Chem. Pharm. Bull. **40**(11) 3030—3035 (1992) Vol. 40, No. 11

Particle Design of Tolbutamide by the Spherical Crystallization Technique. V. Improvement of Dissolution and Bioavailability of Direct Compressed Tablets Prepared Using Tolbutamide Agglomerated Crystals

Akimitsu SANO,*[,a] Takeo KURIKI,[a] Yoshiaki KAWASHIMA,[b] Hirofumi TAKEUCHI,[b] Tomoaki HINO[b] and Toshiyuki NIWA[b]

Pharma Research Laboratories, Hoechst Japan Limited,[a] 1–3–2 Minamidai, Kawagoe, Saitama 350, Japan and Gifu Pharmaceutical University,[b] 5–6–1 Mitahora-higashi, Gifu 502, Japan. *Received March 21, 1992*

Tolbutamide (TBM) agglomerated crystals were prepared by three spherical crystallization techniques, the solvent change (SC) method, neutralization (NT) method and quasi-emulsion solvent diffusion (QESD) method (SC-A, SC-B, NT and QESD agglomerated crystals), followed by mixture with a disintegrating agent and a lubricant (physical mixtures), and then tableting by the direct compression method. Unagglomerated TBM original crystals (bulk) were treated in the same manner. The dissolution rate and bioavailability of TBM from the physical mixtures and tablets were evaluated to look for a correlation between the *in vitro* dissolution profile and *in vivo* bioavailability.

The TBM dissolution rate from the physical mixtures and tablets increased in the order of bulk $\leqq$ QESD < SC-A < SC-B < NT in direct proportion to an increase in the specific surface area of the agglomerated crystals and bulk. A linear relationship could be established between the specific surface area and 75% dissolution time (T_{75}).

In *in vivo* studies in beagle dogs, the physical mixtures and tablets of the agglomerated crystals showed significantly higher values than those of the bulk in the area under the curve of plasma concentration (AUC_{0-8h}), maximum concentration in plasma (C_{max}) and absorption rate constant (k_a), especially high values were obtained with the NT physical mixtures and tablets. A linear correlation could be established between $1/T_{75}$ and k_a. The *in vivo* absorption process and bioavailability of TBM could be estimated from the *in vitro* dissolution profile.

Keywords dissolution rate; bioavailability; absorption rate; specific surface area; direct compressed tablet; tolbutamide; particle design; spherical crystallization technique

Introduction

The authors have been studying the particle design of tolbutamide (TBM), a poorly soluble drug, with the objectives of improving the efficacy of the overall process in tablet manufacture (compressibility characteristics such as the flowability, filling properties, tablet tensil strength) and increasing the functionality such as the solubility and bioavailability of drug particles. We have applied three spherical crystallization techniques, the solvent change (SC) method, neutralization (NT) method and quasi-emulsion solvent diffusion (QESD) method to TBM and evaluated the prepared agglomerated crystals of TBM. Alteration of the types of components and the compositional ratio of the crystallization solvent made it possible to manufacture TBM agglomerated crystals endowed with a large specific surface area, excellent solubility, excellent flowability and high mechanical strength.[1,2] Agglomerated crystals prepared by incorporation of water-soluble polymers showed improved wettability with water and increased solubility.[3] At the time of tableting, the TBM agglomerated crystals were easy to compact, and they resulted in high tablet tensile strength and excellent compressibility.[4] The functionality of the agglomerated crystals themselves could be increased.

It is recognized that the process of dissolution of a poorly-soluble drug from tablets exerts a profound effect on the bioavailability of the drug. A good understanding of the dissolution properties of a drug from tablets is very important in terms of quality control. To predict the *in vivo* absorption process of drugs based on the dissolution properties of the active ingredient from tablets, there have been many reports regarding the correlation between the dissolution properties and the bioavailability of drugs.[5]

In the present study, the authors employed TBM agglomerated crystals prepared by the SC, NT and QESD methods of spherical crystallization. Each type of agglomerated crystal was mixed with a disintegrating agent and a lubricant anticipated to be used in actual tablet manufacture and compressed into tablets by the direct compression method. The dissolution rate of tolbutamide from each of the tablets and the bioavailability in beagle dogs were then evaluated, and the correlation between these two parameters was investigated.

