Control of Prolonged Drug Release and Compression Properties of Ibuprofen Microsponges with Acrylic Polymer, Eudragit RS, by Changing Their Intraparticle Porosity

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Prolonged-release spherical micro-matrices of ibuprofen with Eudragit RS were prepared using a novel emulsion-solvent diffusion method. Those particles were termed "microsponges" due to their characteristic sponge-like texture and unique dissolution and compression properties, unlike conventional microcapsules or microspheres. The internal porosity of microsponges could be easily controlled by changing the concentration of the drug and the polymer in the emulsion droplet (ethanol). With lower concentration of ibuprofen in the ethanol, the resultant microsponges had a higher porosity, about 50%. The drug release rate from the microsponges was interpreted by the Higuchi model of spherical matrices, which depended only on their internal porosity of the microsponges when size distribution and drug content were the same. The tortuosities in the microsponges were found to be almost constant (3—4) irrespective of porosity, suggesting the same internal texture. Microsponge compressibility was much improved over the physical mixture of the drug and polymer owing to the plastic deformation of their sponge-like structure. The more porous microsponges produced stronger tablets.

Keywords microsponge; porosity; tortuosity; compression; stress relaxation; emulsion-solvent diffusion method

In previous reports, we prepared controlled-release spherical matrix (microsponge) of ibuprofen with acrylic polymers using the emulsion-solvent diffusion method,[1-3] which was a simultaneous process including agglomeration and microencapsulation during crystallization. The drug release rate from the resultant microsponges was controlled by the type and amount of the polymers employed. Microsponges with ibuprofen : Eudragit RS = 3 : 1 improved bioavailability of the drug and prolonged its action in beagle dogs.[3]

In this process, an ethanol solution of drug and polymer is poured into aqueous media under agitation, forming quasi o/w emulsion droplets. The ethanol diffuses out of the dispersed ethanol droplets containing drug and polymer into an environmental aqueous medium. In the present study, it was found that the concentration of drug and polymer in the droplets affected the micromeritic properties of the resultant microsponges, although the ibuprofen to Eudragit RS ratio remained constant (3 : 1). With increasing concentration of ibuprofen, the particle density and sphericity of microsponges increased while the internal matrix structure remained unchanged. Therefore, it was assumed that the drug release rate might be controlled by changing the drug concentration in the formulation.

The purpose of the present project was to elucidate the relationship between the drug release rate and the porosity of the microsponges, and to prove that the drug release rate can be controlled by changing the porosity as well as the particle size and polymer content, as reported for microcapsules prepared by emulsion-solvent evaporation,[4] freeze drying or solvent-extraction precipitation.[5] Further, the drug release mechanism of microsponges was investigated using the Higuchi matrix model, and the diffusion coefficient of ibuprofen and tortuosity of the matrix were calculated to describe the microsponge internal structure.

In addition, the unique sponge-like texture of the microsponges encouraged us to investigate the direct compression behavior for the preparation of a matrix tablet of drug and polymer. Although the physical mixture of drug and polymer has been extensively investigated,[6,7] there was no report elucidating the effect of microsponge porosity on its compressibility. In this investigation, it was found that the extensive stress relaxation of microsponges after compression was responsible for their excellent compressibility.

Experimental

Preparation of Microsponges of Ibuprofen The previously described method[2,3] was employed with some modifications. Ibuprofen (Ibu; 2.5 g) and Eudragit RS (Eud. RS; 0.833 g) were dissolved in 3, 5, 8, 10 ml of ethanol corresponding to the concentrations of ibuprofen: 0.833, 0.500, 0.313, 0.250 g/ml, and of Eudragit RS: 0.278, 0.167, 0.104, 0.083 g/ml, respectively. The ethanolic solution was poured into a 0.025% (w/v) aqueous solution (200 ml) of sucrose fatty acid ester (DK-F70, Daiichi Kogyo Seiyaku, Co., Kyoto, Japan) thermally controlled at 25 °C with agitation (300 rpm). Formulations for the preparation of microsponges referred to as MS1, MS2, MS3, and MS4 are tabulated in Table I. After 30 min of agitation, the system was decantated to separate the unagglomerated fine powders, then the microsponges were filtered and dried under reduced pressure for 24 h. The dried microsponges were sieved to 250—1410 μm, and employed for micromeritic analyses, dissolution and direct compression tests.

