 min at 85 °C, the release pattern was changed. It was found that heat-treatment retarded drug release, and its effect was related to heat-treatment temperature and time.

The rate of drug release from coated-pellets composed of triple layers (Table 2, formula SWS-3) decreased dramatically after heat-treatment (Fig. 5). This may be because heat-treatment retarded drug release, mainly by decreasing the porosity of the WAX layer.

(2) Scanning Electron Microscopy (SEM) of Coated Pellets: A cross-section of the coated pellets (Table 2, formula SWS-3) was examined by scanning electron microscopy (SEM) (Fig. 6). SEM analysis indicated that heat-treatment caused the WAX to melt, and the distributed WAX formed a film-like structure (shown with an arrow in Fig. 6). Figure 6(A) is the cross-section of the layer of pellets with no treat-

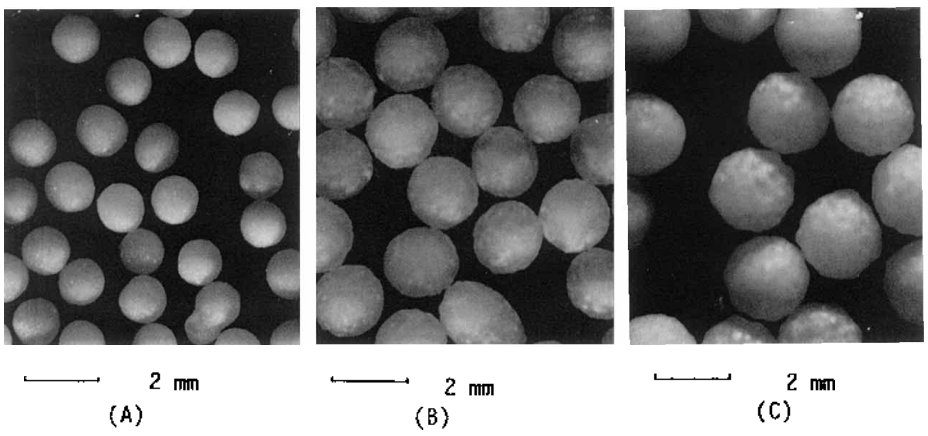

Fig. 1. Optical Photographs of the Pellets Prepared at Each Coating Process Stage

(A) Nonpareil 103 20/24 mesh size pellets (seed cores). (B) Pellets coated with VP-Na powder on Nonpareil 103 pellets (drug cores). (C) Pellets coated with Mg-St powder and WAX powder on drug cores. Formula: No. 3 in Table 1.

Table 1. Formula of VP-Na Sustained Release Pellets

Formula No.	1	2	3	4	5
—VP-Na Core—					
Nonpareil 103 (20/24 mesh size) (g)	160	160	160	160	83
EC 10 (g)					17
VP-Na (g)	320	320	320	320	200
EC 10 (binder) (g)	26	26	26	26	16
—Sustained release layer— (Total amount)					
WAX (g)	160	0	80	120	125
Mg-St (g)	0	160	80	120	125
EC 10 (binder) (g)	14	14	14	24	24
Total (g)	680	680	680	690	590
WAX/Mg-St ratio	∞	0.00	1.00	1.00	1.00
Layer number					
First layer					
WAX (g)	160	—	80	40	—
Mg-St (g)	—	160	—	—	—
WAX (g)/Mg-St (g)	—	—	—	—	125/125
Second layer					
WAX (g)	—	—	—	—	—
Mg-St (g)	—	—	80	40	—
Third layer					
WAX (g)	—	—	—	40	—
Mg-St (g)	—	—	—	—	—
Fourth layer					
WAX (g)	—	—	—	—	—
Mg-St (g)	—	—	—	40	—
Fifth layer					
WAX (g)	—	—	—	40	—
Mg-St (g)	—	—	—	—	—
Sixth layer					
Mg-St (g)	—	—	—	40	—

