Absorption of Ibuprofen Coated by Anhydrous Silicic Acid

Shinji AOKI*,[a] and Kazumi DANJO[b]

Research Laboratory, Taisho Pharmaceutical Co., Ltd.,[a] 1–403 Yoshino-cho, Ohmiya-shi, Saitama 330–8530, Japan and Faculty of Pharmacy, Meijo University,[b] 150 Yagotoyama, Tempaku-ku, Nagoya 468–8503, Japan.
Received July 7, 1998, accepted September 24, 1998

We studied the dissolution and absorption of ibuprofen (IB) from a three-layer tablet: the 1st layer (CIB layer) consisted of IB which was coated with anhydrous silicic acid (CIB), the 2nd layer was bromovalerylurea and anhydrous caffeine, and the 3rd layer was bromovalerylurea and ethenzamide. Differential scanning calorimetry and powder X-ray diffraction studies showed that the crystallinity of IB was not influenced by the preparation of CIB. The dissolution and absorption of IB from the CIB layer of the three-layer tablet were compared with those of a commercial tablet. In a test solution at pH 1.2, the dissolution rate of IB from the CIB layer was higher than that from the commercial tablet; moreover, the time for peak concentration (T_{max}) after administration of the CIB layer was significantly shorter. The T_{max} of the CIB layer tablet was about 52 min, while that of the commercial tablet was about 103 min. The rapid dissolution and absorption of IB in the CIB layer may be due to enhanced permeation, disintegration and disaggregation of CIB.

Key words ibuprofen; absorption; anhydrous silicic acid

Ibuprofen (IB), a propionic acid derivative with anti-inflammatory activity, is a valuable drug. We previously studied its compatibility,[1] controlled-release dosage form,[1] and evaluation of tablet sticking.[1] Here we examined the absorption rate of IB. A number of researchers have investigated the relationship between the drug's dissolution and absorption rates (*e.g.*, Simmons *et al.*,[2a] Herzfeldt and Kummel,[2b] Gillespie *et al.*,[2c] Stead *et al.*,[2d] and Fini *et al.*,[2e]). Albert and Gernaat[3] reported that administration of multiple doses of IB concomitantly with aspirin reduced IB plasma levels to less than half those observed with IB alone. The method of polyvinylpyrroridone solid dispersion was reported by Najib *et al.*,[4] and that of urea solid dispersion was reported by Mura *et al.*[5] Imai *et al.*,[6a] Kimura *et al.*,[6b] and Acarturk *et al.*[6c] reported that low-molecular gelatin was very a effective additive in increasing the absorption rate of IB, since it improved permeation. However, that method requires large amounts of low-molecular gelatin, reducing the IB content in capsules and/or tablets; therefore, large capsules and/or tablets are required. The reason appears to be that the particle size of low-molecular gelatin is larger than that of IB. We found that anhydrous silicic acid is a suitable substance for increasing the permeability of IB, since its particle size is markedly smaller than that of IB.

Materials and Methods

Materials IB (d_{50}; 14.3 μm) purchased from Boots Co., Ltd., anhydrous silicic acid (d_{50}; 12×10^{-3} μm, Aerozil Nippon Co., Ltd., Japan), crystalline cellulose (Asahi Chem. Co., Ltd., Japan), low-substituted hydroxypropilmethylcellulose (Shin-Etsu Chem. Co., Ltd., Japan), hydroxypropylmethylcellulose (Shin-Etsu Chem. Co. Ltd.,), talc (Asada Co., Ltd., Japan) and magnesium stearate (Taihei Chem. Co., Ltd., Japan) were used.

Preparation of coated IB with anhydrous silicic acid (CIB) IB (75.6% w/w), anhydrous silicic acid (6.3% w/w), low-substituted hydroxypropylmethylcellulose (10.5% w/w), crystalline cellulose (4.4% w/w) and hydroxypropylmethylcellulose (3.2% w/w) were mixed. Hydroxypropylmethylcellulose (5.7% w/w) was dissolved and anhydrous silicic acid (4.5% w/w) was suspended in 25% ethanol. The mixed powder was coated with the anhydrous silicic acid suspension, in a 1 : 0.85 proportion by weight, using a fluidized bed granulator.