Measurements of Micromeritic Properties of Microsponges Surface topographies of microsponges were observed by scanning electron microscope (JSM-T300, Nihon Denshi, Tokyo, Japan) after coating with gold. Particle density (ρ_p) of the microsponges fractionated using standard sieves (12—60 mesh) was measured by the photographic counting method with Eq. 1, for which an image-analyser (IBAS, Karl-Zeiss, Germany) was used to determine the volume (V) of n particles (weight, W).

TABLE I. Formulations for the Preparation of Microsponges by the Emulsion-Solvent Diffusion Method

Sample No.	Inner phase				Outer phase	Recovery of MS (%)
	Ibu (g)	Eud.RS (g)	EtOH (ml)	Ibu conc. (g/EtOH ml)	DK-F70 Aq. soln. (w/v%, ml)	
MS1[a)]	2.5	0.833	3	0.833	0.025, 200	86.2
MS2	2.5	0.833	5	0.500	0.025, 200	91.0
MS3	2.5	0.833	8	0.313	0.025, 200	73.1
MS4	2.5	0.833	10	0.250	0.025, 200	22.1

a) Microsponge (Ibu : Eud.RS = 3 : 1).

$$\rho_p = W/V = W/(\sum_1^n \pi d^3/6) \quad (1)$$

where d is the Heywood diameter[8] of the projected image of the microsponge. The porosity (ε) of microsponges was used as another parameter characterizing the internal texture.

$$\varepsilon = 1 - \rho_p/\rho_t \quad (2)$$

where ρ_t is the true density measured using a helium–air pycnometer (model 1302, Micromeritics Instrument Co., U.S.A.). The pore size distribution in the microsponges was measured by the mercury displacement method at various pressures employing a specially designed pycnometer (Poresizer 9305, Shimadzu Co., Ltd., Japan).

Particle shape and size were determined using an image analyser (cis-1, Galai, Israel). The system was calibrated in terms of microns per pixel (picture points) using a linear graticule. The microsponges fractionated by sieve (500—710 μm) were mounted on a black plane plate. After monitoring the projected view, the images produced were edited manually with a light pen to measure the particles individually. The shape factor (ϕ) was calculated as follows, and measurement was made of at least 500 microsponges:

$$\phi = (S/P^2) \times 4\pi \quad (3)$$

where S and P are respectively the area and perimeter of the individual image.

Drug Release Test of Microsponges The dissolution test of microsponges was carried out according to JPXI paddle method. Microsponges fractionated to 250—350, 350—500, 500—710, and 710—1000 μm containing 500 mg of ibuprofen were dispersed into the disintegration test solution No. 2 (900 ml), which was maintained thermally at 37 °C and the stirred at 100 rpm. Three ml of the dissolution medium was sampled, and fresh dissolution medium was simultaneously added to the apparatus to keep the volume constant. The withdrawn sample was filtered with a membrane filter (pore size = 0.3 μm), diluted and assayed spectrophotometrically at 220 nm to determine the dissolved drug concentration using a spectrophotometer (Model 100-60, Hitachi Co., Tokyo, Japan).

The dissolution data were analysed using the theoretical model developed by Higuchi[9] which had been used to describe the diffusional based drug release from polymeric matrices. For a spherical matrix, the drug release kinetics may be expressed by the following Eq. 4:

$$3\{1-(1-M_t/M_\alpha)^{2/3}\} - 2M_t/M_\alpha = Bt \quad (4)$$

$$B = 24 D_{eff} \cdot Cs/Ad_0^2 \quad (5)$$

where M_t and M_α are the amounts of drug released at time t and infinite time, respectively, and B is a constant which describes the combined effect of drug solubility in the release medium (Cs), effective diffusion coefficient (D_{eff}), diameter of matrix (d_0), and the drug loading per unit volume of matrix (A) on the rate of drug release. D_{eff} can be related to the diffusion coefficient in medium (D), the porosity (ε) and tortuosity (τ) of the porous polymer:

$$D_{eff} = D\varepsilon/\tau \quad (6)$$

The diffusion coefficient of the drug in the medium was measured using a diffusion cell,[10] and was found to be 8.28×10^{-6} cm^2/s in JPXI No. 2 solution at 37 °C.