Table 2. Formula of VP-Na Sustained Release Pellets 40%

Formula	M-1	M-2	M-3	WS	MS-1	MS-2	MS-3	SWS-1	SWS-2	SWS-3	WSWS	SWSWS
—VP-Na Core—												
Nonpareil 103 (20/24 mesh size) (g)					120							
VP-Na (g)	←				180							→
EC 10 (binder) (g)					10							
—Sustained release layer— (Total amount)												
WAX (g)	86	64	43	64	64	49	32	64	43	26	64	51
Mg-St (g)	43	64	86	64	64	81	96	64	86	102	64	77
EC 10 (binder) (g)	11	12	11	12	12	11	12	12	11	12	12	12
Total (g)	450	450	450	450	450	450	450	450	450	450	450	450
WAX/Mg-St ratio	2.00	1.00	0.50	1.00	1.00	0.60	0.34	1.00	0.50	0.25	1.00	0.67
Layer number		←			Coating method of sustained release layer						→	
First layer												
WAX (g)	—	—	—	64	—	—	—	—	—	—	32	—
Mg-St (g)	—	—	—	—	—	—	—	32	43	51	—	26
WAX (g)/Mg-St (g)	86/43	64/64	43/86	—	64/32	49/49	32/64	—	—	—	—	—
Second layer												
WAX (g)	—	—	—	—	—	—	—	64	43	26	—	26
Mg-St (g)	—	—	—	64	32	32	32	—	—	—	32	—
Third layer												
WAX (g)	—	—	—	—	—	—	—	—	—	—	32	—
Mg-St (g)	—	—	—	—	—	—	—	32	43	51	—	26
Fourth layer												
WAX (g)	—	—	—	—	—	—	—	—	—	—	—	26
Mg-St (g)	—	—	—	—	—	—	—	—	—	—	32	—
Fifth layer												
Mg-St (g)	—	—	—	—	—	—	—	—	—	—	—	26

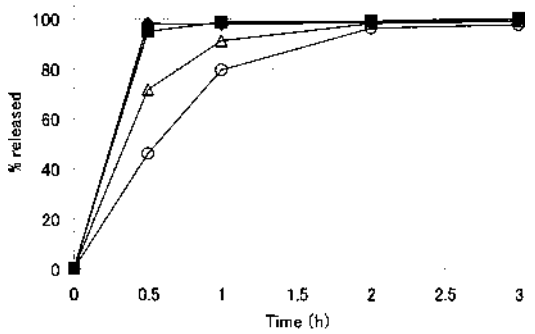

Fig. 2. Effect of Coating Level of WAX on VP-Na Release from the Pellets

Coating level: ◆ 40 g, ■ 80 g, △ 120 g and ○ 160 g. Formula: No. 1 in Table 1.

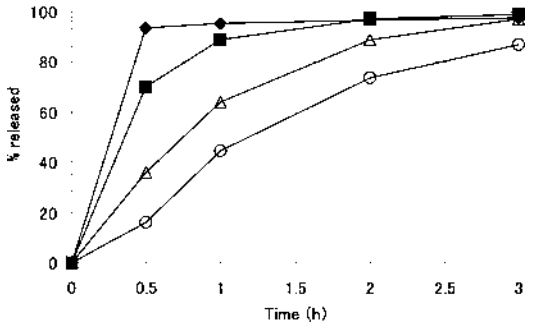

Fig. 3. Effect of Coating Level of Mg-St on VP-Na Release from the Pellets

Coating level: ◆ 40 g, ■ 80 g, △ 120 g and ○ 160 g. Formula: No. 2 in Table 1.

ment. Figures 6(B) and (C) are cross-sections of the layer of pellets with heat-treatment at 75 and 85 °C, respectively. On SEM observations, the volume of the WAX layer decreased, and the WAX layer became dense with an increase in heat-treatment temperature. It was found that the film-like WAX layer could have a great effect in prolonging the drug release rate.

Effect of Structural Difference of Release Controlled Layers on Drug Release Rate Even if compositions are the same, the drug release rate can be affected by structural differences in the release controlled layer. The total weights of coated WAX and Mg-St in formula M-2, WS, MS-1, SWS-1 and WSWS are the same (WAX/Mg-St=1/1; Table 2), but the structures of their sustained release layers are different from one another, leading to individual MDT values. The MDT value (no-treatment) of M-2 is 0.7 h. This value is almost the same as WS (MDT=0.7 h). In the case of a multilayer type (more than 3 layers), the MDT values of SWS-1 (MDT=1.5 h) and WSWS (MDT=1.3 h) were longer than with the other types.

