Low-Substituted Hydroxypropylcellulose as a Sustained-Drug Release Matrix Base or Disintegrant Depending on Its Particle Size and Loading in Formulation

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Received May 6, 1991; accepted August 24, 1992

Tablets of acetaminophen as a model drug were prepared with low-substituted hydroxypropylcellulose (L-HPC) of various particle sizes at various loadings in the formulation. Drug release into an aqueous dissolution medium (pH 1.2) was remarkably sustained from tablets prepared with fine L-HPC (LH41) at loadings of more than 20%. Tablets prepared with less than 20% LH41 or with coarse L-HPCs (LH11, LH21, and LH31) disintegrated in the medium, resulting in rapid release of the drug. The difference in behavior could not be explained in terms of differences in tablet strength, but in swelling and water uptake abilities of the tablet's polymer. Swelling work (swelling force), water penetration speed, and water uptake of LH41 (4.4-μm average particle size) were much smaller than those of coarse L-HPCs. The formation of a continuous gel-like layer on the surface of tablets containing more than 20% LH41 was another factor to sustain the drug release rate.

KEY WORDS: low-substituted hydroxypropylcellulose; swelling work; water uptake; sustained-release; matrix base.

INTRODUCTION

Low-substituted hydroxypropylcellulose (L-HPC) is a widely used excipient with good binding and disintegrating properties. L-HPC particles retain the general properties of the original cellulose, such as plastic deformability and good compressibility, and they act as an effective binder to increase the strength of tablets. Nevertheless, L-HPC particles swell when they come into contact with water, and the swelling force causes the disintegration of the tablets.

Nakagami and Nada (1) first reported that micronized L-HPC can be used as a matrix base for sustained-release tablets. We (2) also examined the effect of the particle size of L-HPC on the drug release rate and tensile strength of directly compressed tablets. There are a number of reports dealing with tablet disintegration, which suggest that water uptake (4–8), swelling rate (4,5), and disintegrating force (5,7,9,10) of the excipient formulated contribute to the disintegration properties of the tablet. Particle size of disintegrants is an important factor determining the disintegration properties of tablets. However, there are few papers dealing with the effect of particle size on both disintegrant (11,12) and matrix base properties.

In this study, the swelling work (swelling force) and the penetration speed of water into powder beds of L-HPC of various particle sizes were measured in order to elucidate the mechanism of the dependency of the drug release rate of L-HPC tablets on the particle size. The properties of fine L-HPC as a matrix base for sustained-release tablets were investigated.

MATERIALS AND METHODS

Materials. Pulverized acetaminophen was obtained from Yamamoto Chemical Industries, Ltd., Japan. Low-substituted hydroxypropylcelluloses (L-HPC) pulverized by a hammer mill and classified with different average particle diameters (μm), as shown in Table I, were supplied by Shin-Etsu Chemical Co., Ltd., Japan.

Micromeritic Properties of L-HPC. The size distributions of L-HPC were determined by a laser-based time of transition analysis system (Galai CIS-1, Central Scientific Commerce, Inc., Japan) in ethanol and by a sieve analysis using the standard sieves specified in JPXI, except for fine L-HPC (average diameter, <27 μm). The shape analysis was conducted with an image analyzer (Galai CIS-1 Camera Control, Central Scientific Commerce, Inc., Japan). The shape factor (S_F) is defined by the following equation:

$$S_F = (A/P^2)4\pi$$

where A is the cumulative image area of the total particles (about 600) and P is the cumulative perimeter of the total particles. When the particle is a sphere, the shape factor becomes a unit. The specific surface area (S_w) was measured by an air permeability method (Type SS-100, Shimadzu Co., Ltd., Japan). Those micromeritic properties are tabulated in Table I.

Preparation of Tablets. Tablets (600 mg) were prepared by directly compressing physically mixed L-HPC and acetaminophen with an IR spectrophotometric tableting press (Riken Seiki Co., Ltd., Japan) under various compression pressures (gauge range, 50–300 kg/cm^2; usually 200 kg/cm^2) for 30 sec using a die 13 mm in diameter.

Tensile Strength of Tablets. Tablet crushing strength was represented by the force required to fracture tablets by diametrical compression (Rheolobot KA-300, Kyowa Co., Ltd., Japan). Tensile strength (T) was determined by applying the following equation (13):

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

where F is the crushing strength, d is the diameter of the tablet, t is the tablet thickness, and ϵ is the porosity of the tablet.

