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Preparation of prolonged-release matrix tablet of acetaminophen with pulverized low-substituted hydroxypropylcellulose via wet granulation

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Summary

Pulverized L-HPC (low-substituted hydroxypropylcellulose, LH41) can be used as a prolonged-release matrix filler. LH41 powders with or without acetaminophen were granulated with ethanol or water to improve their micromeritic properties for practical tabletting by using a high-speed agitator, centrifugal fluidizing granulator or spray dryer. The water-granulated LH41 tablet was readily crushed under mechanical stress and rapidly disintegrated in water, resulting in rapid drug release. The ethanol-granulated LH41 provided a mechanically strong matrix tablet in which the drug was dispersed uniformly, resulting in prolonged drug release in water without disintegration. LH41 granules became swellable due to a physical crosslinking structure formed during granulation. The crosslinking structure in the ethanol-granulated LH41 was broken up during tablet preparation, with loss of the swelling properties. On the other hand, the LH41 granules prepared with water were mechanically strong, so that the physical crosslinking structure was retained in the tablet; consequently the tablet rapidly swelled and disintegrated.

Introduction

The use of polymers for controlling the release of drugs has become important in pharmaceutical formulations as a means of obtaining a higher therapeutic index. Cellulose derivatives are the most commonly used hydrophilic polymers for oral controlled-release tablet formulations, i.e., coating and matrix systems. The former is the best-established system. However, the latter system has been gaining increasing attention because of the simple and low-cost manufacturing process, simply by compressing granules of the active ingredient and polymer or their powdered mixture. There are several articles discussing the use of water-soluble polymers in hydrophilic gel-forming matrices, such as hydroxypropylmethylcellulose (HPMC) (Lapidus and Lordi, 1966; Al-

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derman, 1984; Hogan, 1989; Ranga Rao et al., 1990) and hydroxypropylcellulose (HPC) (Nakano et al., 1983; Johnson et al., 1989).

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 swells when it comes into contact with water. This swelling property results in superior disintegration characteristics of the tablet. However, it was found, surprisingly, that L-HPC acted as a matrix base when it was pulverized (mean particle size $\leqq$ 4.4 μm) and loaded in the formulation at a higher content than 20% (Nakagami and Nada, 1991a; Kawashima et al., 1992a). Nakagami et al. (1991b) evaluated the sustained-release properties of procainamide tablets made from micronized L-HPC in dogs.

The purpose of the present study was to find a suitable granule formulation for tabletting, because it was difficult directly to employ pulverized L-HPC (termed LH41) for practical tabletting due to its poor flowability and packability. The LH41 mixed with or without acetaminophen as a model drug was granulated by using a high-speed agitator, centrifugal fluidizing granulator or spray dryer with distilled water or ethanol. The granules thus obtained were tabletted, and the drug-release properties of the resultant tablets were investigated. It was found that the prolonged-release property depended on whether distilled water or ethanol was used as the granulating fluid. This characteristic was explained in terms of differences in the micromeritic properties of tablets prepared from ethanol-granulated and water-granulated L-HPC.

Materials and Methods

Materials

Acetaminophen crystals were obtained from Yoshitomi Pharmaceutical, Japan and Daiwa Chemical, Japan, and were sieved between 32 mesh (500 μm) and 80 mesh (177 μm) (mean particle size = 385 μm, termed ld) and then pulverized (mean particle size = 30 μm, termed sd, determined by a microphotograph counting method; number of particles counted = 600). Low-substituted hydroxypropylcellulose (L-HPC; LH41, mean particle size = 4.4 μm) as a matrix material was supplied by Shin-Etsu Chemical, Japan. The mean particle size of LH41 was determined by a laser-based time of transition analysis system (Galai CIS-1, Central Scientific Commerce, Inc., Japan) in ethanol.

Preparation of granules

Granules were produced by the following three methods.

(1) The L-HPC (LH41) (30 g) and the drug (sd) (30 g) were blended and granulated by using a high-speed agitator (Mini-supermixer type, Tohyo Packing, Japan). The granulating fluids used were distilled water and ethanol (about 60 ml and 35 ml, respectively). The feeding speed into the agitator was 10 ml/min, and the speed of the agitator blade (diameter 13.3 cm) was 400–500 rpm. The granules prepared with water (termed WG(41 + sd)) and with ethanol (termed EG(41 + sd)) were dried in a hot air oven at 60°C for 4 h. The dried granules sieved between 24 mesh (710 μm) and 80 mesh (177 μm) were evaluated for various micromeritic properties and tabletted.