Tablets Anhydrous silicic acid (18.4% w/w), low-substituted hydroxypropylmathylcellulose (61.3% w/w), talc (18.4% w/w) and magnesium stearate (1.8% w/w) were mixed. CIB and mixed powder were mixed in a 1 : 0.135 proportion by weight. We prepared two granules, one consisting of ethenzamide and bromovalerylurea, and the other of anhydrous caffeine and bromovalerylurea. A three-layer tableting machine (Kikusui Co., Ltd., Japan) was used to obtain the schematic diagram of the three-layer tablet shown in Fig.1.

Thermal Analysis DSC 7 (Perkin Elmer Co., Ltd.) was used for thermal analysis. Thermograms were obtained by heating at a constant rate of 5°C per minute.

Scanning Electron Microscopy A scanning electron microscope (S2500, Hitachi Co., Ltd.,) was used to observe the morphology of the surface of IB and granules.

Powder X-Ray Diffractometry Powder X-ray diffraction patterns were obtained on a Rigaku Denki Geiger RAD-C, using CuKα radiation, over a range of (2θ) 3—40° (speed 4°/min) at room temperature.

Permeability Studies A 0.05 ml drop of water was added to the tablets. The film of the commercial tablet was peeled off in this test, and the time required for the 0.05 ml drop of water to permeate the tablet was recorded.

Disintegration and Disaggregation Studies Disintegration tests were performed according to the JPXIII, using 1st fluid (pH 1.2).

Dissolution Studies Dissolution tests were performed according to the JP XIII, using 1st fluid (pH 1.2, 900 ml) and 2nd fluid (pH 6.8, 900 ml) maintained at 37 °C and a paddle at 100 rpm. The concentration of IB in the solution was determined by HPLC.

***In Vivo* Studies** 1) *In Vivo* Study 1 (Three-Layer Tablet): Six healthy volunteers aged 21—23 years and weighing 50.0—66.0 kg were used in the study with their informed consent. The three-layer tablets were given to the volunteers with 150 ml of water. Blood samples were taken before administration (10 ml), and 10, 20, 30, 40, 60, 120, 180, 240, 360 and 480 min afterward. Serum IB concentrations were measured with HPLC. To 0.5 ml of serum was added 0.25 ml of 1 M HCl, 50 μl of flurbiprofen as an internal standard, and extraction was done with isooctane–isopropyl alcohol (85 : 15 v/v), and the mixture was centrifuged for 5 min at 2000 rpm. The organic phase was evaporated, the residue was dissolved in 1 ml of methanol and 30 μl was injected into HPLC.

2) *In Vivo* Study 2 (Commercial Tablet): From fifteen healthy volunteers aged 21—36 years and weighing 53.0—61.5 kg, blood samples were taken

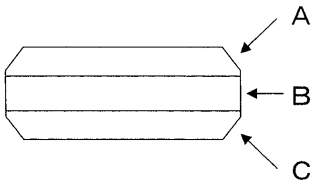

Fig. 1. Schematic Diagram of Three- Layer Tablet

A: CIB layer, B: anhydrous caffeine and bromovalerylurea-layer, C: ethenzamide and bromovalerylurea-layer.

* To whom correspondence should be addressed.