Compressibility of Microsponges The compression properties of ibuprofen microsponges and the physical mixture of the original drug and polymer were investigated using an Instron type press equipped with an automatic strain gauge meter (Autograph AG5000-D, Shimadzu Co.). The samples (0.2 g) fractionated to 250—350, 350—500, 500—710, 710—1000, or 1000—1410 μm were compressed with a lubricated punch and die set with an 8 mm diameter and flat-face. Loads were applied by driving punch at 2 mm/min. The punch was held for 60 s when the loads reached 100, 300, 500, 750, 1000, 1500, 2000, or 3000 kg/cm^2, then the loads were released by removing the punch at the same rate. The detected pressure drop of upper punch during 60 s was assumed to be a stress relaxation, describing a plastic deforming property. After measuring the weight and thickness of the resultant compact (tablet), the diametrical breaking strength of each tablet was measured using the Autograph in its single compression mode. The upper punch was driven at 0.5 mm/min to compress the tablet placed on the surface of the lower punch. The tensile strength (σ)[11] was calculated by means of Eq. 7:

$$\sigma = 2F/\pi Dl \quad (7)$$

where F is the load required to cause fracture, and D and l are diameter and thickness of the tablet, respectively. Tablet porosity was calculated from the true densities measured by the helium–air pycnometer and the apparent densities taken from the weight and volume of the tablet. The values were the average of triplicate data.

Results and Discussion

Effect of Concentration of Ibuprofen in Ethanol on Property of Microsponges When the ethanol solution with drug and polymer was poured into the aqueous medium, coacervate-like droplets of the ethanol solution were instantly formed; these gradually solidified to spherical microsponges as ethanol diffused from the droplets to the environmental medium. It was found that with decrease in the concentration of ibuprofen in ethanol to lower than 0.3 g/ml, the recovery of microsponges decreased sharply (Table I). With formulations Nos. MS1 and MS2, the whole system turned to dispersed coacervate-like droplets having 200—1000 μm in diameter at the initial stage, and these were solidified with their coacervate sizes reserved. On the other hand, at lower concentrations of ibuprofen of less than 0.35 g/ml (samples Nos. MS3, MS4), some parts of the ethanolic solutions were quickly dispersed into numerous fine nanometer-size droplets which dispersed in a milk-like fashion. Their size distribution ranged from 100 to 300 nm as measured by a dynamic light scattering analyser (LPA-3100, Otsuka Electoric, Japan). These emulsion droplets transformed into unagglomerated crystals about 50 μm in diameter without coalescence. Other parts of the ethanolic solution turned into coacervate-like droplets, producing aggregations of larger spherical microsponges.

At higher concentration of the drug, the ethanol bound with the drug molecule might be separated from the aqueous phase, forming a viscous coacervate droplet in which co-crystallization of the drug and the polymer slowly occurred, producing a spherical microsponge. At lower drug concentration, rapid intermixing of the free ethanol with the aqueous phase induced a drastic reduction in the size of ethanol droplets and a rapid preferential crystallization of the drug. These actions might produce nanometer sized sponges with polymer and unagglomerated crystals of the drug without polymer.

The surface morphology of microsponge was thus dependent on the concentration of drug in the ethanol droplet as demonstrated in Fig. 1. With a decrease in the concentration, the surface became rough and porous (A-3, A-4). These topographs were more clearly found on the surface of microsponges recovered after dissolution test for 24 h (Fig. 1B). At higher concentration, a smooth shell-like structure with small pores was formed on the surface of microsponges (B-1, B-2), while those prepared with lower concentration had an agglomerate-like structure with large cracks, which was explained by the aggregating mechanism described previously. The drug content in the microsponges agreed well with the theoretical value calculated from the formulation; therefore, the difference in topography of each microsponges could not be explained by the variation in their composition.