Experimental

Methods for Preparation of TBM Agglomerated Crystals The following methods were employed to prepare TBM agglomerated crystals by each of the SC, NT and QESD methods of spherical crystallization. Further details are provided in the authors' earlier reports.[1–3]

SC-A Method: 250 ml of a 0.025% sucrose fatty acid ester aqueous solution was placed in a cylindrical vessel. While stirring, a mixture consisting of 50 ml of ethanol containing 5 g of dissolved TBM and 15 ml of isopropyl acetate was added. The TBM was crystallized out, followed by agglomeration of the crystals for 40 min.

SC-B Method: 50 ml of ethanol containing 5 g of dissolved TBM was placed in a cylindrical vessel. While stirring, 250 ml of a 0.025% sucrose fatty acid ester aqueous solution was added to crystallize out the TBM. Two min later, 22 ml of an isopropyl acetate–ethanol mixture was added dropwise at a rate of 10 ml/min, and agglomeration was performed for 40 min.

NT Method: 25 ml of 1 N sodium hydroxide in which 5 g of TBM had been dissolved was placed in a cylindrical vessel. While stirring, 250 ml of an aqueous solution of 2% hydroxypropylmethylcellulose and 25 ml of 1 N hydrochloric acid were added to neutralize the NaOH solution of TBM and crystallize out the TBM. Then 29 ml of ethyl ether was added dropwise at a rate of 10 ml/min, followed by agglomeration of the TBM crystals for 40 min.

QESD Method: 275 ml of a 0.025% sucrose fatty acid ester aqueous solution was placed in a cylindrical vessel. While stirring, 5 ml of dimethylformamide in which 2.7 g of TBM had been dissolved was added, followed by agglomeration of the TBM crystals for 15 min.

The form of the resultant TBM crystals was A-form for SC-A, NT, QESD and the unagglomerated bulk, while it was B-form for SC-B.[1]

Method for Preparation of Tablets, and Decision of Preparation Conditions Prior to the preparation of the tablets to be employed in the dissolution tests and *in vivo* tests, Kollidon CL (mean particle diameter:

20 μm; BASF Japan) was selected as a disintegrating agent known to impart excellent disintegration properties, and magnesium stearate (MgSt) as a lubricant which is in wide use. Studies were then carried out to decide the amount of these excipients to be added to the TBM agglomerated crystals and to decide the compression pressure to be applied at the time of tableting. Tablets were then prepared according to the following method. The particle size of SC-B agglomerated crystals was adjusted to within a range of 250—500 μm (30—60 mesh) with a sieve shaker, and then MgSt and Kollidon CL were added in various amounts and mixed (Table I). These formulations were then compacted into tablets using a single-punch machine (Okada Seiko; Model N-30) equipped with flat-faced punches having a diameter of 13 mm, operated at a compression speed of 2.4 cm/s and a compression pressure of 700 kg/cm^2. Tablets of formulation C were prepared at compression pressures of 300 and 500 kg/cm^2.

Among the tablets of formulations A—D, formulation C tablets showed the most rapid disintegration and dissolution. Considering this result and the tablet strength in practical use, the formulation C tablet prepared at 700 kg/cm^2 was selected for the present study.

Physical Measurements on TBM Agglomerated Crystals and Bulk The agglomerated crystals and the bulk were employed as samples. Tablets were disintegrated in a saturated aqueous solution of TBM and passed through a 200-mesh sieve. The agglomerated crystals and bulk on the sieve were dried and also employed as samples. The particle size distribution of each sample was determined from the particle size (circle equivalent diameter) of about 300 particles dispersed on a slide glass which was measured using an apparatus (Nikon; Luzex 3U) equipped with a microscope and an image analyzing processor. The mean particle diameter was presented as the arithmetic mean. The apparent particle density (ρ_{app}) and apparent specific surface area (S_{wapp}) were calculated from equations $\rho_{app} = W\phi/n\pi d^3$ and $S_{wapp} = \phi/\rho_{app} \cdot d$, respectively. The number of particles (n) was counted on a photo of a known weight (w) of samples dispersed on a slide glass. The specific shape coefficient (ϕ) was assumed to be 6 because of the sample shape being spherical. In addition, the surface of the agglomerated crystals was observed using a scanning electron microscope (JEOL; Model JMS-25SIII).