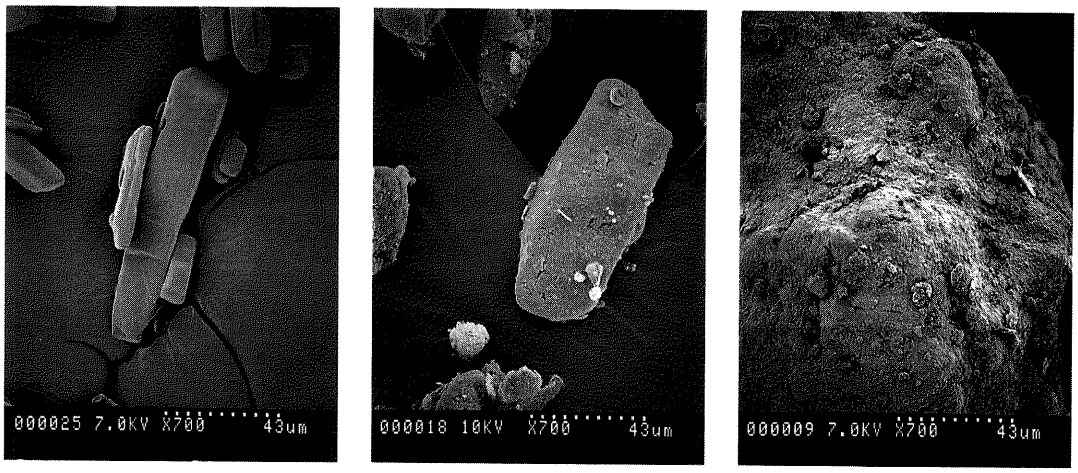

Fig. 2. Scanning Electron Micrographs
A: ibuprofen, B and C: CIB.

before administration and 15, 30, 60, 120, 240, 360 and 480 min afterward. The design of *in vivo* study 2 and measurement of IB concentration were the same as for *in vivo* study 1.

Results and Discussion

Scanning electron micrographs of IB are shown in Fig. 2A, and that of CIB in Figs. 2B and 2C . A large CIB particle (*e.g.* Fig. 2C) was an agglomerate of fine CIB particles (e.g. Fig. 2B). The surface of IB (Fig. 2A) was smooth, in contrast to the rough surface of CIB, suggesting that IB was completely coated with anhydrous silicic acid.

The crystallinity of IB in CIB was compared with that of IB and/or the mixture of coating materials, as determined by thermal analysis (Fig. 3) and powder X-ray diffraction (Fig. 4). The DSC thermograms of IB revealed a sharp endotherm (melting point) at 76 °C; the mixture of coating materials exhibited no peak, and CIB exhibited a sharp peak endotherm at about 76 °C. This result indicates that no interaction exists between the coating materials and IB. The diffraction pattern of CIB was the same as that of IB, and the diffraction pattern of the mixture of coating materials exhibited only a halo. The crystallinity of IB was about 59.17% and that of CIB was about 56.42%, which were determined by Ruland method. This result indicated that the crystallinity of IB in CIB was not affected by the method of preparation.

The process involved in getting IB into solution and its absorption from a solid dosage form can be briefly represented by the following schema: Solid dosage form disintegration granule or aggregate disaggregation fine particle dissolution drug in solution gastric or intestinal absorption bioavailability. Permeability is one of the important factors affecting dissolution rate, as well as disintegration and disaggregation. The results of permeability testing are shown in Table 1. IB shows poor wettability, so that its permeation time was more than 600 s. However, the permeation time of the CIB layer of the three-layer tablet was 7 s, although it would be thought that anhydrous silicic acid would make the surface of CIB hydrophilic. And the permeation time of the CIB layer of the three-layer tablet was shorter than that of the commercial tablet, although the film of the commercial tablet was peeled in this test. Thus, *in vivo*, the CIB layer of the three-layer tablet may result in significantly shorter permeation time

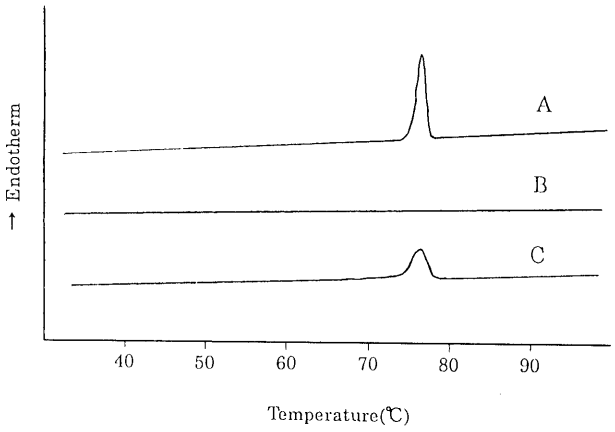

Fig. 3. DSC Thermograms
A: IB, B: mixture of coating materials, C: CIB.