As suggested by scanning electron microscope photographs, the internal structure of microsponges might be determined by the concentration of ibuprofen in ethanol.

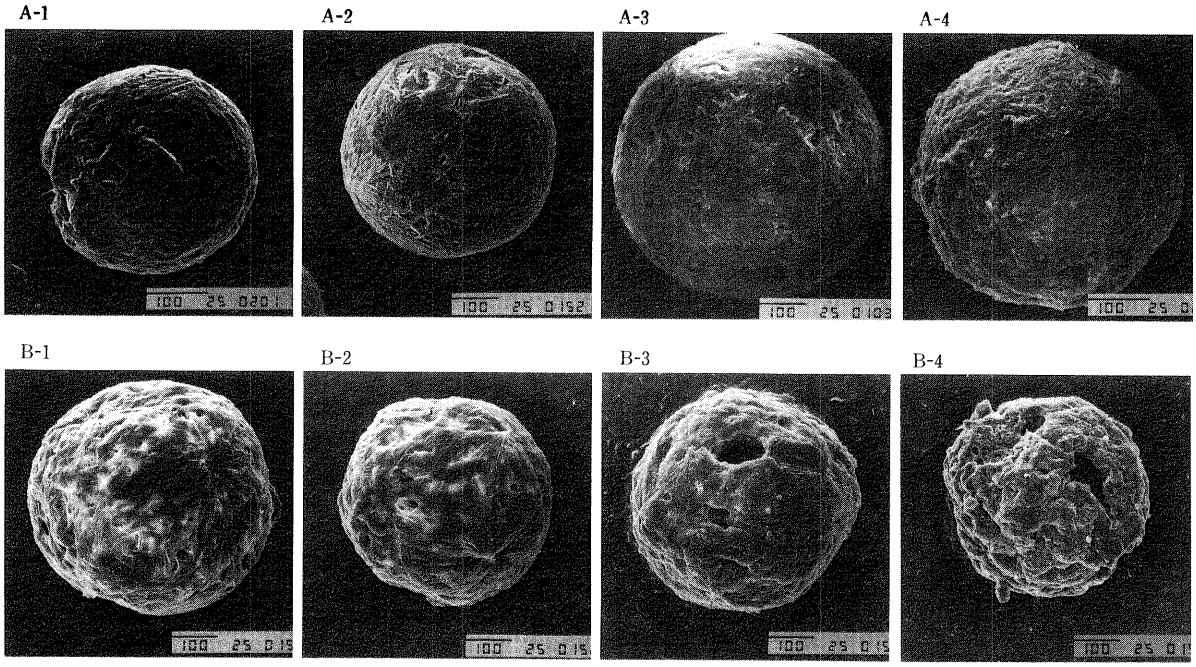

Fig. 1. Scanning Electron Microphotographs of Microsponges Before (A) and After (B) the Dissolution Test

Sample No., concentration (g/ml): (1) MS1, 0.833; (2) MS2, 0.500; (3) MS3, 0.313; (4) MS4, 0.250. Bar: 100 μm.

TABLE II. Particle Density, Porosity and Sphericity of Ibuprofen Microsponges Prepared with Various Concentrations

Sample No.	Ibu conc. (g/EtOH ml)	Density (g/cm^3)	Porosity (%)	Shape factor[b] (−)
MS1[a]	0.833	0.892	25.2	0.936
MS2	0.500	0.875	26.6	0.957
MS3	0.313	0.668	44.0	0.962
MS4	0.250	0.641	46.3	0.885

a) Microsponge (Ibu : Eud.RS = 3 : 1, 500—710 μm). *b*) Shape factor = (area/perimeter^2) × 4π.