Figure 7 shows the three types of release controlled layers; that is, (A) single layer type (Table 2, formula M-2 (MDT=0.7 h)), (B) double layer type (Table 2, formula MS-1 (MDT=1.0 h)) and (C) triple layer type (Table 2, formula SWS-1 (MDT=1.5 h)). The numbers (*i.e.* 32, 64) in Fig. 7 are the weight of the coated powder. In these three types, the weight of the Mg-St used is the same as that of the WAX used. According to the listed MDT values, it was found that drug release rates were influenced significantly by structural

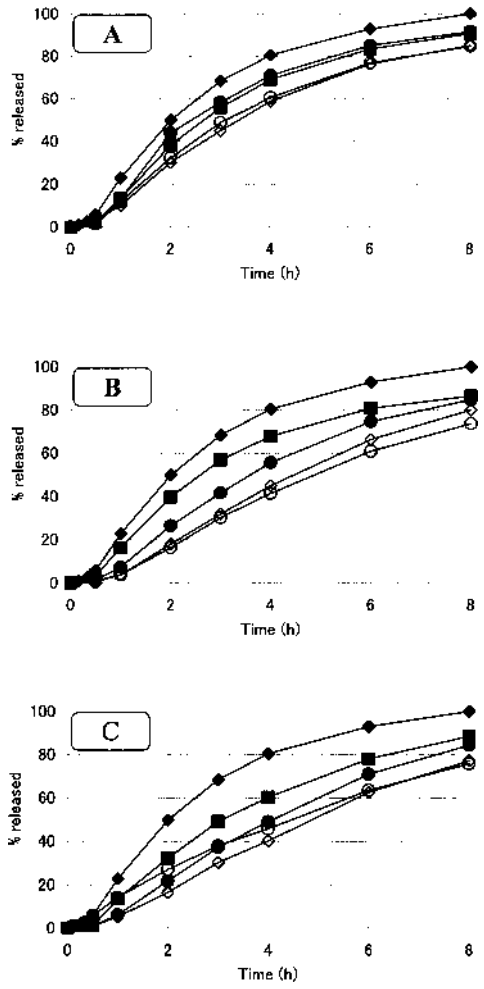

Fig. 4. Effect of Heat-Treatment Temperature and Time on VP-Na Release Rate

A, heat-treatment at 70 °C; B, heat-treatment at 75 °C; C, heat-treatment at 85 °C. Heat-treatment time: ◆, 0 min; ■, 2 min; ●, 5 min; ◇, 10 min; ○, 30 min. Formula: No. 4 in Table 1.

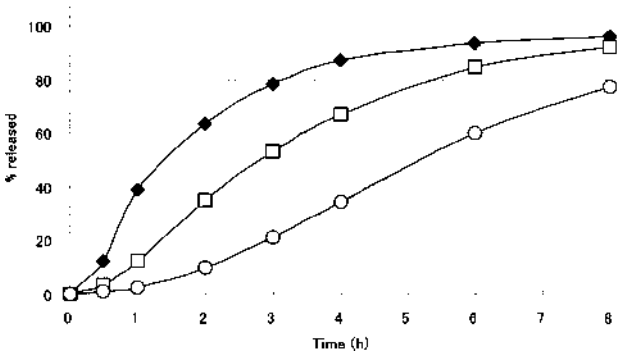

Fig. 5. Effect of Heat-Treatment Temperature on VP-Na Release Rate

◆ without heat-treatment, □ heat-treatment at 75 °C, ○ heat-treatment at 85 °C. Formula : SWS-3 in Table 2.

differences of the release controlled layer. Among these three types, the triple layer type (sandwich type) was most effective in prolonging the drug release rate. This was because the uniform WAX layer between Mg-St layers was effective for achieving a dense layer.