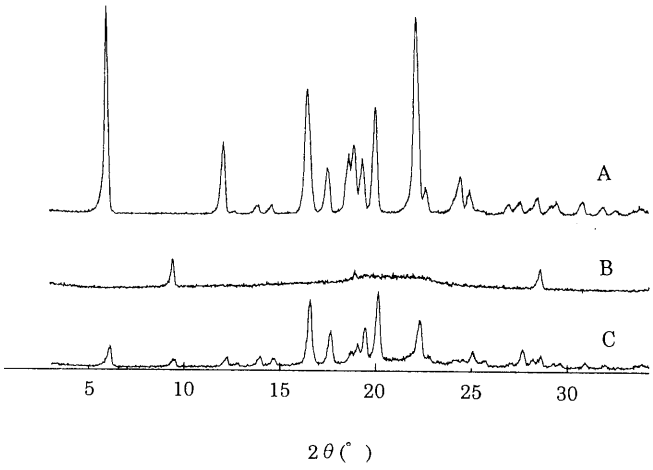

Fig. 4. Powder X-Ray Diffraction
A: IB, B: mixture of coating materials, C: CIB.

than that of the commercial tablet.

Table 2 shows the disintegration and disaggregation times of the CIB layer of the three-layer tablet compared with those of the commercial tablet. These times were difficult to distinguish, therefore, the disaggregation time was determined by

Table 1. Permeation Time

	Permeation time (s)
IB[a)]	>600
CIB layer	7
Commercial tablet	18

a) IB alone.

Table 2. Tablet Disintegration Time and Disaggregation Time

	Disintegration time (s)	Disaggregation time (s)
CIB layer	40 (35—42)	55 (53—56)
Commercial tablet	120 (110—150)	280 (270—290)

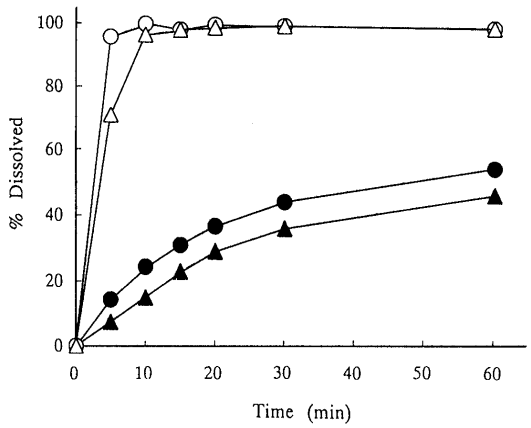

Fig. 5. Dissolution Profiles of IB

●: The CIB layer of the three-layer tablet at pH 1.2.
▲: Commercial tablet at pH 1.2.
○: The CIB layer of the three-layer tablet at pH 6.8.
△: Commercial tablet at pH 6.8.

subtracting the disintegration time using the auxiliary tube (wire openings: 0.42 mm) from the disintegration time using JP XIII.

The disintegration time of the CIB layer of the three-layer tablet was 40 s, while that of the commercial tablet was 120 s. Both these disintegration times may have been shorter than the other normal commercial tablets. The disaggregation time of the CIB layer of the three-layer tablet (55 s) was markedly shorter than that of the commercial tablet (280 s).

Figure 5 illustrates the profiles of dissolution of IB from the CIB layer of the three-layer and the commercial tablets. The rate of dissolution of IB from the CIB layer was higher than that from the commercial tablet at pH 1.2, but the dissolution profiles of IB for these two tablets were almost the same at pH 6.8.