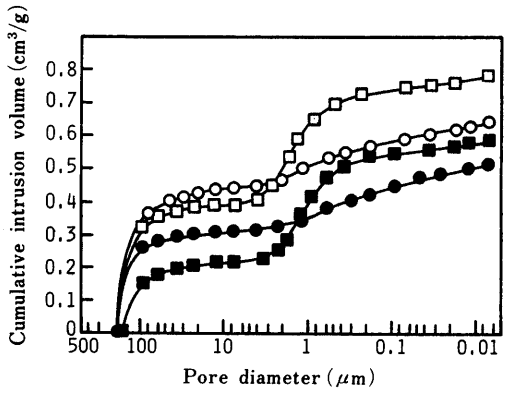

Fig. 2. Cumulative Pore Size Distribution of Microsponges (500—710 μm) Prepared with Various Concentrations

Sample No., porosity (%): (●) MS1, 25.2; (○) MS2, 26.6; (□) MS3, 44.0; (■) MS4, 46.3.

It was found that the internal porosity of the particles increased with the decrease of drug concentration (see Table II). Pore size distributions of microsponge are shown in Fig. 2. The pore sizes of intraparticles ranged from 0.01 to 3 μm, and those of microsponges produced from the low drug concentration formulations (MS3, MS4) were primarily

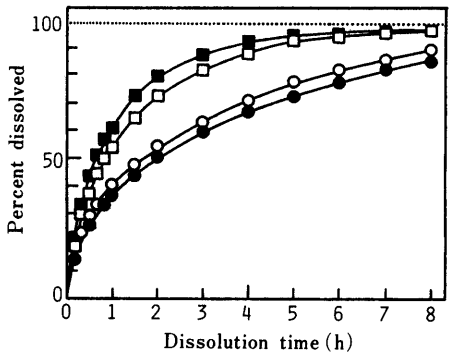

Fig. 3. Release Profiles of Ibuprofen from Microsponges (500—710 μm) Having Various Porosities

Key as in Fig. 2.

between 0.3 and 3 μm. These findings suggested that these pores provided a channel for release of the drug from the microsponges. The drastic difference of porosity between microsponges MS1, MS2 and microsponges MS3, MS4 as shown in Table II was explained by their different preparation mechanisms, *i.e.* the direct transformation from emulsion to solid microsponge for MS1, MS2 and the solidification of aggregated emulsion for MS3, MS4. The very low shape factor for MS4 microsponge suggested the frequent coalescence of microsponges as shown in Table II. Differences in the internal texture affected the release and compressing properties of the microsponges as discussed in the following paragraphs.

Drug Release Property of Microsponges The microsponges prepared with the formulations MS1 to MS4 differed in their drug release rate, although they had the same size distribution and the same drug content (Fig. 3). Furthermore, X-ray powder diffractometry (RAD-IC, Rigaku, Japan) revealed that the crystal form and the crystallinity of drug in the microsponges were identical.

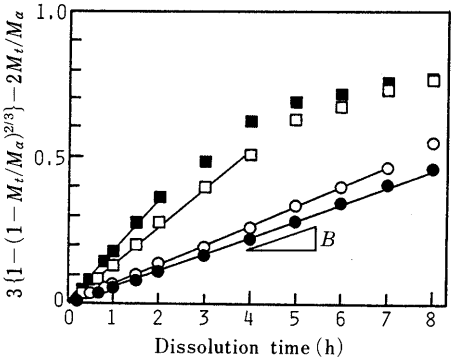

Fig. 4. Release Profiles of Ibuprofen from Microsponges (500—710 μm) as Described by the Higuchi Model of Spherical Matrices

Key as in Fig. 2. *B*: slope of regression line.

TABLE III. Drug Release Parameters of Ibuprofen Microsponges Prepared with Various Concentrations

Sample No.	Ibu conc. (g/EtOH ml)	Slope (*B*) (/s)	D_{eff} [b] (cm^2/s)	τ [c]	ε [d] (%)
MS1[a]	0.833	1.62×10^{-5}	5.24×10^{-7}	3.99	25.2
MS2	0.500	1.88×10^{-5}	5.98×10^{-7}	3.68	26.6
MS3	0.313	3.83×10^{-5}	9.33×10^{-7}	3.90	44.0
MS4	0.250	5.20×10^{-5}	1.21×10^{-6}	3.16	46.3

a) Microsponge (Ibu: Eud.RS = 3 : 1, 500—710 μm). *b*) D_{eff}: effective diffusion coefficient. *c*) τ: tortuosity. *d*) ε: porosity.