Dissolution and Disintegration of Tablets. The dissolution test was carried out with the JPXI paddle method (100 rpm) with pH 1.2 medium (900 mL) at 37 ± 0.5°C. The concentration of acetaminophen was measured using a spectrophotometer (λ_{max} = 244 nm). Disintegration time in disintegration medium No. 1 (pH 1.2) at 37 ± 0.5°C was measured using the JPXI disintegration apparatus with disks.

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0724-8741/93/0300-0351$07.00/0

Table I. Properties of L-HPC of Various Particle Sizes[a]

Grade	Average particle size (μm)		Size range (15–85% undersize) (μm)	Shape factor	Specific surface area per unit weight × 10^{-3} (cm^2/g)	Water-soluble components (%, w/w)	Average degree of hydroxypropoxyl substitution of L-HPC material (%)	Degree of hydroxypropoxyl substitution of water-soluble components (%)
LH11	50.6[b]	42.5[c]	19.9–90.8[c]	0.58	2.70	2.42	10.0–13.0	—
LH21	41.7	37.8	16.5–74.9	0.59	3.20	3.43	10.0–13.0	14.5
LH31	—	26.9	10.9–53.7	0.65	5.24	4.29	10.0–13.0	—
LH41	—	4.4	1.3–8.9	0.75	31.60	9.33	10.0–13.0	16.4

[a] All data are the mean value (n = 3).
[b] From sieve analysis.
[c] From laser-based time of transition analysis.

Swelling Work. Figure 1 shows the apparatus used for measuring the swelling work according to Nogami *et al.* (3), with some modification. Each sample of the powder (200 mg) was compressed to the powder bed having almost the same thickness (0.535 cm) and porosity (0.662) using an Instron-type hydraulic press (Autograph, Shimadzu Co., Ltd., Japan). The porosity (ϵ) of the powder beds was calculated from the equation:

$$\epsilon = 1 - \rho_T/\rho_t$$

where ρ_t is the true density of L-HPC and ρ_T is the bulk density of the powder bed. As the particles swelled in the apparatus, they swelled initially into the pore space between them. After filling the pore-free space, they lifted a load (6.305 g) placed on top of the powder bed. The initial swelling work was assumed to be considerably small compared with the later work. In the powder bed saturated with water after lifting the load, there is water filling the pore space as well as water swelling the polymer proper. The pore space was filled spontaneously with water spread over the internal surface of the pore due to the hydrophilic property of the polymer. Therefore the force migrating the load up to the equilibrium position was assumed to be the swelling force of polymer. The swelling work (W) made by unit weight of the polymer bed was determined using the following equation:

$$W = M \cdot g \cdot L/G$$

where M is the mass of the load, g is the gravitational acceleration, L is the distance of migration, and G is the powder weight.

Penetration Speed of Water. The apparatus shown in Fig. 1 was also used to measure the penetration speed of water into the powder bed. Powder beds compressed by the autograph at different compression pressures (range, 1–10 kg/cm^2) were placed in the apparatus without any load on top of the powder bed. The amount of water taken up into the powder bed was observed at appropriate time intervals. The penetration speed of water was determined from the slope of the initial linear portion of the plot of water uptake (mL) against time (min).

Measurement of Water-Soluble Components of L-HPC. One gram of L-HPC was suspended in distilled water (20 mL), then the suspension was shaken for 30 min to dissolve the water-soluble components and centrifuged at 3000 rpm for 20 min. The supernatant liquid was filtered off with a membrane filter (pore size = 0.45 μm). The filtrate (10 mL) was dried at 105°C for 2 hr and the residue (water-soluble components) was weighed.

RESULTS AND DISCUSSION

Dependency of Drug Release from Tablets on the Particle Size and Loading of L-HPC in the Formulation

The times required for 50% drug release (T_{50}) from the tablets of variously sized L-HPC (LH11, LH21, LH31, or LH41) and acetaminophen (1:1) and their disintegration times are given in Table II. The decreases in T_{50} and disintegration time with increasing particle size of L-HPC indicated that the drug-release rate was strongly dependent on the particle size of L-HPC and was closely correlated with the disintegration time. The tablet prepared with LH41 did not disintegrate during the dissolution test, exhibiting a sustained-release characteristic. In contrast, the tablets prepared with coarse L-HPCs (LH11, LH21, and LH31) exhibited rapid drug release due to the disintegration of the tablets.