LH41 powder alone was granulated by the same method with water (termed WG41) or ethanol (termed EG41).

(2) Acetaminophen (ld) particles (100 g) as core materials were fed into a centrifugal fluidizing granulator (Model CF-360, Freund, Japan), operated at a rotor speed of 120 rpm. Then, LH41 powder (100 g) was gradually added to the granulator, while 50 ml of distilled water or ethanol as the granulating fluid was sprayed. The granules prepared with water (termed WG(41 + ld)) and with ethanol (termed EG(41 + ld)) were dried and sieved as described above (1), and then tabletted.

(3) The aqueous suspension of LH41 powder was spray-dried by using a spray dryer (Model L-12, Ohkawara Kakoki, Japan), and the spray-dried product (SD41) was mixed physically with acetaminophen (ld) for tabletting.

The types of granules prepared in the present study and their synopses are tabulated in Table 1.

Preparation of tablets and measurement of their crushing strengths

The tablets were prepared by the following two methods.

(1) Granules (200 mg) obtained by each of the aforementioned granulation methods (e.g., WG(41 + sd), EG(41 + sd), WG(41 + ld) and EG(41 + ld) granules) were directly compressed by an Instron-type hydraulic press (Autograph AG-5000D, Shimadzu, Japan) under various compression pressures (1.0–5.0 ton/cm^2; usually 2.0 ton/cm^2 unless otherwise mentioned) at an upper punch compressing speed of 2 mm/min, using flat-faced punches and a die with a diameter of 8.0 mm.

The physical mixtures of the drug (sd or ld) and granulated L-HPC (e.g., WG41, EG41 and SD41) or LH41 (termed WG41 + ld, EG41 + ld, SD41 + ld, LH41 + ld and LH41 + sd) in various mixing weight ratios (drug/L-HPC = 50 : 50, 30:70, 10:90, 5:95; usually 50:50 unless otherwise mentioned) were tabletted in the same manner as described for tabletting the L-HPC granules containing the drug.

(2) WG(41 + sd) granules, EG(41 + sd) granules or a physical mixture of LH41 and acetaminophen (sd) (mixing weight ratio = 1:1) were mixed with magnesium stearate (0.3%) and compressed continuously by a single-punch tabletting machine (KT-2 type, Kimura, Japan) equipped with flat-faced punches and having a die diameter of 8.0 mm at a rate of 60 tablets/min. The compression force was set at about 1.0 ton, as measured 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 strength was represented by the force required to fracture the tablet by diametrical compression (Autograph AG-5000D, Shimadzu, Japan). Tensile strength (T) to crushing was determined by applying the following equation (Eqn 1) (Fell and Newton, 1970):

$$T = 2F/(\pi\, d\, t) \qquad (1)$$

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

Evaluation of tablets

The dissolution test of tablets was carried out by using the JP XII paddle method (100 rpm) with distilled water (900 ml) at 37 ± 0.5°C. The concentration of acetaminophen was measured by using a spectrophotometer (λ_{max} = 244 nm). T_{50}, the time required for release of 50% of the drug, was obtained from a plot of the drug released against time. The pore size distribution curves of tablets compressed by the Autograph at the compression pressure of 2 ton/cm^2 were obtained by using a mercury penetration porosimeter (Autoscan-33, Quantachrome, U.S.A.). Fig. 1 shows the apparatus used for measuring the swelling force of tablets according to Caramella (1991), with some modification. The tablet compressed by the Autograph at the compression pressure of 2.0 ton/cm^2 was placed between the glass filter and the top of the load cell. The swelling force of tablets was recorded by the recorder when water penetrated into the tablet through the glass filter. At least three runs were performed in all of the above experiments.

Characterization of granules

Angle of repose of the samples was measured by using a repose angle tester (Konishi-FK type,

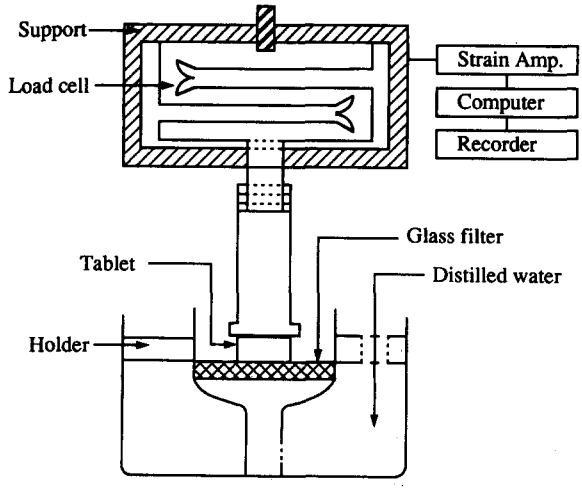

Fig. 1. Apparatus for measurement of swelling force of tablet.