Effect of Component Difference of Release Controlled Layers on Drug Release Rate Even if the structure of the

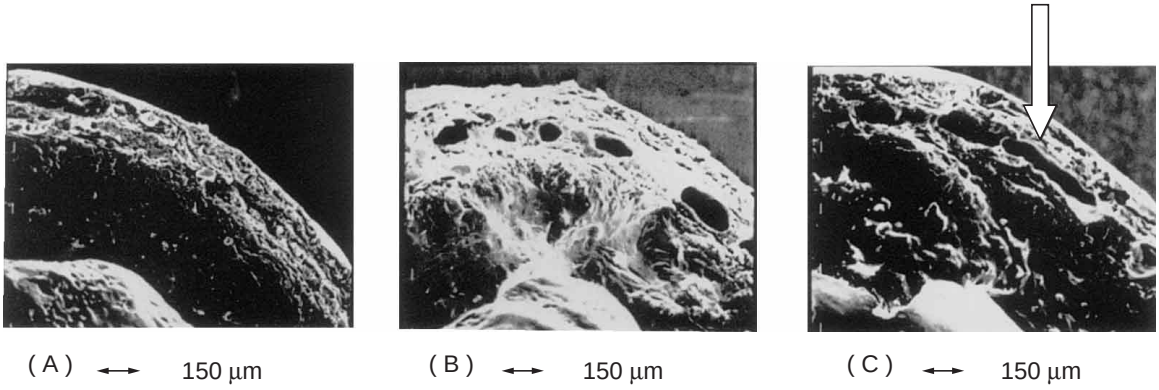

Fig. 6. SEMs of the Cross Section of Sustained Release Layer of VP-Na Sustained Release Pellets 40%
(A) No-treatment, (B) heat-treatment at 75 °C, (C) heat-treatment at 85 °C. Formula: SWS-3 in Table 2.

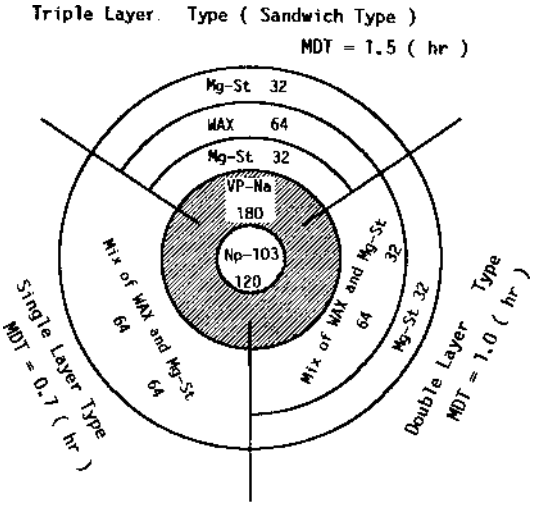

Fig. 7. Various Types of Release Controlled Layer (VP-Na Content=40 w/w %, Mg-St/WAX=1/1 w/w %)
The numbers in Fig. 7 are the weights which were used for preparing the various sustained release pellets of VP-Na.

Table 3. Operating Conditions

Rotation speed (rpm)	250
Slit air volume (l/min)	100
Slit air temp. (°C)	30
Spray air volume (l/min)	10
Powder feeding rate (g/min)	6
Binder flow rate (ml/min)	17

Table 4. Heat-Treatment Conditions

Rotation speed (rpm)	250
Slit air volume (l/min)	300—400
Slit air temp. (°C)	70, 75 or 85
Heat treatment time (min)	2, 5, 10 or 30

release controlled layer and the loading weight of water-insoluble polymers was the same, the characteristics of drug release would depend on the different components of the release controlled layer.

(1) Single Layer Type: Judging from the MDT values of formulas M-1, M-2 and M-3 (Table 5), the effect of the mixture layer of the WAX and the Mg-St on prolonging the drug release rate was not significantly observed. Among the samples of the single layer type tried in this study, as the WAX/Mg-St ratio decreased, the MDT value increased. In the case of single layer type, heat-treatment could not be performed because of the aggregation between particles.

(2) Double Layer Type: Table 2 shows the formulas of a release controlled layer. The MDT values of a double layer type (formula WS, MS-1, MS-2 and MS-3) are shown in Table 5. In all the double layer types prepared in this study, heat-treatment could be performed at 85 °C. The formula of WS and MS-1 was the same, but the effect on prolonging the release rate was higher in the case of MS-1, where the WAX was mixed with the Mg-St. As the mixing ratio of the WAX increased, the effect on prolonging the release rate decreased in the case of non-heat-treatment. The MDT values increased as heat-treatment temperature increased.