For determination of the contact angle, TBM agglomerated crystals and the bulk were compacted into tablets (diameter: 8 mm; porosity: 0.1 or less), respectively. One drop of saturated TBM aqueous solution was placed on the surface of the compacted tablet using a microsyringe, and a contact angle meter (Kyowa Kagaku; Model CA-A) was used to directly measure the contact angle. Since the contact angle is known to change with time as the liquid drop permeates into the compacted tablet, the value at $t=0$ was extrapolated in accordance with the report of Ito *et al.*[6]

Dissolution Test The dissolution rate of physical mixtures obtained by the addition of Kollidon CL and MgSt to the TBM agglomerated crystals and the bulk as well as to the tablets (each containing the equivalent of 500 mg of TBM) prepared by direct tableting of these physical mixtures was determined in accordance with the Japan Pharmacopoeia XII using a dissolution tester (Toyama Sangyo; Model NTR-VS6). The dissolution fluid consisted of 900 ml of pH 6.5 phosphate buffer solution [prepared from 0.2 M monobasic potassium phosphate (250 ml), 0.2 M NaOH (76 ml) and water (674 ml)]. The test was carried out for 60 min at 100 rpm by the paddle method, and samples were collected with the passage of time. The amount of dissolved TBM was determined by measuring the absorbance at λ_{max} 229 nm using a UV spectrophotometer (Hitachi; Model 340).

***In Vivo* Test** Samples (each at the equivalent of 8.3 mg/kg of TBM) were orally administered together with 20 ml of water to three male beagle dogs weighing 10—13 kg. The dogs were fasted for the period from 24 h prior to administration through 8 h post-administration. The administrations were performed by the crossover method, with a washout period of at least one week between administrations. At 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after each administration, 3 ml of blood was collected from a foreleg vein and immediately centrifuged.

Assay of TBM Concentration in Plasma In accordance with the method of Raghow *et al.*,[7] 0.5 ml of plasma was mixed with 0.5 ml of water, 0.1 ml of 0.5 N HCl, 0.5 ml of internal standard (parabutyl benzoic acid) and 5 ml of ethyl ether, followed by agitation for 5 min. After centrifugation at 3000 rpm, the ether layer was isolated and evaporated to dryness under a stream of nitrogen gas. The residue was then dissolved in 0.5 ml of acetonitrile and 10 μl of this solution was injected into a high performance liquid chromatograph (HPLC). The concentration of TBM in the plasma was calculated from the peak area ratio of TBM to the peak area of the internal standard, using a newly-prepared working curve.

HPLC Operation Conditions: Pump, JASCO VIP-I; detector, detection wavelength 254 nm, JASCO, UVIDEC V-100; column, Nucleosil C18 (250 × 4 mm i.d., particle diameter, 10 μm); mobile phase, 0.05 M phosphate buffer (pH 3.9) and acetonitrile mixed solution (55 : 45); flow rate, 1 ml/min; limit of detection, 1 μg/ml.

Analysis of Pharmacokinetic Parameters and Statistical Analysis of Data The TBM concentration in the plasma was plotted against time on a graph, and the values of the maximum plasma concentration (C_{max}) and the time of occurrence of the C_{max} (T_{max}) were then determined from the graph. In addition, for the 8-h period after administration of the test preparations, the value for the area under the curve (AUC_{0-8h}) of plasma concentration of TBM was calculated by the trapezoid method. The absorption rate constant (k_a) fitted the oral compartment model and was calculated by the non-linear least squares method.

The values for C_{max}, T_{max}, AUC_{0-8h} and k_a were analyzed for significant difference by the paired t test.