TABLE 1

Granulating methods and their symbols used in the text

Granulating fluid	Equipment		
	High-speed agitator	Centrifugal fluidizing granulator	Spray dryer
Water	WG(41 + sd) [a], WG41 [b]	WG(41 + ld) [a]	SD41 [b]
Ethanol	EG(41 + sd) [a], EG41 [b]	EG(41 + ld) [a]	

[a] Prepared with LH41 and acetaminophen (sd or ld) with a mixing weight ratio of 1 : 1. sd and ld: drugs having mean particle sizes of 30 and 385 μm, respectively.
[b] Prepared with LH41 alone.

Konishi Seisakujyo, Japan). The samples were passed through a funnel at an even rate to form a stable cone. The funnel was maintained at a fixed height (10 cm) in all experiments. Angle of repose of these samples was directly read from the angle of the cone. Bulk density of the samples was determined by using a tap density tester (RHK type, Konishi Seisakujyo, Japan). A sample of about 12 g of granules was carefully introduced into a 50 ml graduated cylinder. The fixed cylinder was dropped three times from a height of 2.5 cm at 2 s intervals. The bulk density was then obtained by dividing the weight of the sample in g by the final volume in cm^3 of the sample contained in the cylinder. The samples (200 and 100 mg) were carefully compressed to form a powder bed having almost the same relative thickness (about 0.450 and 0.225 cm, respectively) and porosity (about 0.580) in a glass tube (diameter, 10 mm) by using the Autograph for measuring swelling work and force, respectively. The apparatus and principle of measurement were described in the previous reports (Kawashima et al., 1992b,c): a constant load method was used for measuring the swelling work of the sample, and a constant volume method for measuring the swelling force of the sample. The porosity of these granules was calculated from the true density and cumulative pore volume (i.e., void volume). The true density was measured with an air comparison pycnometer (Model 930, Beckman-Toshiba, Japan). The cumulative pore volume

TABLE 2

Properties of granules and physical mixture of LH41 and the drug

	(1) LH41 + sd	(2) WG(41 + sd)	(3) EG(41 + sd)
Angle of repose (°)	49	38	35
Bulk density (g/cm^3)	0.248	0.600	0.559
Porosity	–	0.064	0.330
Crushing strength (kg, $n = 20$)	–	0.626 [a]	0.064
Swelling work ($\times 10^{-3}$) (erg)	0.552	2.410	1.594
Swelling force (kg)	0.432	0.838	0.788
Crystallinity (%) [b]	4.70	6.53 [c]	5.10

(1) Physical mixture of LH41 and acetaminophen (sd) (mixing weight ratio = 1 : 1).
(2) Granules of LH41 + sd prepared with distilled water in a high-speed agitator.
(3) Granules of LH41 + sd prepared with ethanol in a high-speed agitator.
[a] One-third of the granules were plastically deformed.
[b] Measured for intact LH41 powder and LH41 granules (WG41 and EG41).
[c] Crystallinity of WG41 was significantly different from those of LH41 and EG41 (Tukey's test, $P < 0.01$).
All of the data are the average values of at least three runs.

was measured by using a mercury penetration porosimeter (Autoscan-33, Quantachrome, U.S.A.). The crushing strength of these granules sieved between 28 mesh (590μm) and 32 mesh (500 μm) was determined by measuring the force required to fracture the granules by diametrical compression using the Autograph. The lower limit of accuracy of the measurement for crushing strength by the Autograph was 0.001 kg. The crystallinity of the samples was determined by Ruland's method (Nakai et al., 1982) with powder X-ray diffraction patterns obtained by using a diffractometer (RAD-IC, Rigaku, Japan). The X-ray diffraction patterns between $2\theta = 2°$ and 140° were used to calculate the crystallinity. All of the above data listed in Table 2 are mean values of at least three runs.