Thus, microsponges having a more porous internal structure exhibited a faster drug release rate than that of rigid microspheres, suggesting that the sustained-release characteristics of the microsponge system depended greatly on internal porosity.

In order to explain the release rate of ibuprofen quantitatively and to obtain more information on the release kinetics, the dissolution data were replotted according to the spherical matrix model developed by Higuchi[9] (Fig. 4). Good linear relationships were found ($r>0.998$) with up to 80—90% releasing of the drug contained, indicating that the microsponges had a heterogenous and spherical matrix-like structure, and that the release rate depended upon drug diffusion out of the matrix through water-filled channels.[12] The release rate constants (*B*) were calculated from the slope of each fitting line and are shown in Table III. Then, the effective diffusion coefficient of ibuprofen and the tortuosity in the spongy matrix were calculated using the *B* values according to Eqs. 5 and 6. The diffusion rate increased with the increase of internal porosity in the microsponges, but the tortuosity was almost constant (3—4) for each sample, which agreed with an average value of $\tau=3$ for porous matrix as reported by Higuchi.[9] These results indicate that ibuprofen existed in the polymeric matrix in the same way because the drug and the polymer were simultaneously coprecipitated with the same composition ratio in each formulation. In our previous report, the drug release rate was controlled by the particle size and the drug loading in the microsponge system.[3] In the present system, it was found that the drug release rate could be controlled by changing the porosity of the microsponge without changing the particle size or drug loading as shown in Fig. 5. It was also

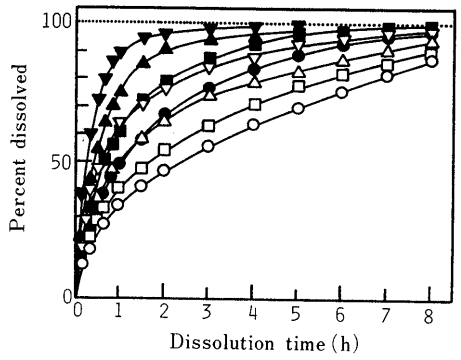

Fig. 5. Release Profiles of Ibuprofen from Microsponges (Ibuprofen: Eudragit RS = 3 : 1) Prepared at 0.50 g/ml (Open Symbols) and 0.25 g/ml (Closed Symbols) of Ibuprofen Concentration in Ethanol

Size fractions: (▽, ▼) 250—350 μm; (△, ▲) 350—500 μm; (□, ■) 500—710 μm; (○, ●) 710—1000 μm.

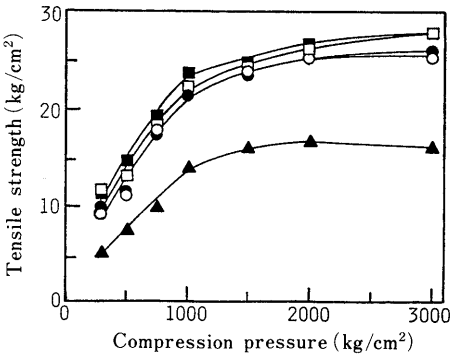

Fig. 6. Compressibility of Ibuprofen Microsponges (500—710 μm) Having Various Porosities

Sample No., porosity (%): (●) MS1, 25.2; (○) MS2, 26.6; (□) MS3, 44.0; (■) MS4, 46.3; (▲) physical mixture (ibuprofen: Eudragit RS = 3 : 1).

possible to realize the same release profiles even if using samples different in size, keeping the drug content being constant (ibuprofen: Eudragit RS = 3 : 1). Using this system, we examined the effect of particle size of microsponges having the same drug release behavior *in vitro* on bioavailability when orally administered to dogs.[13]

