Preparation of a Sustained-Release Matrix Tablet of Acetaminophen with Pulverized Low-Substituted Hydroxypropylcellulose *via* Dry Granulation

Yoshiaki KAWASHIMA,*[,a] Hirofumi TAKEUCHI,[a] Tomoaki HINO,[a] Toshiyuki NIWA,[a] Tzu-Lang LIN,[a] and Fujio SEKIGAWA[b]

Gifu Pharmaceutical University,[a] 5–6–1 Mitahora-higashi, Gifu 502, Japan and Shin-Etsu Chemical Co., Ltd.,[b] 6–1 Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100, Japan. Received April 9, 1993

Pulverized L-HPC (low-substituted hydroxypropylcellulose, LH41) can be used as a sustained-release matrix filler. In previous papers, we had reported that the flowability and packability of LH41 powder with or without acetaminophen was improved by wet granulation for practical uses. In the present report, dry granulation *via* slugging was employed to avoid the use of an organic solvent (*e.g.* ethanol). The sustained-releasing functions of the original LH41 were maintained during granulation with lower slugging pressures ($\leqq$10 MPa), whereas they were lost with higher slugging pressures ($\geqq$20 MPa). The sustained-releasing function of the tablet prepared with the granules of LH41 and the drug (acetaminophen) was determined by a function of internal pore size distribution and the swelling property of the tablet. The granules of LH41 and the drug prepared by a roller compactor were applied practically to prepare a controlled-release matrix tablet using a single-punch tabletting machine. It was possible to widely control the drug release of the resultant tablets (*i.e.* rapid- to sustained-release) by changing the roller compaction pressure.

Keywords low-substituted hydroxypropylcellulose; sustained-release; dry granulation; swelling force

Low-substituted hydroxypropylcellulose (L-HPC), produced by substituting hydroxy groups of cellulose with hydroxypropoxyl groups to the extent of 7.0—16.0%, is insoluble in water but swell, when it comes into contact with water. This swelling property results in superior disintegration characteristics of the tablet. In the previous papers,[1] it was found that the disintegrating properties of tablets formulated with L-HPC strongly depended on the particle size and the loading ratio of L-HPC to the drug. Particularly, by increasing the loading ratio of pulverized L-HPC (LH41, mean particle size = 4.4 μm), the drug release from the matrix tablets could be drastically sustained. Nakagami *et al.*[2] found that procainamide tablets with micronized L-HPC maintained sustained-release and unerosible properties in dogs as well as *in vitro*, but HPC and wax matrices were erosible.

In the previous paper,[3] we had improved the flowability and packability of LH41 by wet granulation for use in the practical preparation of tablets. The sustained-releasing functions of the original LH41 were maintained through granulation with ethanol, whereas they were lost with water.

In the present report, the dry granulation of pulverized L-HPC with or without acetaminophen as a model drug was investigated rather than granulation by an organic solvent, and it was confirmed that the sustained-releasing functions of LH41 were maintained even after the granulation. The granules thus obtained were tabletted and the drug-release properties of the resultant tablets were investigated to clear the parameters determining the drug-release rate. The granules were prepared practically using a roller compaction technique, and the controlled-release matrix tablets with rapid- to sustained-release properties were prepared by direct compression with a single-punch tabletting machine.

Experimental

Materials Acetaminophen crystals were obtained from Yoshitomi Pharmaceutical, Japan and Daiwa Chemical, Japan. These were sieved between 32 mesh (500 μm) and 80 mesh (177 μm) (mean particle size = 385 μm, termed ld) and pulverized (mean particle size = 30 μm, termed sd), respectively. The pulverized low-substituted hydroxypropylcellulose (L-HPC: LH41, mean particle size = 4.4 μm) as a matrix material was supplied by Shin-Etsu Chemical, Japan.

Preparation of Granules The granules were prepared by the following two methods.

(1) Tablets (slugs) containing either LH41 (2.0 g) alone or the binary powder mixture (2.0 g) of LH41 and the drug (sd) (loading ratio = 1 : 1) were prepared by an Instron-type hydraulic press (Autograph AG-5000D, Shimadzu, Japan) under various compression (slugging) pressures (3 to 100 MPa) using flat-faced punches and a die with a diameter of 2.0 cm. They were crushed to prepare the granules of LH41 as well as the mixture of LH41 and the drug, termed SG41 and SG(41 + sd), respectively, by a roller mill (TG2S, Erweka, Germany). Then, the granules sieved between 24 mesh (710 μm) and 80 mesh (177 μm) were tabletted.