The effect of the amount of L-HPC compounded in the tablet on the drug release properties (T_{50}) was examined (Fig. 2). It was found that the tablets prepared with LH41 exhibited sustained drug release when they contained at

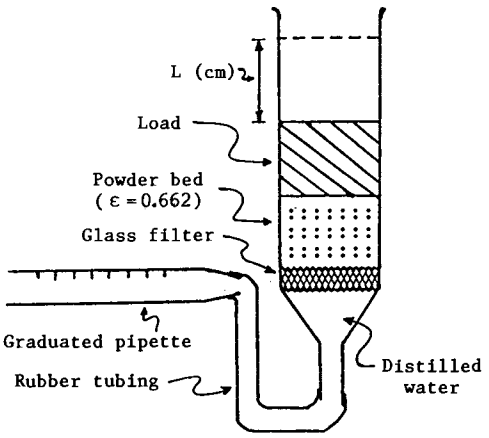

Fig. 1. Apparatus for measurement of swelling work.

Table II. T_{50}, Disintegration Time, and Tensile Strength of Tablets of L-HPC and Acetaminophen (1:1)[a]

L-HPC	T_{50} (min)	Disintegration time (min)	Tensile strength (kg/cm^2)
LH11	0.4	0.6	20.6
LH21	0.6	0.8	22.1
LH31	1.5	1.8	25.4
LH41	525.0	496.8	36.6

[a] All data are the mean value (n = 3–6).
[b] Properties (particle size) of L-HPC are shown in Table I.

least 20% LH41. When the amount of LH41 was between 2.5 and 5.0%, the tablets showed a rapid drug release, because of disintegration (disintegration time = 5–6 min), compared to the control (0%), exhibiting only erosion of the surface. The tablets prepared with LH11 (not shown), LH21, and LH31 (not shown) always disintegrated quickly irrespective of the composition ratio in the formulation, although the drug release rate gradually declined with increasing L-HPC content.

Effect of Tablet Strength on the Drug Release Rate

The tensile strength of tablets was measured to see whether it might be correlated with the drug release rate. The tensile strength of tablets increased with decreasing particle size of L-HPC as shown in Table II, probably because of the increases in interparticulate friction and cohesive force due to the increased specific surface area of the fine L-HPC particles in Table I. Scanning electron micrographs of particles of L-HPC (LH21 and LH41) showed that the surfaces have a fibrous appearance, and LH41 is present as aggregates of fine particles (Fig. 3). The correlations of the tensile strength of tablets and the drug release rate, represented by T_{50}, and disintegration time are shown in Fig. 4. A slight increase in T_{50} and disintegration time with increasing tensile strength of tablets was found. Tablets of LH21 with a higher tablet strength than tablets of LH41 still showed much more rapid drug release and disintegration. This finding indicated that the nondisintegrating and sustained-release properties of tablets prepared with LH41 could not be explained simply in terms of its high tensile strength.

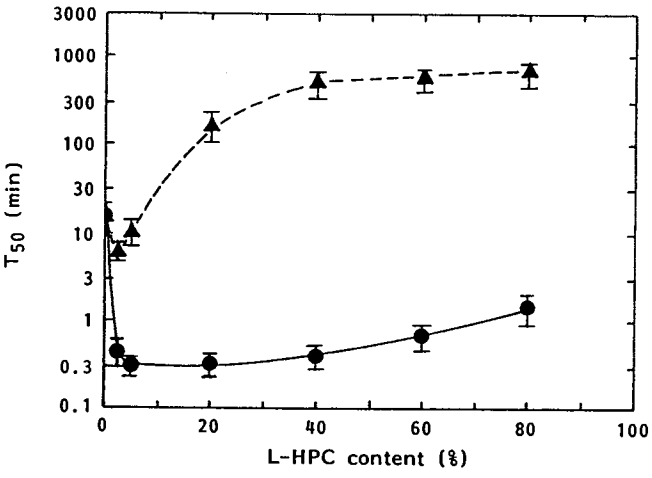

Fig. 2. Effect of composition ratio (L-HPC:drug) on drug release properties (T_{50}; n = 3) of tablets, (●) LH21 and (▲) LH41.