Compression Characteristics of Microsponge It was assumed that the microsponges might possess an unique compression property due to their matrix- or sponge-like structure which differed from conventional microcapsules or physical powder mixture. In addition, the compressibility of microsponges was evaluated in detail as a model matrix granule with polymer for preparation of matrix tablet by direct compression, which was extensively investigated by many authors.[6,7] Compressibility was evaluated by a diametrical fracture test of the compact (*i.e.*, tablet) prepared with microsponges. The microsponge tablets were found to have much higher tensile strength than that of a physical mixture of the drug and polymer with the same mixing ratio of the microsponges employed as shown in Fig. 6. The X-ray powder diffraction patterns of the crystals in the microsponges coincided with that of the physical mixture of the original powders, which suggested that tablet hardness was not related to the crystallinity as reported by Morita *et al.* with lactose.[14]

The improvement in compressibility was probably attributable to the sponge-like structure of the microsponges. As shown in the photographs of the surface of a

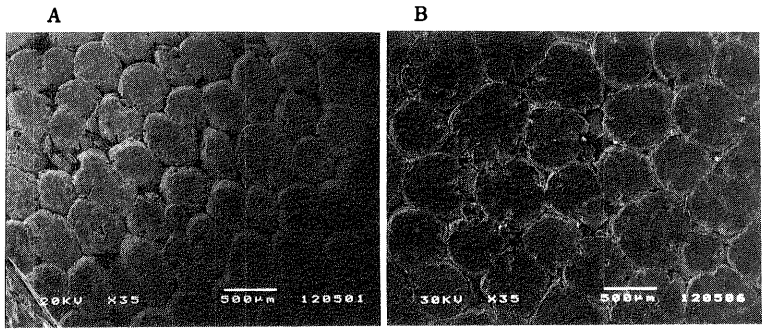

Fig. 7. Scanning Electron Microphotographs of Matrix Tablet of Microsponges (500—710 μm) Compressed at 300 kg/cm²
(A) Lateral surface topograph; (B) top surface topograph.

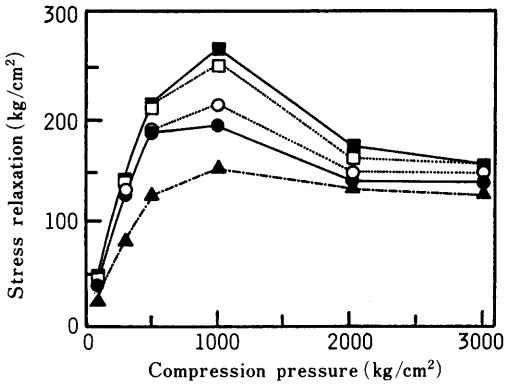

Fig. 8. Stress Relaxation of Compressed Ibuprofen Microsponges (500—710 μm) Having Various Porosities
Key as in Fig. 6.

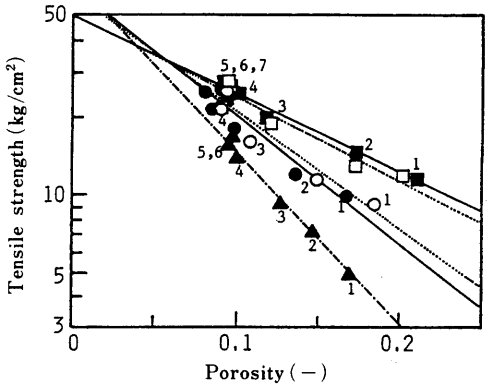

Fig. 9. Relationship between Porosity and Tensile Strength of Compressed Tablets of Microsponges (500—710 μm) Having Various Porosities
Key as in Fig. 6. Compression pressure (kg/cm²); (1) 300, (2) 500, (3) 750, (4) 1000, (5) 1500, (6) 2000, (7) 3000.

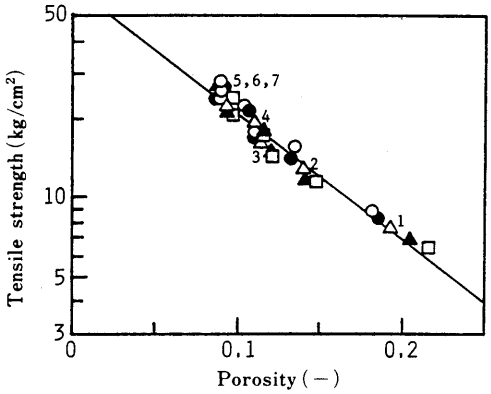

Fig. 10 Relationship between Porosity and Tensile Strength of Compressed Tablets of Microsponges in Various Size Fractions Prepared at 0.50 g/ml of Concentration
Size fractions: (□) 250—350 μm; (▲) 350—500 μm; (△) 500—710 μm; (●) 710—1000 μm; (○) 1000—1410 μm. Compression pressure (kg/cm²); (1) 300, (2) 500, (3) 750, (4) 1000, (5) 1500, (6) 2000, (7) 3000.