(2) The binary powder mixture containing LH41 and the drug (sd) (1 : 1) was flaked using a roller compactor (mini type, Freund, Japan) under various roller pressures and was ground by a roller-rotator equipped with a 20 mesh (840 μm) screen. Next, any dry granules, termed DG (41 + sd), which remained over 80 mesh (177 μm) were tabletted.

The variety of physical mixtures and their granules prepared in the present study, and their synopses, are tabulated in Table I.

Preparation of Tablets and Measurement of Their Crushing Strengths The tablets were prepared by the following two methods.

(1) Granules (200 mg) prepared by the aforementioned granulation methods (*e.g.* SG(41 + sd) and DG(41 + sd) granules) were directly compressed by the Autograph (AG-5000D, Shimadzu, Japan) under various compression pressures (100 to 500 MPa; usually 200 MPa unless otherwise mentioned), using flat-faced punches and a die with a diameter of 8.0 mm. The physical mixtures of the granules (SG41 or LH41) and the drug (ld or sd) in various loading ratios (matrix material : drug = 50 : 50, 30 : 70,

TABLE I. Explanation of the Symbols of Granulating Methods and Physical Mixtures Used in the Text

Method	Granulating method		Physical mixture[d]
	Slug	Roller compaction	
Symbol	SG41[a] SG(41 + sd)[b]	DG(41 + sd)[c]	SG41 + ld LH41 + ld LH41 + sd

a) Prepared with LH41 alone. *b, c*) Prepared with LH41 and acetaminophen (sd) (loading ratio = 1 : 1) under various slugging pressures *b*) and roller pressures *c*). *d*) Physical mixtures of SG41 and acetaminophen (ld), of LH41 and ld, and of LH41 and sd with various loading ratios, usually 1 : 1, unless otherwise mentioned.

10 : 90 and 95 : 5; usually 50 : 50 unless otherwise mentioned) were tabletted in the same manner as described for tabletting the granules containing the drug using the Autograph. (2) The DG(41 + sd) granules mixed with magnesium stearate (0.3%) were compressed continuously by a single-punch tabletting machine (KT-2 type, Kimura, Japan) equipped with flat-faced punches in a die having a diameter of 8.0 mm at the rate of 60 tablets/min. The weight and compression pressure of the tablets was set at about 200 mg and about 200 MPa, respectively. The compression pressure was detected with a strain gauge (load cell) attached to the lower punch. The mean weight, weight variation and coefficient of variation (CV) of 20 tablets sampled randomly were calculated.

Tablet crushing strengths were represented by the force required to fracture the tablet under diametrical compression (Autograph AG-5000D, Shimadzu, Japan). The crushing strength was transferred to tensile strength (T) by applying the following equation (Eq. 1).[4]

$$T = 2F/(\pi dt) \quad (1)$$

where F is the crushing strength, d is the diameter of the tablet and t is the tablet thickness. The value of crushing strength employed was the mean of five runs.

Evaluation of Physicochemical Properties of Tablets The dissolution test of the tablets was carried out by the JP XII paddle method (100 rpm) with distilled water (900 ml) at 37 ± 0.5 °C. The concentration of acetaminophen was measured by a spectrophotometer (λ_{max} = 244 nm). T_{50}, the time required for 50% of the drug to be released, was obtained from a plot of the percent (%) of the drug released against dissolution time. Disintegration time in the disintegration medium (distilled water) at 37 ± 0.5 °C was measured using the JP XII disintegration apparatus with disks. The pore size distribution curves of tablets were obtained using a mercury penetration porosimeter (Autoscan-33, Quantachrome, U.S.A.). The apparatus and principles of measurement of the swelling force of tablets were described in a previous report.[3] Tablets compressed by the Autograph at a compression pressure of 200 MPa were placed between a glass filter and a load cell equipped with the Autograph. The swelling force of the tablets was detected by the load cell when water penetrated into the tablet through the glass filter. At least three runs were done in all of the above experiments.