Results and Discussion

Drug-release properties of tablets prepared by compressing the physical mixture of granulated L-HPC and the drug or the granules of L-HPC and the drug

The drug-release profiles of tablets prepared by compressing physical mixtures of granulated (or ungranulated) L-HPC and the drug are shown in Fig. 2. As expected from the previous report (Kawashima et al., 1992a), the drug release rate from the tablet with ungranulated LH41 decreased with increasing loading of LH41. At higher loading than 90%, the drug-release rate was greatly prolonged, exhibiting zero-order release kinetics. On the other hand, it was found that the drug-release behavior of the tablets of granulated LH41 and the drug was determined by the type of granulating fluid, i.e., water or ethanol, employed in the granulation of LH41. When the granules of LH41 were prepared with ethanol, the prolonged-release properties of tablet were well maintained, although the drug-release profiles changed to some degree due to the reduced gel-forming ability of granulated LH41. At lower loadings than 70%, the tablet disintegrated readily compared to the tablet of ungranulated LH41. The tablet prepared with water-granulated LH41 quickly disintegrated when brought into contact with water, causing rapid release of the drug, irrespective of the granulation method, e.g., high-speed agitation or spray drying, even at higher loading than 95%.

The drug-release profiles of tablets prepared from granules of LH41 and the drug are shown in Fig. 3. The tablet of EG(41 + sd) granules prepared by using the high-speed agitator exhibited sustained drug release, as did the tablet with the physical mixture of LH41 and the drug (LH41 + sd). However, the tablet of WG(41 + sd) granules rapidly released the drug. The tablets of the granules (EG(41 + ld) or WG(41 + ld)) prepared by using the centrifugal fluidizing granulator showed similar drug-release behavior to that found for tablets of the granules prepared by

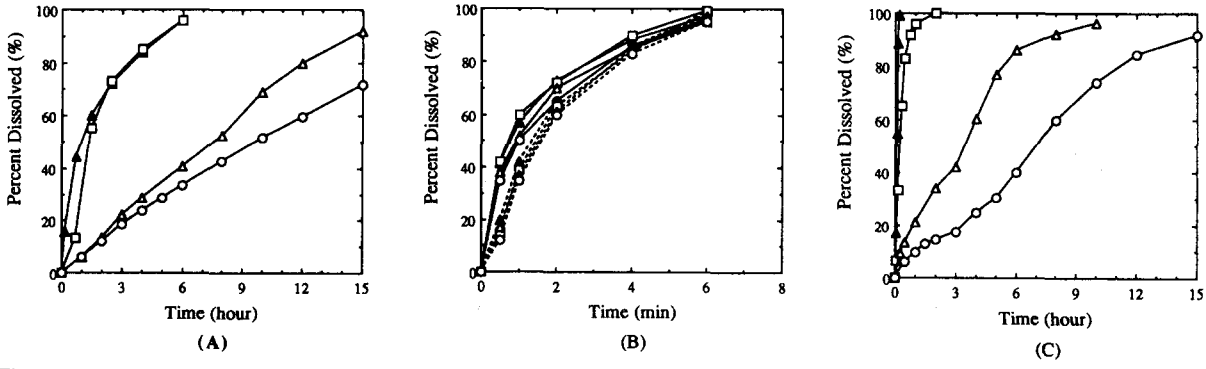

Fig. 2. Dissolution profiles of acetaminophen (ld) tablets prepared with physical mixtures of various loading ratios of (A) LH41 and ld, LH41 + ld, (B) WG41 granules and ld, WG41 + ld, (or SD41 granules and ld, SD41 + ld, dotted lines) or (C) EG41 granules and ld, EG41 + ld, by using the Autograph. (○) 5%, (△) 10%, (□) 30% and (▲) 50% acetaminophen ($n = 3$).

using the high-speed agitator, i.e., the behavior depended on whether water or ethanol had been used for granulation. The drug release from the tablet of EG(41 + sd) granules was more prolonged than that in the case of EG(41 + ld) granules.

The findings in Figs 2 and 3 show that the sustained drug-releasing property of LH41 was retained after granulation with ethanol, whereas it was lost following granulation with water. The rank order of the tablets for prolonged drug-release property was as follows: granules of LH41 and smaller-sized drug (EG(41 + sd)) > granules of LH41 and coarser-sized drug (EG(41 + ld)) > mixture of granulated LH41 and drug (EG41 + ld). This result indicated that a uniform matrix structure with finely dispersed drug was required to obtain prolonged drug release. When the tablet disintegrated, the tablet containing smaller-sized drug particles showed faster drug release than that containing coarse drug particles, as expected.