TABLE I. Formulations of Physical Mixtures for Tablets

Component (mg)	Formulation			
	A	B	C	D
Tolbutamide	500	500	500	500
Kollidon CL	25	50	100	100
Magnesium stearate	2.5	2.5	2.5	1.0

Results and Discussion

Dissolution Rates of the TBM Agglomerated Crystals, Bulk, and Their Tablets Figure 1 presents the plots of the data on the amounts of TBM dissolved from the physical mixtures prepared by adding Kollidon CL and MgSt to the agglomerated crystals and the bulk, as well as from the

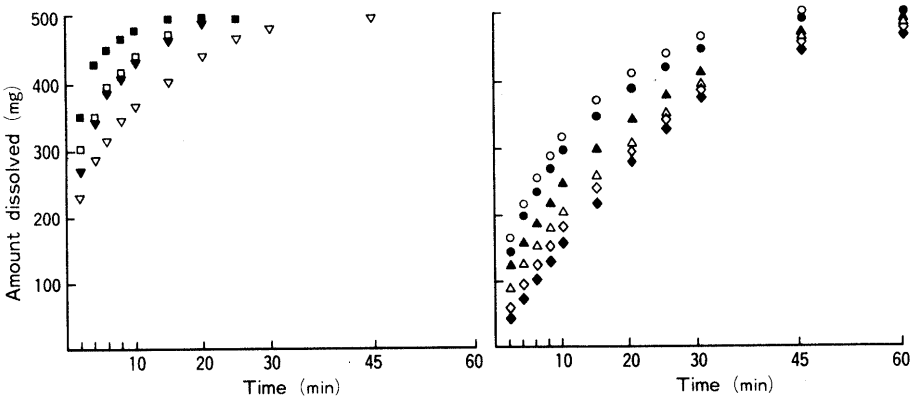

Fig. 1. Dissolution Profiles of TBM from Physical Mixtures and Tablets

Solid symbols, physical mixtures; open symbols, tablets. □, NT; ▽, SC-B; ○, SC-A; △, QESD; ◇, bulk.

TABLE II. Data on Physical Properties and Dissolution Rates (T_{75}) of TBM Agglomerated Crystals and Bulk before and after Tableting

Sample	Tableting	Mean particle diameter (μm)	Apparent particle density (g/cm^3)	Apparent specific surface area (cm^2/g)	T_{75} (min)	Ratio[a]	Ratio[b]
SC-A	Before	385	0.846	184	16	1.15	1.06
	After	315	0.973	195	14		
SC-B	Before	315	0.667	285	5.5	1.67	0.84
	After	225	1.111	240	8		
NT	Before	315	0.730	261	2.2	1.55	0.92
	After	220	1.130	241	5.0		
QESD	Before	375	0.954	168	20	1.25	0.93
	After	320	1.194	157	26		
Bulk	Before	395	0.999	152	28	1.04	1.09
	After	350	1.036	160	26		

a) Ratio of apparent particle density of after to before tableting. *b*) Ratio of apparent specific surface area of after to before tableting.

tablets prepared from those physical mixtures. The times required for 75% dissolution (T_{75}) of TBM from the physical mixtures were calculated from the graphs, and they showed a decreasing order of bulk > QESD > SC-A > SC-B > NT; the respective calculated times were 28 > 20 > 16 > 5.5 > 2.2 min (Table II). The values for T_{75} for the tablets showed a similar pattern, with a decreasing order of bulk = QESD > SC-A > SC-B > NT; the respective calculated times were 26 = 26 > 14 > 8 > 5 min (Table II). The values for T_{75} of the SC-A and bulk tablets compacted from the physical mixtures became slightly shorter than for the physical mixtures themselves, whereas the NT, SC-B and QESD tablets showed the opposite tendency, *i.e.*, T_{75} became longer than for the physical mixtures. Thus, there were differences in the dissolution rates from these tablets, but it was found that each of the tablets disintegrated within one min, and it was therefore surmised that the disintegration of the tablets was not involved in the difference in dissolution rate between the tablets. In addition, most of the particles that had resulted from the disintegration of the tablets were similar in shape and size to the agglomerated crystals and the bulk before tableting, but there were also some particles which had become smaller than the original because they had been subjected to compaction or partial breakage during the compression process. Moreover, the physical mixtures and also the particles resulting from disintegration of the tablets were observed to dissolve without accompanying distintegration.

On the basis of these findings, it was surmised that the difference in dissolution rate among the tablet preparations were due to differences among the agglomerated crystals in terms of the effect of the compaction (*i.e.*, the degree of deformation of the primary crystals comprising the agglomerated crystals).[8] Accordingly, we carried out a comparative study of the physical properties of the agglomerated crystals and the bulk before and after tableting.