Swelling Work and Force of Granules of the Mixture of LH41 and the Drug The granules (SG(41 + sd), 200 and 100 mg) 177 μm to 710 μm in diameter prepared with various slugging pressures were carefully compacted to form a granule bed which had almost uniform porosity (about 0.580) in a glass tube (diameter, 10.0 mm) using the Autograph for measureing the swelling work and force of the granule bed. The apparatus and principles of measurement were described in previous papers[5]: constant load and volume methods were used for measuring the swelling work and the force of the granule bed, respectively.

Results and Discussion

Effect of Slugging Pressure on the Drug-Release Properties and Tensile Strength of Tablets The physical mixtures (200 mg) of the granules (SG41) of LH41 prepared under several slugging pressures and acetaminophen (1d) (loading ratio = 1 : 1) were compressed into tablets. The physical mixture of SG41 and the pulverized acetaminophen (sd) was not employed in this investigation, because of the poor miscibility of sd particles with SG41. The effects of slugging pressure employed on the drug-release properties (represented by T_{50}), disintegration time, and tensile strength of the resultant tablets are shown in Fig. 1A. The results indicated that T_{50}, the disintegration time and the tensile strengths of the tablets decreased as the slugging pressure employed to prepare the granules (SG41) increased. The sustained-releasing functions of the original LH41 were almost lost at a slugging pressure ≧ 100 MPa. Tablets with the SG41 prepared at 100 MPa immediately swelled and then disintegrated when dispersed in the dissolution medium. In Fig. 2, the effects of the loading ratio of SG41 granules in the tablet on the drug-release rate are shown as a function of the slugging pressure. With an increase in loading ratio or a decrease in the slugging pressure, the drug-release rate decreased. At higher loading (≧90%) of SG41 granules, the drug release was sustained, although it still depended somewhat on the slugging pressure, as shown in Fig. 2. It was assumed that with a higher loading of SG41 granules, a continuous phase of L-HPC enveloping the drug was constructed in the tablet, leading to its sustained-release property.

The tensile strength, T_{50} and disintegration time of the tablets of the SG(41 + sd) granules containing LH41 and the drug (loading ratio = 1 : 1) are shown in Fig. 1B, in order to investigate the effect of slugging pressure on these properties. The results indicated that the tensile strength, T_{50} and disintegration time of the tablets decreased as the slugging pressure greater than 10 MPa increased. The tablets of SG(41 + sd) granules produced at pressures lower than 10 MPa sustained the drug release as well as that of the physical mixture of the original LH41 and the drug (sd), termed the LH41 + sd mixture. The tablet of SG(41 + sd) granules sustained the drug-release rate longer than did the mixture of SG41 granules and the drug. In the tablet SG (41 + sd) granules, a more uniform matrix structure with LH41 enveloping the drug should be constructed, compared to that of SG41 + 1d mixture. This might result in differences in drug-release properties.

In Fig. 1B it was revealed that the drug-release rate,

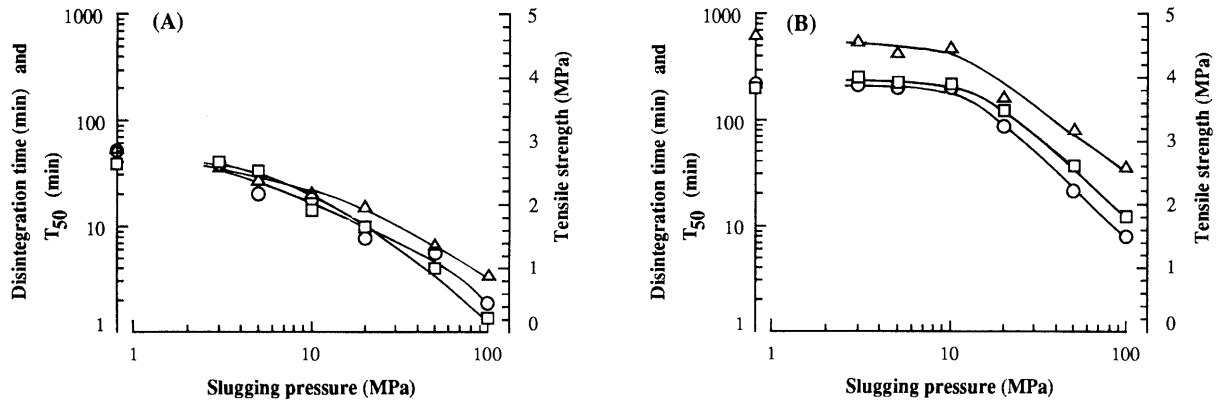

Fig. 1. Effect of Slugging Pressure Employed on (○) Drug-Release Rate (T_{50}, n = 3), (□) Disintegration Time (n = 3—6), and (△) Tensile Strength (n = 5) and of Tablets Prepared with (A) SG41 + 1d Mixture or (B) SG(41 + sd) Granules