To explain the drastic difference in the drug-release behavior between the tablets prepared from LH41 granulated with ethanol and with water, the relationship of the micromeritic properties of the tablets, such as crushing strength and swelling force, to the drug-release properties was investigated.

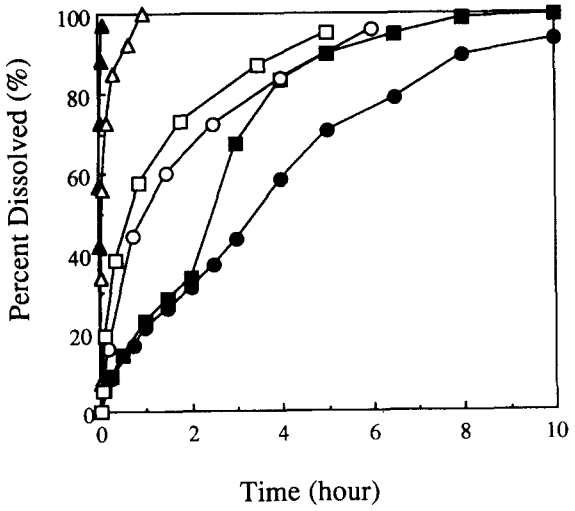

Fig. 3. Dissolution profiles of acetaminophen tablet prepared with (●) LH41 + sd mixture, (○) LH41 + ld mixture, (▲) WG(41 + sd) granules, (△) WG(41 + ld) granules, (■) EG(41 + sd) granules or (□) EG(41 + ld) granules by using the Autograph ($n = 3$).

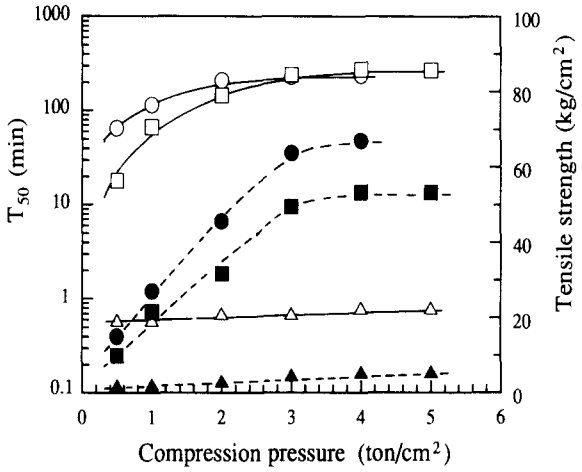

Fig. 4. Effect of compression pressure on the drug release rate (T_{50}, open symbols, $n = 3$) and tensile strength (closed symbols, $n = 5$) of tablets prepared with (○, ●) LH41 + sd mixture, (△, ▲) WG(41 + sd) granules or (□, ■) EG(41 + sd) granules by using the Autograph.

Relationship between the crushing strength and the drug-release properties of tablets

The relationship between T_{50} and tensile strength of tablets prepared under various compression pressures is shown in Fig. 4. With increasing compression pressure, T_{50} and tensile strength of tablets prepared from EG(41 + sd) granules and the physical mixture of LH41 and the drug (LH41 + sd) increased linearly up to the compression pressure of 3.0 ton/cm^2. However, T_{50} and tensile strength of WG(41 + sd) were significantly lower than those of the tablets of EG(41 + sd) and LH41 + sd. In addition, they remained essentially unchanged with increasing compression pressure.

This finding indicated that the tablets of EG(41 + sd) and LH41 + sd had similar matrix structures, while that of WG(41 + sd) was different. Scanning electron photographs of cross-sections of tablets of LH41 + sd, WG(41 + sd) and EG(41 + sd) are shown in Fig. 5. At the fracture plane of the tablet of WG(41 + sd), the granules and the cleavages between them were clearly observed. The cross-section of the tablet of