Effects of Compression on Dissolution Rate of TBM 1. Particle Diameter and Apparent Particle Density of Agglomerated Crystals and Bulk before and after Tableting Figure 2 shows the particle size distributions of TBM agglomerated crystals and bulk before and after tableting. The particle size distribution before tableting was log-normal distribution. Tableting compacted and partially broke the agglomerated crystals and bulk, and the number

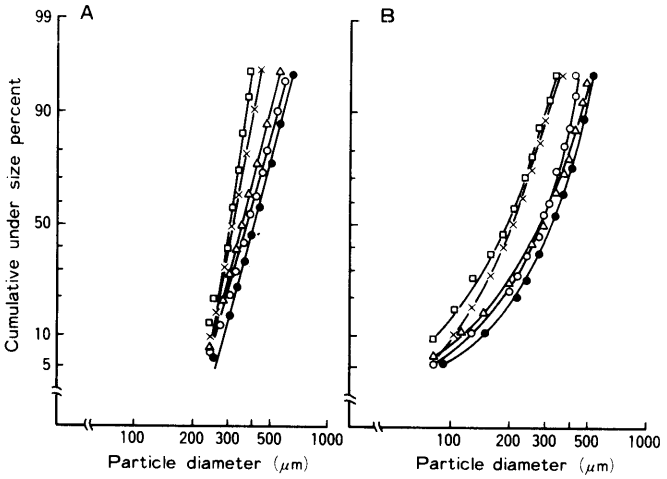

Fig. 2. Particle Size Distributions of Agglomerated Crystals and Bulk before and after Tableting

A, before tableting; B, after tableting. ○, SC-A; ×, SC-B; □, NT; △, QESD; ●, bulk.

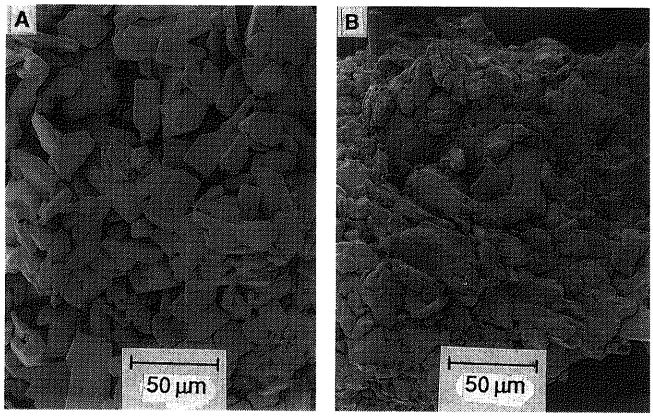

Fig. 3. Electron Microscopic Photographs of Surface of NT Agglomerated Crystals before and after Tableting

A, before tableting; B, after tableting.

of particles of $\leq 250\,\mu$m increased, which resulted in wider particle size distributions. Each sample showed a nearly log-normal distribution pattern, though the average particle size was reduced (Table II). On the basis of this finding, it was speculated that the dissolution of the TBM from the tablets would be increased. However, whereas the

dissolution from the SC-A tablets and bulk tablets was increased, the dissolution from the SC-B tablets, NT tablets and QESD tablets was decreased. These findings indicate that, in addition to the particle diameter, the particle density was also altered by the compression process. Accordingly, we measured the apparent particle density of the TBM agglomerated crystals and bulk before and after tableting (Table II). Except for the case of the bulk tablets, the degree of compaction differed for the agglomerated crystals in the tablets, and the apparent particle density was increased after tableting. Electron microscopic photographs also revealed that densification had occurred as a result of the compression procedure (Fig. 3). These results suggested that the dissolution of TBM from the physical mixtures and the tablets might be greatly affected by the specific surface area of the particles.