The plots on the left ordinate are the values of tablets prepared with the LH41 + 1d or LH41 + sd mixture without slugging.

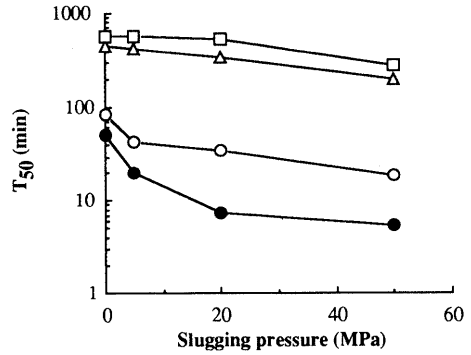

Fig. 2. Effect of Slugging Pressure Employed on Drug-Release Rates (T_{50}, $n=3$) of Tablets Prepared with Various Loading Ratios of SG41 to Acetaminophen (1d), (●) 50:50, (○) 70:30, (△) 90:10, (□) 95:5

The plots on the left ordinate are the values of tablets prepared with various loading ratios of LH41 to 1d.

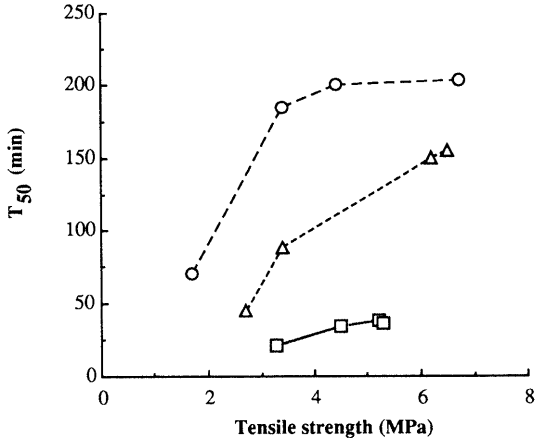

Fig. 3. Effect of Tensile Strength ($n=5$) on Drug-Release Rate (T_{50}, $n=3$) of Tablets of SG(41+sd) Granules Produced by Slugging at (○) 5 MPa, (△) 20 MPa, and (□) 50 MPa

i.e.. T_{50}, disintegration time and the mechanical strength, *i.e.* tensile strength, of tablets were determined by the slugging pressure employed to produce the granules. This finding suggested that a clear correlation might be seen between those parameters, *e.g.* T_{50} and tensile strength of the tablet. The effect of the tensile strength of tablets on the drug-release rate (T_{50}) was investigated, as shown in Fig. 3. T_{50} of the tablets of SG(41+sd) granules produced by slugging at 5 and 20 MPa increased as their tensile strengths increased. Even if the tensile strengths of tablets were same, the T_{50} of the tablets differed when different slugging pressures were applied. This finding indicated that the tensile strength of a tablet was not always the main factor in determining the drug-release rate.

To clarify the physical significance of slugging and compression pressures and their effect on the drug-release properties of a tablet, the correlation between T_{50} of the tablets of SG(41+sd) granules (prepared under 200 MPa compression pressure) and the slugging pressures, and between T_{50} of the tablets of the LH41+sd mixture and the compression pressures were compared in Figs. 1 and 4. T_{50} of the LH41+sd mixture tablets increased with a compression pressure increase at a compression higher than 10 MPa. Whereas, at the slugging pressure employed higher than 10 MPa, the T_{50} of the tablets rapidly decreased. It