EG(41 + sd) exhibited more uniformly condensed structures than that of the tablet of WG(41 + sd), although a faint granular structure was observed. In the tablet of LH41 + sd, the drug crystals were randomly dispersed in the polymer matrix (Fig. 5). The tablet of WG(41 + sd) might easily break along the deep cleavages surrounding the granules, when compressed. On the other hand, the granules in the tablet of EG(41 + sd) had coalesced to construct a more uniform matrix structure resembling that of the tablet of LH41 + sd. This finding indicated that the WG(41 + sd) granules were less readily compressible than the EG(41 + sd) granules. Indeed, it was found that the porosity of WG(41 + sd) granules was much lower than that of EG(41 + sd) granules (Table 2). Further, the WG(41 + sd) granules were mechanically stronger than the EG(41 + sd) granules: one-third of them were plastically deformed during the crushing strength measurement (Table 2). Millili and Schwartz (1990) reported similar results on the strength of pellets of binary mixtures of 10% active ingredient and 90% microcrystalline cellulose (Avicel PH101) granulated with water/ethanol mixtures. The pellet strength increased with increasing amount ratio of water to ethanol. Water might penetrate more easily into the tablet of WG(41 + sd) along the intergranular cleavages as compared with EG(41 + sd), resulting in faster disintegration of the tablet of WG(41 + sd). This was confirmed by the following swelling tests of the tablets.

Swelling properties of the tablets of EG(41 + sd) and WG(41 + sd) granules

Swelling properties of the tablets were investigated in order to explain the differences in disintegration behavior between the tablets of EG(41 + sd) and WG(41 + sd) granules. The tablets prepared with WG(41 + sd) granules swelled rapidly on contact with water, which generated a swelling force that increased sharply at the initial stage, followed by a gradual diminution due to disintegration of the tablet as shown in Fig. 6. In contrast, the tablets prepared with either EG(41 + sd) granules or the physical mixture of LH41 + sd did not disintegrate during the swelling experiment. Their swelling forces gradually increased until an equilibrium state was reached. This great difference in swelling behavior between the tablets is considered to be correlated with the characteristic differences in the internal structure of the tablet as shown in Fig. 5.

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. 7). The radii of the macro pores of the tablet of WG(41 + sd), maximum peak = 310 nm, corresponding to cleavage between the granules in the tablet as shown in Fig. 5, were larger than those of the tablets of EG(41 + sd) and LH41 + sd, maximum peaks = 70 and 130 nm, respectively. Micro pores in the matrix of drug

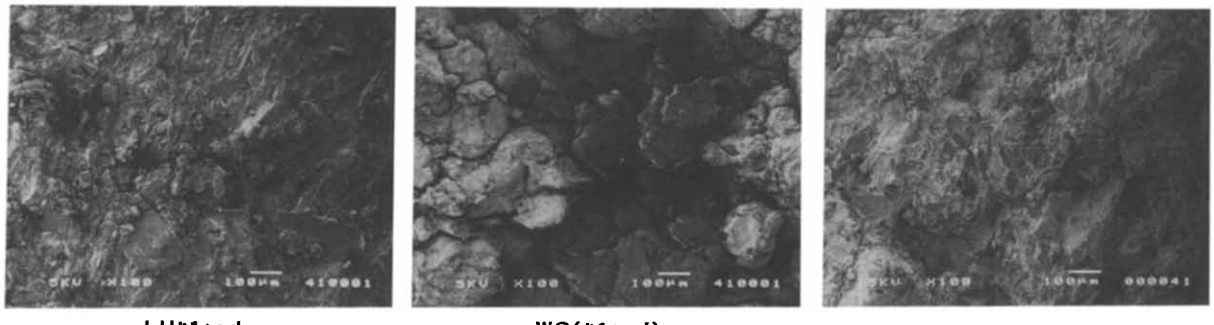

Fig. 5. Scanning electron micrographs of cross-sections of tablets.

and polymer of the WG(41 + sd) granules were smaller than those of EG(41 + sd) granules or the physical mixture of LH41 + sd. The median pore radii of the tablets of WG(41 + sd) and EG(41 + sd) were 0.222 and 0.069 μm, respectively. According to Washburn's (1921) equation (Eqn 2), the water-penetrating speed (dl/dt) into a capillary is a function of the radius of the capillary (Eqn 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 denotes the capillary radius, γ is the liquid surface tension, η represents the liquid viscosity, t is time and θ denotes the contact angle. Assuming that the radius of the capillary can be represented by the median pore radius and that the other parameters in Eqn 2 are the same for the tablets, the penetration speed of water into the WG(41 + sd) tablet might be about 3-times faster than that into the EG(41 + sd) tablet. This rapid penetration would promote the disintegration of tablets prepared from WG(41 + sd) granules.