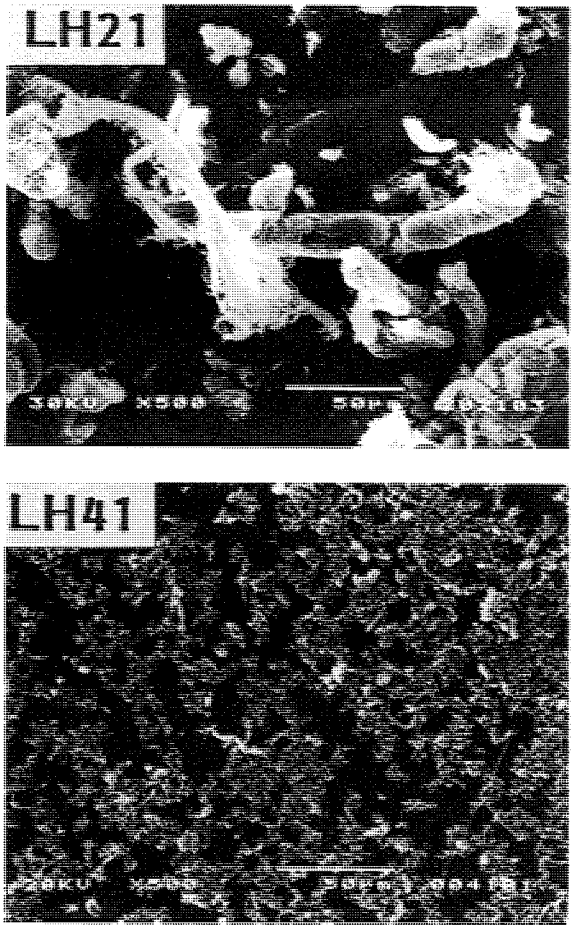

Fig. 3. Scanning electron micrographs of particles of L-HPC.

Effect of Swelling Properties of L-HPC on the Drug Release Rate

The properties of disintegrants have been evaluated in terms of water uptake (4–8), swelling rate (4,5), and disintegrating force (5,7,9,10) to interpret the drug release behavior of tablets. The swelling capacities of L-HPCs with different particle sizes were investigated by measuring the swelling work of particles in a slightly compressed powder bed of a given weight (200 mg) and porosity (0.662). The swelling work made of L-HPC per unit weight and the normalized one (erg/g polymer/mL water) for maximum water uptake at equilibrium state are shown in Fig. 5. The values of swelling work of LH11, LH21, and LH31 were nearly the same, but that for LH41 was extremely small. Those behaviors were clearly found even if the data were normalized in Fig. 5. Due to the large specific surface area of fine particles of LH41, hydrogen bonding between the LH41 particles should be much more extensive than between coarse particles, and this may greatly reduce the swelling ability of LH41.

The water uptake profiles of L-HPC particles with different particle sizes are shown in Fig. 6. The total amounts of water absorbed in the powder beds of LH11, LH21, and

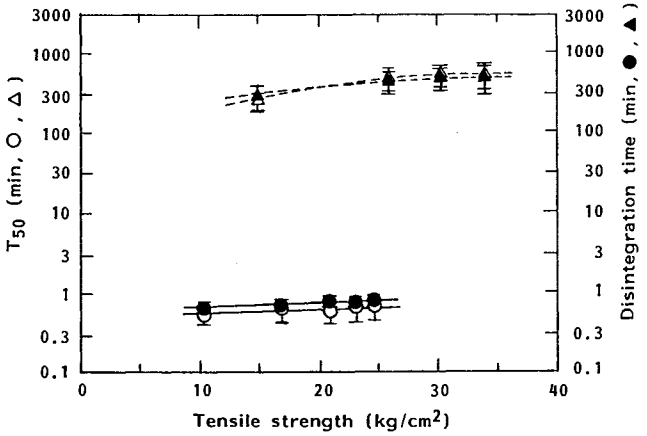

Fig. 4. Effect of tensile strength (n = 5) on drug release properties (T_{50}; n = 3) and disintegration time (n = 6) of tablets prepared with LH41 and acetaminophen (1:1) at different compression pressures (○, ●) LH21 and (△, ▲) LH41.