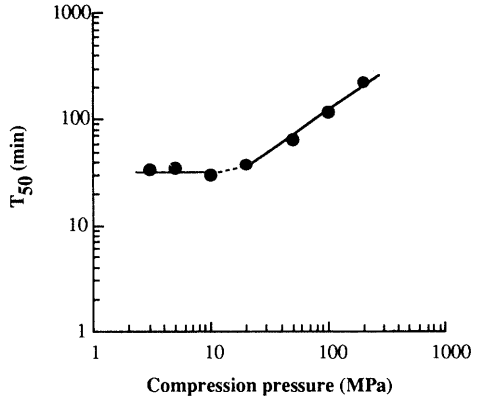

Fig. 4. Correlations between the T_{50} ($n=3$) of Tablets of the LH41+sd Mixture and Compression Pressure

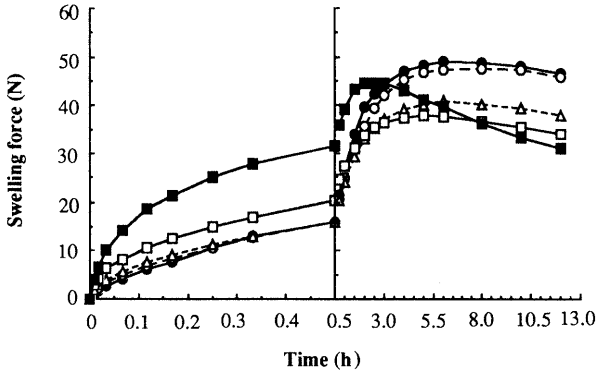

Fig. 5. Swelling Force of Tablets ($n=3$) Prepared with (●) LH41+sd Mixture or with SG(41+sd) Granules Prepared by Slugging at (○) 5 MPa, (△) 20 MPa, (□) 50 MPa, and (■) 100 MPa

was found that the SG(41+sd) granules with greater than 10 MPa slugging pressure lost the sustained-releasing functions of the original LH41.

Effect of Slugging Pressure on the Swelling Properties of the Tablets of SG(41+sd) Granules The swelling properties of the tablets were investigated in order to explain the differences in drug-release rates of the tablets of SG (41+sd) granules produced under the various slugging pressures listed in Fig. 5. The tablets of SG(41+sd) granules produced with higher slugging pressures ($\geqq$20 MPa) swelled rapidly on contact with water. The swelling force increased with an increase in the slugging pressure at the initial stage, but afterwards, the swelling force decreased due to the disintegration of the tablets by absorbed water. This was especially apparent when the slugging pressure was higher than 100 MPa, as shown in Fig. 5. The swelling forces of tablets prepared with SG(41+sd) granules produced by slugging at 5 MPa and those prepared with the LH41+sd mixture showed similar behavior. The differences in swelling behaviors of the tablets might depend on the internal structure of the tablet.

To clarify the internal structure of the tablets, pore size distributions were investigated. The pore size distributions of the tablets showed two main peaks corresponding to macro (20 nm $\leqq$pore radius$\leqq$5000 nm) and micro pores (pore radius$\leqq$20 nm) (Fig. 6). Macro and micro pores might correspond to the interstitial pores between coarse particles (*e.g.* SG(41+sd) granules) and fine particles (polymer or

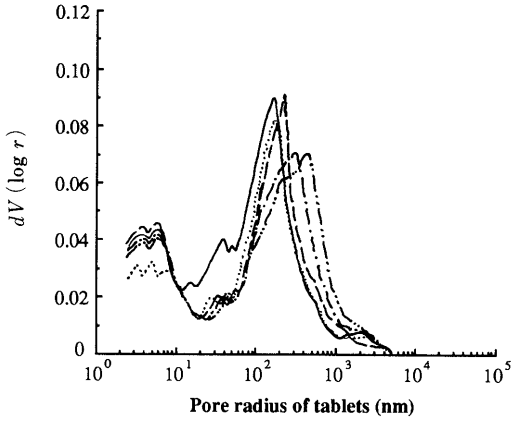

Fig. 6. Pore Size Distribution of Tablets ($n=5$) Prepared with (——) LH41+sd Mixture, or SG(41+sd) Granules Produced by Slugging at (------) 5 MPa, (——) 20 MPa, (—·—) 50 MPa, and (—···—) 100 MPa (Ordinate: V, Volume; r, Pore Radius)

TABLE II. Median Pore Radius of Tablets of SG(41+sd) Granules Prepared by Various Slugging Pressures