compressed tablet of microsponges at 300 kg/cm² (Fig. 7), the individual microsponges were not fractured but were consolidated accompanying the plastic deformation, retaining their sponge-like structure after compression. In addition, the axial elastic recovery of each tablet ejected from the die was relatively small (about 6—7%) after removal of the pressure. The sponge-like structure was reserved even compressed at pressure above 1000 kg/cm². The stress relaxation of powder bed under constant strain, described by the decreased upper punch pressure for 60 s, was measured as an index of the plastic deformation according to the previous reports.[15,16] At compression pressure lower than 1000 kg/cm² the compacts of microsponges showed larger stress relaxation than those of the physical mixture of drug and polymer in Fig. 8. The increase of stress relaxation of the microsponges was derived from the deformable property of each one (Fig. 7), but not from the fracture of particles and/or crystals. This improvement in the plastic deformation probably led to a strengthened bonding between particles, resulting in strong tablets. On the other hand, at above 1000 kg/cm² of compression pressure, the stress relaxation of compact of the microsponges decreased and gradually approached that of the physical mixture. This characteristic behavior might be explained by the phenomenon that the stress dissipation in the compact caused by the structural deformation of the sponges no longer occurred because the deformable structure of the microsponges was lost at higher compression pressure. The stress relaxation was increased with the increase in internal porosity of the microsponge as expected (MS4 > MS3 > MS2 > MS1).

In Fig. 9, the logarithm of tensile strength is shown as a function of the internal porosity of the tablet, which was calculated by measuring the dimensions and the weight of tablets upon completion of elastic recovery. It is possible to compare the internal porosities of tablets with the same tensile strength among four microsponges having various porosities. The regression lines of compacts with porous microsponges (MS3, MS4) were situated to the right side

of those with rigid microsponges (MS1, MS2) at lower compression pressure. This finding suggested that MS3 and MS4 were compressed into stronger tablets with less change in their internal porosities. Therefore, the residual porosity in a microsponge after compression might not be directly correlated with the tensile strength of the compact. At pressure over 1000 kg/cm^2, all plots of data in Fig. 9 converged to one point, indicating the internal porosity of microsponges had completely disappeared. The relationship between the tensile strengths and porosities of tablets prepared with microsponges having internal porosity ($\varepsilon = 27\%$), prepared with formulation MS2 (drug concentration 0.5 g/ml) is exhibited in Fig. 10. All logarithmic tensile strengths were well correlated linearly with porosities, irrespective of the size of microsponges compressed. Considering that the porosity of the intact microsponges before compression was almost constant, the tensile strength of compacts would not depend upon the internal porosity remaining in the sponge-like structure, but mainly upon the interparticle porosity between microsponges. The smaller microsponges were hardly consolidated in the die because of their larger contact points between particles. In fact, traces of the microsponge figure were found on the fracture plane of a tablet after breaking. The cracking plane developed along the surface of microsponges composing the tablet.

In conclusion, it was found that the porosity of microsponges could be controlled by changing the concentrations of drug and polymer in the formulation while maintaining their content ratio constant. It was possible to control the drug release rate from the microsponges by changing only the porosity without altering the particle size or polymer concentration. Their plastic properties allowed microsponges to be more easily compressed by direct compression to produce a mechanically strong tablet than the physical mixture of drug and polymer. This characteristic property is advantageous for the preparation of matrix tablet with polymer for controlled release. Preliminary drug release tests of the tablets prepared with microsponges exhibited typical drug release profiles characterized by the Higuchi-matrix model. Further investigations are being made.

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