The swelling properties of granules were investigated to cast light on the tablet swelling behavior. The swelling work and force of WG(41 + sd) granules were larger than those of EG(41 + sd) granules, as shown in Table 2. During the drying process in granulation, crosslinked networks of polymer might be constructed. In particular, water would strengthen such networks through its strong hydrogen-bonding ability. After evaporation of the water, tightly crosslinked networks of polymers would remain; the interchain binding may be sufficiently strong to produce crystalline like structure. This could account for the increase of crystallinity of LH41 granulated with water (WG41), as shown in Table 2. Similar phenomena have been reported (Watase, 1983; Watase and Nishinari, 1985; Yokoyama et al., 1986; Hyon et al., 1989; Peppas and Stauffer, 1991) in the preparation of poly(vinyl alcohol) hydrogels by a cyclic freeze-thaw process: microcrystalline structure was formed in the hydrogel by hydrogen bonding, and the physical crosslinking in the hydrogel enhances the viscoelasticity and swelling character.

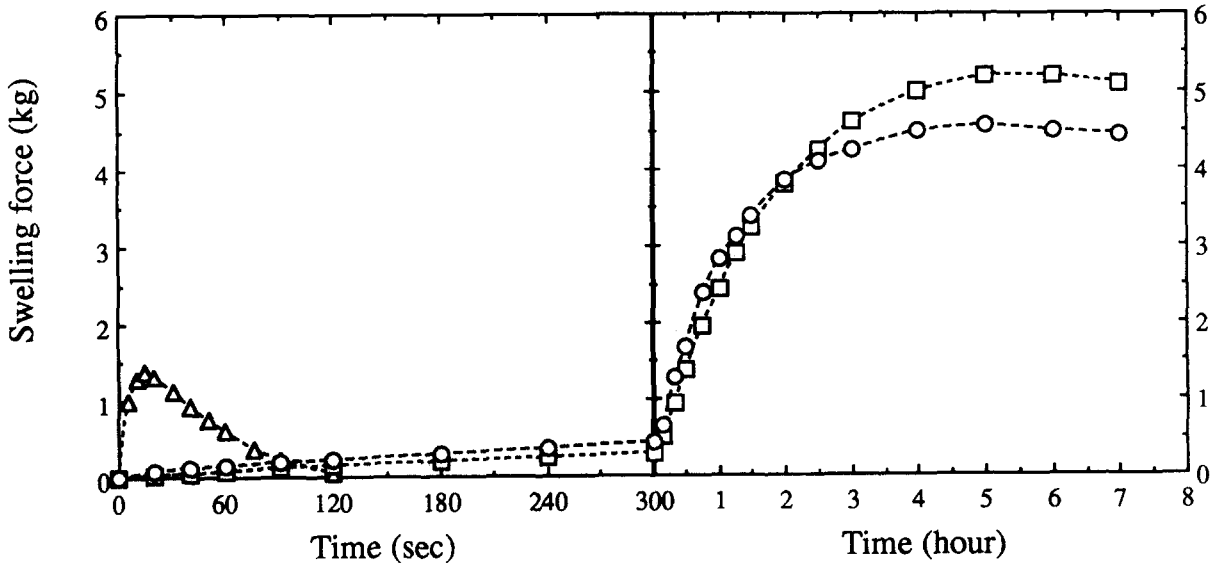

Fig. 6. Swelling force of tablets prepared with (○) LH41 + sd mixture, (△) WG(41 + sd) granules or (□) EG(41 + sd) granules by using the Autograph. The data are the average values of three runs.

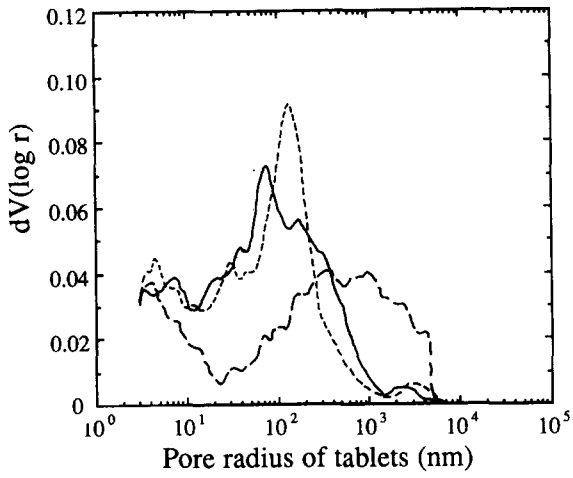

Fig. 7. The pore size distribution curves of tablets prepared with (------) LH41 + sd mixture, (— — —) WG(41 + sd) granules or (———) EG(41 + sd) granules by using the Autograph (n = 5) (ordinate, V, volume; r, pore radius).