Slugging pressure (MPa)	0[a]	5	20	50	100
Median pore radius (μm)[b]	0.063	0.076	0.087	0.111	0.132

a) LH41+sd mixture. *b*) Tablets of LH41+sd mixture or SG(41+sd) granules under 200 MPa compression pressure ($n=5$).

constituent particles of the granule), respectively. The tablets of SG(41+sd) granules produced by a lower slugging pressure ($\leqq$10 MPa, *viz.* 5 MPa) showed a pore size distribution similar to that of the LH41+sd mixture. It was assumed that such granules could be easily crushed to reconstruct a new matrix structure like the LH41+sd compressed mixture. However, SG(41+sd) granules produced with higher slugging pressures ($\geqq$20 MPa) were assumed to be mechanically strong, whereby it was difficult to destruct or to crush the individual granules into constituent fine powders. Therefore, the peaks of macropore distributions shifted toward the larger pore size (radius). The median pore radii of the tablets of SG(41+sd) granules are listed in Table II. The results indicated that the median pore radius of the tablet of SG(41+sd) granules increased by increasing the slugging pressure. According to Washburn's equation (Eq. 2),[6] the water-penetrating speed (dl/dt) into a capillary is proportional to the radius of the capillary (Eq. 3).

$$l^2 = r\gamma \cos\theta t/(2\eta) \quad (2)$$

or

$$dl/dt = r\gamma \cos\theta/(4\eta l) \quad (3)$$

where l is the length of penetration, r is the capillary radius, γ is the liquid surface tension, η is the liquid viscosity, t is time and θ is the contact angle. Assuming that the radius of the capillary can be represented by the median pore radius, and that the other parameters in Eq. 3 are the same for all tablets, the penetration speed of water into the tablet became faster as the pore radius increased. A rapid penetration of water into the tablet could promote the disintegration of tablets of SG(41+sd) granules prepared with higher slugging pressures.

TABLE III. Swelling Work of SG(41+sd) Granules Prepared by Various Slugging Pressures

Slugging pressure (MPa)	0[a]	5	20	50	100
Swelling work ($\times 10^{-4}$ J)[b]	0.371	0.711	1.050	1.421	1.514

a) LH41+sd mixture. *b*) 200 mg of LH41+sd mixture or SG(41+sd) granules (powder bed) was used ($n=3$).

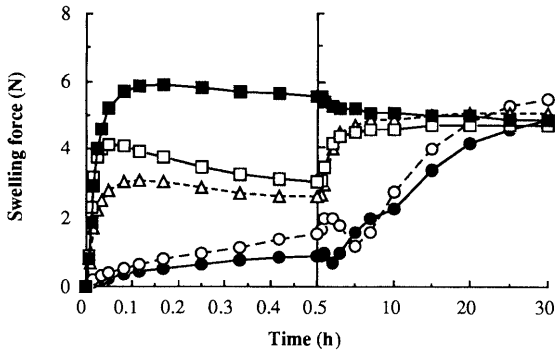

Fig. 7. Swelling Force of (●) LH41+sd Mixture ($n=3$) and of SG (41+sd) Granules Produced by Slugging at (○) 5 MPa, (△) 20 MPa, (□) 50 MPa, and (■) 100 MPa

The swelling work of SG(41+sd) granules produced under various slugging pressures was measured by a constant load method.[5] The swelling work of these granules increased as the slugging pressure increased (Table III). The swelling force of SG(41+sd) granules was measured by a constant volume method,[5] as shown in Fig. 7. The results indicated that the swelling force of these granules prepared under higher slugging pressures ($\geqq$20 MPa) rapidly increased at the initial stage. All powder beds of SG(41+sd) granules were set to have uniform porosity (*ca.* 0.580) in this study. The intra-porosity of the SG(41+sd) granule decreased by increasing the slugging pressure. Therefore, the powder bed of SG(41+sd) granules prepared under a higher slugging pressure had a higher interstitial porosity between the granules packed in the bed, corresponding to the macropore in the tablet (Fig. 6), which led to the rapid penetration of water into the bed at the initial stage. This resulted in a rapid swelling of the granules, producing a sharply increased swelling force. During swelling, L-HPC particles might rearrange in the bed to relax the swelling force as shown in Fig. 7. Thereafter, the swelling force increased gradually with further penetration of water into the bed of granules prepared by slugging at a lower pressure. Finally almost the same swelling force was produced by the swelling of the bed, irrespective of slugging pressure. Those findings in Figs. 5 and 7 suggested that the initial internal structure of the compact (tablet or bed) was a main factor in determining its swelling behavior.