2. Apparent Specific Surface Area and Dissolution Time (T_{75}) of Agglomerated Crystals and Bulk before and after Tableting Table II also presents data on the apparent specific surface area of the TBM agglomerated crystals and bulk before and after tableting. The apparent specific surface areas of the SC-B, NT and QESD agglomerated crystals decreased as a result of the compression process, whereas the apparent specific surface areas of the SC-A agglomerated crystals and the bulk increased. It is thought that this difference is because, as we demonstrated in an earlier paper,[4] the SC-B, NT and QESD agglomerated crystals are more readily compacted than the SC-A agglomerated crystals and the bulk. The value of T_{75} showed good correlation with the change in the apparent specific surface area as a result of the compression. The values of T_{75} for both the SC-A tablets and bulk tablets were slightly shorter compared with the values for their physical mixtures, whereas the values of T_{75} for the SC-B tablets, NT tablets and QESD tablets were longer. Accordingly, we investigated the relationship between the apparent specific surface area and the reciprocal of the 75% dissolution time ($1/T_{75}$) (Fig. 4). The plots of the data revealed a linear relationship between the apparent specific surface area and the value of $1/T_{75}$ for each of the test articles except NT, and it was elucidated that the dissolution of TBM increased as the apparent specific surface area increased. In addition, the reason for the large deviation from linearity seen with NT was the difference between NT agglomerated crystals and the other samples in terms of wettability with water. That is, whereas the other agglomerated crystal samples and the bulk have a contact angle of 65—70 °C to water, NT is instantaneously permeated with water and thus shows strikingly greater wettability than the other samples. The reason for this superior wettability of NT agglomerated crystals and tablets is that, at the time of the crystalline agglomeration process, hydrophilic hydroxypropylmethylcellulose in the crystallization solvent adheres uniformly to the agglomerated crystals. These results inferred that the dissolution of TBM from its preparations having nearly the same wettabilities with water can be estimated from the

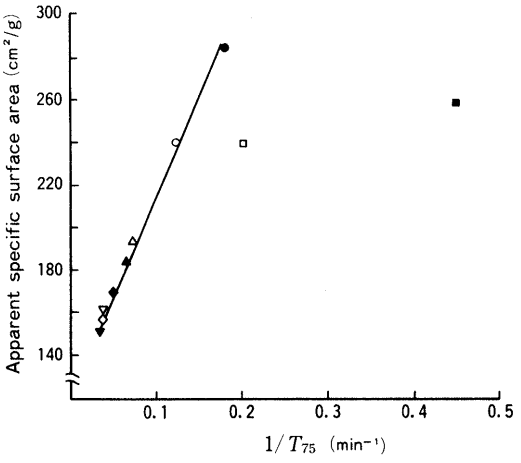

Fig. 4. Relationship between Dissolution Time ($1/T_{75}$) and Apparent Specific Surface Area

Solid symbols, physical mixtures; open symbols, tablets. △, SC-A; ○, SC-B; □, NT; ◇, QESD; ▽, bulk.

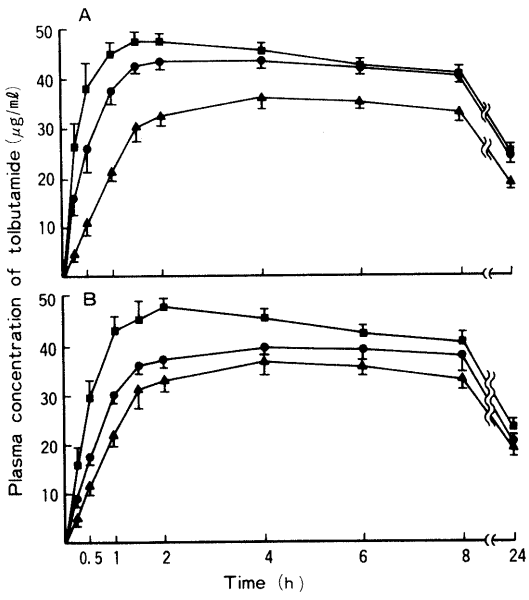

Fig. 5. Plasma Concentration of TBM after Oral Administration of the Physical Mixtures and Tablets

A, physical mixtures; B, tablets. ■, NT; ●, SC-B; ▲, bulk.