(3) Triple Layer Type: Table 2 shows the formulas of the release controlled layer. The MDT values of the sandwich type (triple layer type) (formula SWS-1, -2, -3) are shown in Table 5. The sandwich type layer was more effective in obtaining sustained release than the other types.

As mentioned above, heat-treatment was operated by a CF-Granulator (Table 4). The external Mg-St layer inhibits the aggregation between particles caused by the melting WAX. Heat-treatment was effective in prolonging the release rate, even at 75 °C. The weight ratio of the Mg-St to the WAX was changed to control the drug release rate. In the case of formulas SWS-1 and SWS-2, heat-treatment at 85 °C could not be performed because of the aggregation between particles. Heat-treatment at 85 °C could be performed only in the case of the formula SWS-3, *i.e.* the ratio of the weight of the WAX to the Mg-St was the smallest. This was because that the WAX did not move into the outer layer at this ratio. The preparation of formula SWS-3, which was heat-treated at 85 °C, was the most effective in prolonging the drug release rate among the preparations tested in this study. A thin WAX layer between Mg-St layers of adequate thickness is effective in obtaining a dense layer with heat-treatment. The heat-conductivity to the WAX layer depends on the thickness. As the thickness of the WAX layer increases, the heat-conductivity to the WAX layer decreases, and it is hard to obtain a uniform dense layer. Furthermore, as the thickness of the WAX layer increases, aggregation problems between par-

Table 5. Mean Dissolution Time (MDT) of VP-Na Sustained Release Pellets 40%

	Single layer type			Double layer type				Triple layer type		
Formula	M-1	M-2	M-3	WS	MS-1	MS-2	MS-3	SWS-1	SWS-2	SWS-3
WAX/Mg-St ratio	2	1	0.5	1	1	0.6	0.34	1	0.5	0.25
MDT (no-treatment) (h)	0.6	0.7	0.8	0.7	1	1.5	1.6	1.5	2.2	1.9
MDT (heat-treatment at 75 °C) (h)	I.P.	I.P.	I.P.	1.2	1.5	2.2	1.9	2.9	3.1	3
MDT (heat-treatment at 85 °C) (h)	I.P.	I.P.	I.P.	1.9	2.5	3.9	3.9	I.P.	I.P.	4.4

I.P.: Heat-treatment was impossible because of the aggregation between particles.

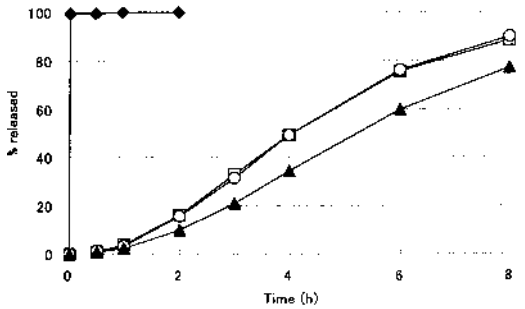

Fig. 8. Release Profiles of VP-Na from the VP-Na Powder and Three Preparations Heat-Treatment at 85 °C

◆ VP-Na powder: The release profile of the VP-Na from the VP-Na powder. □ MS-2: The release profile of the VP-Na from the pellets (Formula: MS-2 in Table 2). ○ MS-3: The release profile of the VP-Na from the pellets (Formula: MS-3 in Table 2). ▲ SWS-3: The release profile of the VP-Na from the pellets (Formula: SWS-3 in Table 2).

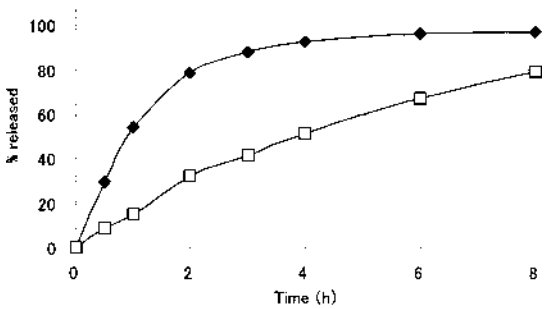

Fig. 9. Release Profiles of VP-Na from the Pellets with and without Heat-Treatment

◆ without heat-treatment, □ heat-treatment at 75 °C. Formula: WSWS in Table 2.