Preparation of Sustained-Release Tablets Using a Single-Punch Tabletting Machine The drug-release profiles of tablets of DG(41+sd) granules, produced with an LH41+sd mixture by a roller compactor operated at various roller compaction pressures, and prepared by compression with the Autograph at 200 MPa, are shown in Fig. 8. The drug-release rates of tablets increased with increasing the roller compaction pressure, as expected. These findings were similar to the results shown in Fig. 1,

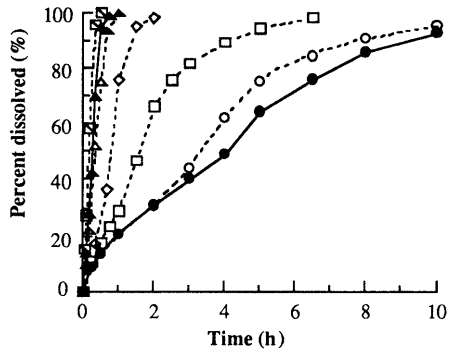

Fig. 8. Dissolution Profiles of Acetaminophen Tablets Prepared with DG(41+sd) Granules (Produced by a Roller Compactor under Various Roller Pressures, (○, ●) 0.2—1 MPa, (□) 1—2 MPa, (◇) 2—3 MPa, (△, ▲) 5 MPa, and (▨) 8 MPa) Using the Autograph (Open Symbols, $n=3$) or a Single-Punch Tabletting Machine (Closed Symbols, $n=3$)

TABLE IV. Properties of Tablets Prepared Continuously by a Single-Punch Tabletting Machine

Roller pressure (MPa)	DG(41+sd)[a]	
	0.2—1	5
Tablet weight (mg)[b]	202.5±1.4	202.4±1.5
Coefficient of variation (%)	0.69	0.74
Deviation range (%)	−1.59—1.2	−0.896—1.53
Tensile strength (MPa)	2.8	1.3
Tablet density (g/cm^3)	1.202	1.181

a) The symbol is explained in Table I. *b*) Mean±S.D. ($n=20$).

although the T_{50} of DG(41+sd) tablets was rather reduced when compared at the same pressures exerted by the roller compactor and hydraulic press (by Autograph). This results suggested that the roller pressure with a roller compactor cannot directly correspond to the slugging pressure with a hydraulic press. This difference should be investigated further.

As found in the previous paper,[3] it was difficult to continuously compress the LH41+sd mixture by a single-punch tabletting machine due to its extremely low bulk density. To accomplish continuous tabletting, the formulation of DG(41+sd) granules mixed with 0.3% magnesium stearate was found to be suitable. The properties of the resultant tablets of DG(41+sd) granules produced under 0.2—1 and 5 MPa roller pressures are given in Table IV. Excellent uniformity of the weight of tablets in Table IV indicated that the DG(41+sd) granules were uniformly fed into the die cavity, due to their free flowing properties. The drug-release profiles of the tablets are shown in Fig. 8. The tablet of DG(41+sd) granules produced under 0.2—1 MPa roller pressure showed a sustained-release profile, whereas the drug-release rate from the tablet of DG(41+sd) granules prepared under 5 MPa roller pressure was extremely fast, because the tablets rapidly disintegrated when dispersed in the dissolution medium, as expected.

In conclusion, by increasing the loading of SG41 granules in the tablet, the drug release from the tablet was drastically sustained, as well as the original LH41 formulation. The sustained-releasing functions of LH41 formulated in SG (41+sd) granules prepared with lower slugging pressures ($\leqq$10 MPa) were maintained, whereas those functions were lost when prepared at higher slugging pressures ($\geqq$20 MPa). The DG(41+sd) granules of LH41 and the drug produced using a roller compactor could be continuously compressed by a single-punch tabletting machine. It was found that the drug release from the resultant tablet was widely controlled (*i.e.* from rapid- to sustained-release) by employing granules prepared under lower to higher roller compaction pressures (0.2—8 MPa).

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