Such a crosslinked structure could account for the characteristic properties of WG(41 + sd) granules, i.e., mechanical strength and good swellability. Although EG(41 + sd) granules had good swelling ability, they would have lost this ability in the tablet, because the granules were crushed and a new matrix structure was formed in the tablet, as shown in Figs 5 and 7. On the other hand, the swelling capacity of WG(41 + sd) granules was retained in the tablet, because their crosslinked structure was not broken during compression. Consequently, the tablets of WG(41 + sd) granules rapidly released the drug, whereas the tablets of EG(41 + sd) granules gave prolonged drug release, as did the tablets of the physical mixture of LH41 and the drug.

Preparation of prolonged-release tablets by using a continuous single-punch tabletting machine

Tablets were prepared with WG(41 + sd) and EG(41 + sd) granules and LH41 + sd (Table 2) by using a single-punch tabletting machine set to produce the same bulk volume under constant compression pressure. The properties of the resultant tablets are shown in Table 3. The weight of tablets of LH41 + sd and its coefficient of variation were much smaller and larger than those of the granules, respectively. Therefore, the present granulation process is useful and recommended to prepare uniform tablets. The drug-release profiles of the tablets of the granules are shown in Fig. 8. The tablet of EG(41 + sd) showed a prolonged-release profile, whereas the drug release rate from the tablet of WG(41 + sd) was extremely fast, as expected.

The dissolution rate of EG(41 + sd) tablets prepared by using the single-punch tabletting machine was faster than that prepared by the Autograph in Fig. 3. The Autograph made the matrix structure of tablet rather densified than by using the single-punch machine. The tensile strength (31.7 kg/cm^2) of the tablets with the Autograph was higher than that (25.5 kg/cm^2) with the single-punch machine. The compression energy applied by the Autograph was more effectively dissipated to build the matrix structure due to employing much slower compression speed compared to the single-punch machine. Such a matrix structure difference produced different dissolution behaviors as found in Figs 3 and 8.

In conclusion, prolonged-release tablets could be prepared with pulverized L-HPC after granulation with ethanol to improve the micromeritic

TABLE 3

Properties of tablets prepared continuously by a single-punch tabletting machine

	LH41 + sd [a]	WG(41 + sd)	EG(41 + sd)
Tablet weight (mg)	81.3 ± 3.6 [b]	231.2 ± 1.5	219.3 ± 0.6
Coefficient of variation (%)	4.4	0.6	0.3
Deviation range (%)	−9.9–13.8	−1.3–1.2	−0.6–0.5
Tensile strength (kg/cm^2)	–	3.09	25.5
Tablet density (g/cm^3)	–	1.174	1.215
Tablet diameter (mm)	–	8.13	8.07

[a] Same as in Table 2.
[b] Mean ± SD (n = 20).

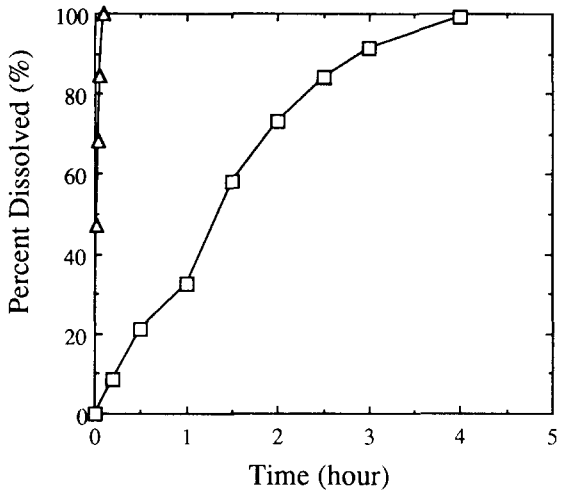

Fig. 8. Dissolution profiles of acetaminophen tablets prepared with (△) WG(41 + sd) granules or (□) EG(41 + sd) granules by using a single-punch tabletting machine ($n = 3$).

properties for tabletting while retaining the sustained-release function. It should be possible to extend the formulability of L-HPC to cover the range from rapid- to slow-release systems by appropriately selecting the granulating fluid.

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