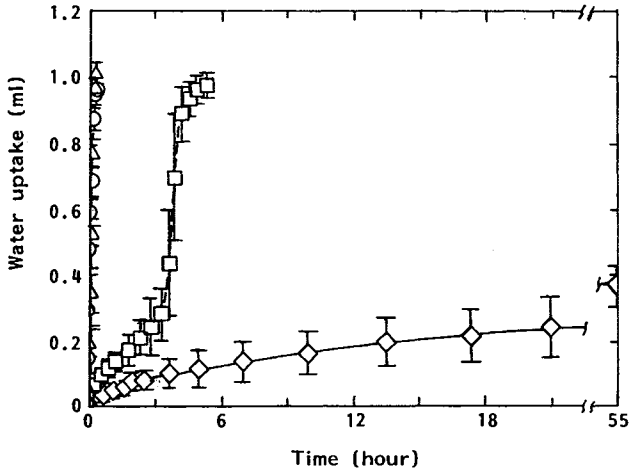

Fig. 6. Water uptake of powder bed of L-HPC compressed under 10 kg/cm²: (○) LH11, (△) LH21, (□) LH31, and (◇) LH41. Each datum is the mean ± SD; n = 3.

LH31 were almost the same, while that for LH41 was considerably small. The rate of water uptake, *viz.*, penetration speed of water, decreased with decreasing particle size of L-HPC, and depended on the compression pressure of the powder bed. Penetration speeds of water for all samples tested are summarized in Fig. 7. There was little dependence on particle size when the powder beds were noncompressed. However, an increase in the compression pressure depressed the penetration speed of water into the powder bed, especially for fine particles of L-HPC (LH41). With increasing compression pressure, hydrogen-bonding networks between the fine LH41 particles should become more extensive due to the large specific surface area, and this would tend to prevent water penetration into the powder bed.

Further, a gel-like layer was observed at the boundary of the penetrating water front in the powder beds. In such a highly viscous gel layer, the diffusion rate of water should be greatly reduced. It was assumed that the gel-like layer would be formed from water-soluble components in L-HPC, which were produced by crushing L-HPC. Several articles discussing the hydrophilic gel-forming matrices with water-soluble polymer supported the present finding (14,15). As shown in Table I, the contents of water-soluble components in LH41 were higher than those in the coarse L-HPCs. The degree of hydroxypropoxyl substitution of the water-soluble components was slightly higher than that of original powdered L-HPC (10.0–13.0%). This finding suggested that a higher hydroxypropoxyl substituted moiety of the polymer might be more easily cleavaged by grinding. Although coarse L-HPC particles could form the gel-like layer, they would exert a greater swelling pressure, breaking the gel-like layer (see Fig. 5). With LH31, the water penetration speed into the powder bed at the initial stage was rather slow because of the gel formed firmly in the pores smaller than those of LH11 and LH21. At the later stage, once LH31 adsorbed sufficient water for swelling, swelling occurred drastically and accelerated the water penetration rate, resulting in the characteristic sigmoid curve (Fig. 6). Such water uptake curves of tablets were also reported by Ferrari *et al.* (16).

The effect of the composition ratio (L-HPC:drug) of the powder bed (compressed at 10 kg/cm²) on the water penetration speed was investigated. It was observed that the water penetration speed into the powder bed decreased with

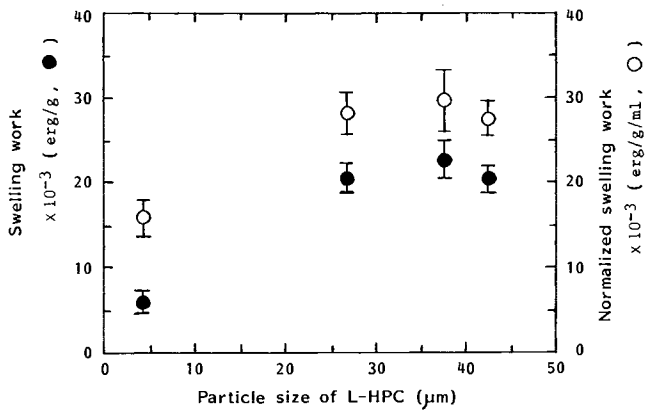

Fig. 5. Correlation between swelling work per unit weight, normalized work, and particle size. Each datum is the mean ± SD; n = 5.

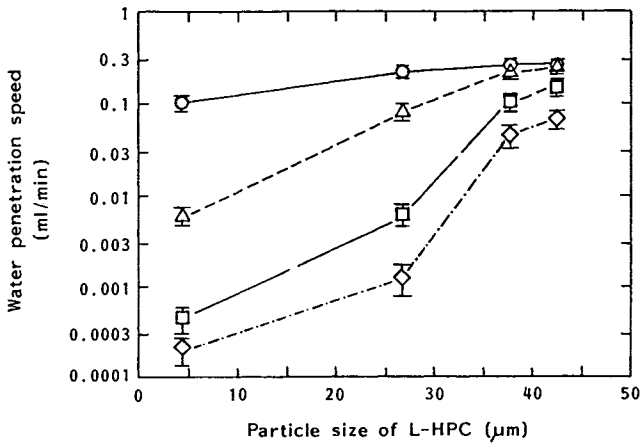

Fig. 7. Effect of particle size on penetration speed of water into powder beds of L-HPC compressed at various compression pressures; (○) 0 kg/cm², (△) 1 kg/cm², (□) 5 kg/cm², and (◇) 10 kg/cm². Each datum is the mean ± SD; n = 2–4.