TABLE III. Pharmacokinetic Parameters of Physical Mixtures and Tablets

Pharmacokinetic parameter	Physical mixtures			Tablets		
	Bulk	SC-B	NT	Bulk	SC-B	NT
AUC_{0-8h} (μg·h/ml)	245.9±4.3	319.7±4.2[b]	342.5±5.2[d]	250.8±8.4	285.1±13.8[a]	333.2±8.1[d]
C_{max} (μg/ml)	36.9±1.1	43.8±0.9[b]	49.8±0.6[d]	38.1±1.6	40.6±2.0	49.1±3.6[c]
T_{max} (h)	3.3±0.9	1.8±0.2	1.5±0.4	3.3±0.9	2.7±0.9	1.7±0.2
k_a[e] (h^{-1})	0.328±0.084	1.31±0.39[a]	3.14±0.88[c]	0.431±0.116	0.993±0.149[a]	1.55±0.41[c]

a) Bulk *vs.* SC-B: significant difference ($p<0.05$). *b*) Bulk *vs.* SC-B: significant difference ($p<0.01$). *c*) Bulk *vs.* NT: significant difference ($p<0.05$). *d*) Bulk *vs.* NT: significant difference ($p<0.01$). *e*) Absorption rate constant.

apparent specific surface area calculated by an equation, $S_{wapp}=\phi/\rho_{app}\cdot d$, and depends on the effective surface area of the particles.

***In Vivo* Evaluation of the TBM Agglomerated Crystals, Bulk and Their Tablets** For *in vivo* evaluation, we selected the SC-B and NT agglomerated crystals because of their excellent solubility and excellent compressibility, *i.e.*, good densification at the time of tableting, high tensile strength, *etc.*[4] The bulk was also evaluated for comparison. The *in vivo* test was carried out on these physical mixtures and their tablets. In addition to this comparative study, the correlation with the results of the dissolution test was evaluated.

1. TBM Concentration in Plasma and Pharmacokinetic Parameters Figure 5 presents the plots of the plasma concentration of TBM with the passage of time. Table III compiles the data on the various pharmacokinetic parameters, *i.e.*, AUC_{0-8h}, C_{max}, T_{max} and k_a, obtained by the non-linear least squares method. The values for AUC_{0-8h}, C_{max} and k_a for the physical mixtures of the agglomerated crystals and their tablets were significantly higher than for the bulk. In addition, although the differences in the values for T_{max} were not statistically significant, these values were shorter for the agglomerated crystal samples compared with the bulk. These results closely reflected the findings of the dissolution test. It is known that the action of TBM in lowering the blood glucose level varies in direct proportion to the concentration of TBM in the plasma and its absorption rate,[9] and it would be extremely advantageous for the values of AUC_{0-8h} and k_a to be increased and the value of T_{max} to be shortened. In other words, since the blood glucose level of a patient increases within a short period of time after consumption of a meal, the above characteristics would make it possible to achieve rapid expression of TBM's blood glucose lowering action after ingestion of the drug. Moreover, it is thought that increasing the AUC would make it possible to reduce the dose and the size of the tablets, and these changes would provide further benefits in terms of reducting adverse effects and improving patient compliance.

2. Correlations between the Pharmacokinetic Parameters and Dissolution Time (T_{75}) and the Apparent Specific Surface Area It has been reported that there is a correlation between the TBM dissolution process and the absorption process in the digestive tract.[10] In addition, Nelson *et al.*[11] reported that, in the case of oral administration of TBM to humans, there was a correlation between the amount of TBM metabolites excreted in the urine and the effective surface area of the granules. In this connection, we investigated the relationship of the k_a value to the dissolution times ($1/T_{75}$) of the physical mixtures and tablets, as well as the relationships of the k_a value and the AUC_{0-8h} value to the apparent specific surface area. As can be seen from Fig. 6, the values of $1/T_{75}$ and k_a showed a linear relationship, and the absorption process in the digestive tract can be predicted from the dissolution characteristics. The positive correlation between these parameters was thus proven. Moreover, this study also established that the apparent specific surface area shows (Fig. 7) a linear correlation with both the k_a and the AUC_{0-8h} value in the cases of the SC-B agglomerated crystals and the bulk, for which a linear correlation between the apparent specific surface area and $1/T_{75}$ had already been demonstrated in Fig. 4.

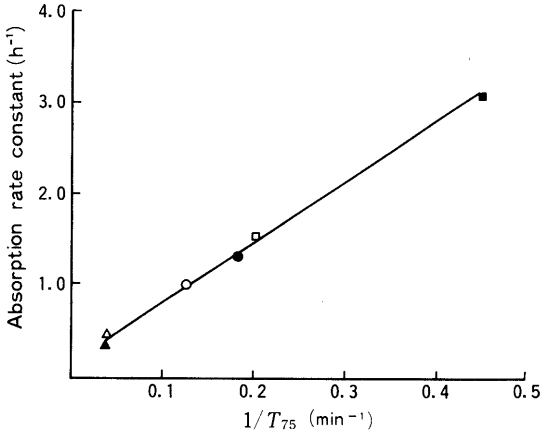

Fig. 6. Relationship between Dissolution Time ($1/T_{75}$) and Absorption Rate Constant

Solid symbols, physical mixtures; open symbols, tablets. □, NT; ○, SC-B; △, bulk.