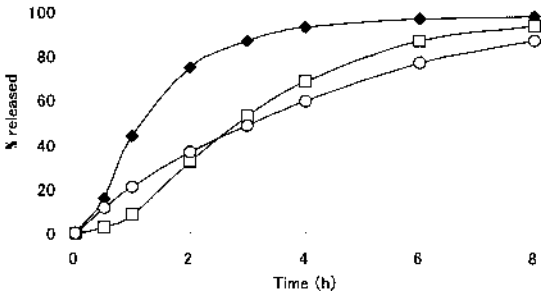

Fig. 10. Release Profiles of VP-Na from the Pellets with and without Heat-Treatment

◆ without heat-treatment, □ heat-treatment at 75 °C, ○ heat-treatment at 85 °C. Formula: SWSWS in Table 2.

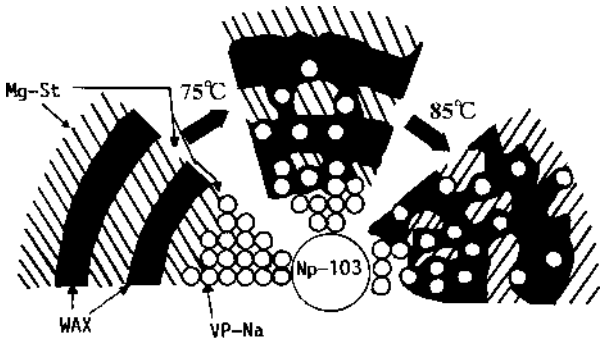

Fig. 11. Schematic Hypothesis of Shortening a Drug Release Lag Time

ticles occur.

Shortening the Release Lag-Time It is often observed that the slower the drug release rate, the longer the lag-time of drug release.[10] The duration of the lag time increased with increasing heat-treatment temperature and time.[11] Figure 8 shows the release profiles of VP-Na powder and the three kinds of pellets with heat-treatment at 85 °C. The release rate of three sustained release pellets were significantly slower than that of VP-Na powder, but a lag time of drug release was observed. For shortening drug release lag time, more multi-thin-layer type pellets were prepared. In the case of pellets with four sustained release layers (WSWS), zero order drug release occurred without a drug release lag time after heat-treatment at 75 °C (Fig. 9).

Figure 10 shows the release profiles of VP-Na from the sustained release pellets composed of 5 layers with the Mg-St (S) and the WAX (W), in the order of SWSWS. The formula is shown in Table 2 (formula SWSWS). Sustained release pellets with heat-treatment at 75 °C showed a sigmoid release profile with an initial lag time, but this lag time significantly diminished after heat-treatment at 85 °C. Figure 11 shows the hypothesis to explain why the drug is released without a lag time and with nearly zero order kinetics. First of all, melted WAX moved into the Mg-St layer through the gap of the Mg-St powder. It is presumed some of the VP-Na dispersed in the melted WAX with an increase in heat-treatment temperature, and VP-Na then moved into the release controlled layer. Also, the VP-Na concentration gradient in the sustained release layer of VP-Na-sustained release pellets was good for diminishing the lag time and producing a nearly zero order release. The structural change of the sustained release layer by heat-treatment strongly affected drug release. Thus, a slow and zero-order drug release was obtained with heat-treatment at 85 °C, while a first-order release pattern with a drug release lag-time was obtained with heat-treatment at 75 °C. Proper design of the heat-treated

multi-layer was proposed as a way to obtain approximate long-sustained zero-order release.

Conclusion

Sustained release preparations of VP-Na (a highly water-soluble drug) could be prepared by constructing layers composed of the WAX and Mg-St powders by a CF-Granulator. The layer which was prepared by powder coating was effective in prolonging the drug release rate, but in the case of using a highly water-soluble drug, it took a lot of weight of the coating powder. However, the combination of the WAX, the Mg-St layer and heat-treatment appears to retard drug release, mainly by decreasing the porosity of the WAX layer. The Mg-St layer was useful for protecting the aggregation between particles caused by the melted WAX.

Drug release profiles were influenced by structural differences and component differences of sustained release layers. The sandwich type layer was more effective in sustaining drug release than other types. Heat-treatment was very effective at the temperature of 85 °C. Slow and zero-order drug release was obtained by a multi-thin-layer with heat-treatment. This is because the structure of the sustained release layer changed with heat-treatment at 85 °C.

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