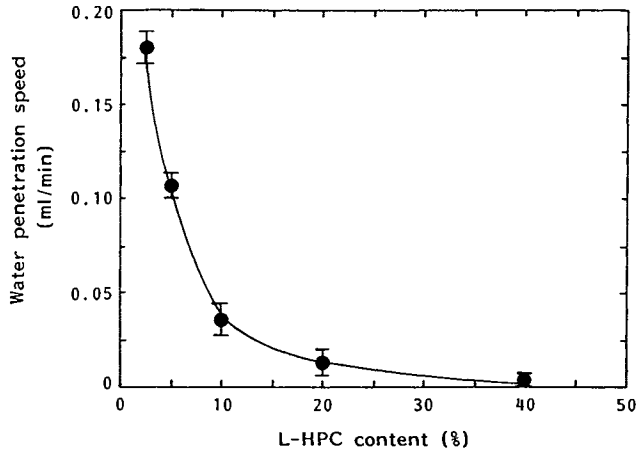

Fig. 8. Effect of composition ratio (LH41:drug) on the penetration speed of water into powder beds compressed at 10 kg/cm^2. Each datum is the mean ± SD; n = 3.

increasing amounts of L-HPC (LH41), as shown in Fig. 8. A good linear relationship was obtained between the drug release rate (T_{50}) of tablets prepared with different compositions of LH41 and the drug and the penetration speed of water into the corresponding powder bed on a log–log scale. It is suggested that the drug release rate of these tablets can be predicted from the water uptake characteristics of the corresponding powder beds. A similar relationship was obtained for tablets formulated with L-HPC of different particle sizes at the same ratio (1:1) and the corresponding powder bed, as shown in Fig. 9. Those correlations were proved to be statistically significant by R test at the 1% level.

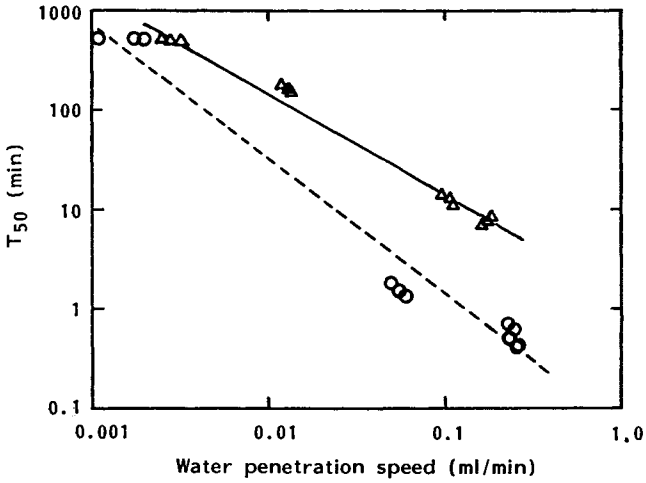

Fig. 9. Correlation between drug release properties (T_{50}; n = 3) of tablets and water penetration speed (n = 3) into powder beds compressed at 10 kg/cm^2, prepared with (△) different compositions of LH41:drug and (○) different particle sizes of L-HPC (L-HPC:drug = 1:1). Correlation coefficients ($=r_0$) for (△) different composition and (○) particle size are −0.994 and −0.986, respectively (both significant at 1% level). $|r_0| > r(\phi, P) = 0.7079$, $\phi = 10$, $P = 0.01$.

In conclusion, the drug release rate of tablets containing L-HPC depends strongly on the particle size of the excipient determining their swelling abilities. Fine L-HPC, having a smaller swelling force than coarse L-HPC, can be used either as a matrix base for sustained-release tablets or as a disintegrant, depending on the formulation ratio. Testing of swelling work and water penetration speed into a powder bed using the apparatus shown in Fig. 1 is useful to predict the drug release rate of tablets with the same formulation.

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