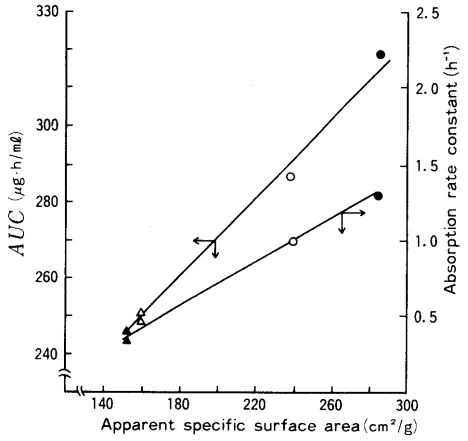

Fig. 7. Relationships between Apparent Specific Surface Area and AUC and Absorption Rate Constant

Solid symbols, physical mixtures; open symbols, tablets. AUC: ○, SC-B; △, bulk. Absorption rate constant: ○, SC-B; △, bulk.

References

1) A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi and T. Niwa, *Chem. Pharm. Bull.*, **37**, 2183 (1989).
2) A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi, T. Hino and T. Niwa, *Chem. Pharm. Bull.*, **38**, 733 (1990).
3) A. Sano, T. Kuriki, T. Handa, H. Takeuchi and Y. Kawashima, *J. Pharm. Sci.*, **76**, 471 (1987).
4) A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi, T. Hino and T. Niwa, *Chem. Pharm. Bull.*, **40**, 1573 (1992).
5) K. Kohno, M. Mizobe, K. Noda, Y. Takeuchi and M. Kakemi, *Yakuzaigaku*, **42**, 294 (1982); M. Mizobe, K. Kohno and Y. Takeuchi, *ibid.*, **42**, 306 (1982); I. Yamada, M. Kawata, T. Shibata, K. Ogawa and T. Yokobe, *Yakugaku Zasshi*, **109**, 932 (1989); S. Kimura, T. Imai, Y. Imamura, M. Ueno, T. Iijima and M. Otagiri, *ibid.*, **109**, 755 (1989).
6) T. Itoh and M. Koishi, *Shikizai*, **50**, 488 (1977).
7) G. Raghow and M. C. Meyer, *J. Pharm. Sci.*, **70**, 1166 (1981).
8) G. Levy, J. M. Antkowiak, J. A. Procknal and D. C. White, *J. Pharm. Sci.*, **52**, 1047 (1963); H. L. Smith, C. A. Baker and J. H. Wood, *J. Pharm. Pharmacol.*, **23**, 536 (1971); M. C. B. Van Oudtshoorn, F. J. Potgieter, C. J. De Blaey and J. Polderman, *ibid.*, **23**, 583 (1971); M. G. Dedhiya, C. W. Woodruff, F. A. Menard and C. T. Rhodes, *Drug Dev. Ind. Pharm.*, **14**, 53 (1988); S. Zubair, S. Esezobo and N. Pilpel, *J. Pharm. Pharmacol.*, **40**, 278 (1988).

9) E. Nelson, E. L. Knoechel, W. E. Hamlin and J. G. Wagner, *J. Pharm. Sci.*, **51**, 509 (1962).
10) D. L. Simmons, A. A. Legore, P. Picotte, K. S. Lee and N. N. Joshi, *J. Pharmacokinet. Biopharm.*, **3**, 39 (1975); H. Sekikawa, T. Naganuma, J. Fujiwara, M. Nakano and T. Arita, *Chem. Pharm. Bull.*, **27**, 31 (1979); H. El-Shattawy, A. Kassen, M. Abdel-Ali and A. Fawzi, *Sci. Pharm.*, **49**, 162 (1981).
11) E. Nelson, S. Long and J. G. Wagner, *J. Pharm. Sci.*, **53**, 1224 (1964).