Figure 6 shows the mean serum concentrations of IB against time after oral administration to humans. The bioavailability parameters were calculated from serum concentration–time curves up to 8 h, and the results are summarized in Table 3. The time for peak concentration (T_{max}) of IB from the CIB layer of the three-layer tablet was less than that for the commercial tablet. The tablets contained ethenzamide, anhydrous caffeine and bromovarerylurea; there is no report that these drugs affect the rate of absorption of IB. Furthermore, these drugs did not affect the crystallinity of IB in CIB, because they were not contained in the CIB layer

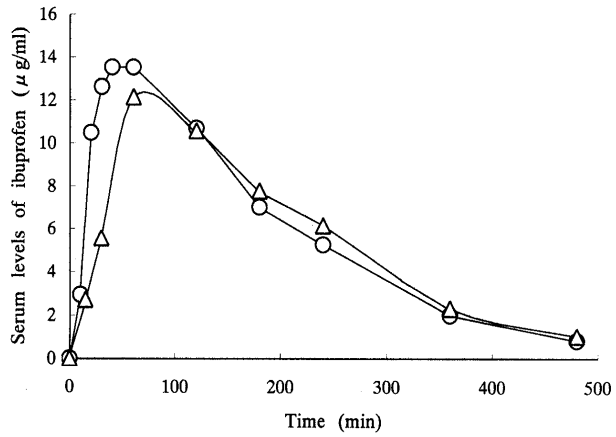

Fig. 6. Serum Concentrations of IB

○: The CIB layer of the three-layer tablet, △: commercial tablet.

Table 3. Pharmacokinetic Parameters of IB

	Dose (mg)	T_{max} (m)	C_{max} (μg/ml)	$AUC^{0—8}$ (h·μg/ml)
CIB layer	144	52.00	14.96	2843.7
Commercial tablet	150	103.32	13.72	2920.7

Table 4. T_{max} Comparison

Sample	T_{max} (h)
Capsule A[a)]	2.17
Tablet B[a)]	1.32
Capsule C[a)]	2
Capsule D[a)]	1.25
Tablet E[a)]	1.39
Solution F[a)]	0.46—0.53
Tablet G[b)]	1.38
Tablet H[b)]	1.70
Tablet I[b)]	2.48
Tablet J[b)]	1.88
Tablet K[b)]	2.07
Tablet L[c)]	1.9
Tablet M[d)]	2.04
Tablet N[d)]	1.36
Effervescent tablet[d)]	2.11
Commercial tablet	1.72
The CIB layer of the three-layer tablet	0.87

a) Ref. 2*c*); *b*) Ref. 2*d*); *c*) Ref. 3; *d*) Ref. 7.

(Fig. 1).

Many studies have been performed in attempts to improve the bioavailability of IB. Table 4 shows values of T_{max} as an index of the absorption rate of IB in recent studies. T_{max} of the solid dosage form was about 1.3—2.4 h, while T_{max} of the solution dosage form was 0.5 h, and the T_{max} of the CIB layer of the three-layer tablet was 0.87 h. These findings suggested that the rate of absorption of IB from the CIB layer of the three-layer tablet was the fastest of all solid dosage forms. It is known that IB dissolves only minimally in stomach but readily dissolves in the small intestine, and that dissolved IB is rapidly absorbed in there. It appears that the absorption rate of IB from the solid dosage form was increased because the rate of movement of IB into the small intestine was increased. Tables 1 and 2 suggest that the CIB layer of the three-layer tablet disintegrated and disaggregated in stomach,

and rapidly moved into the small intestine. Thus, the rate of absorption of IB from the CIB layer of the three-layer tablet is rapid.

In addition, Imai *et al.*[6a] reported that the solid IB formulation using low-molecular gelatin improved the rate of absorption (T_{max} was about 0.7 h) of IB. Their report is not included in Table 4. It was difficult to compare the absorption rate of the CIB layer of the three-layer tablet with that of the solid IB formulation using low-molecular gelatin, because their in vivo absorption studies used not humans, but beagle dogs. The solid IB formulation using low-molecular gelatin did not affect the crystallinity of IB but did improve wettability; these findings were the same as for CIB. It might be assumed that the absorption rate of the solid IB formulation using low-molecular gelatin and the CIB layer of the three-layer tablet were nearly the same. However, CIB has the advantages of high IB content and productivity. The IB content of the solid IB formulation using low-molecular gelatin was lower, at 50% w/w, than that of CIB, 69.1% w/w. These findings suggest that anhydrous silicic acid is significantly more effective than low-molecular gelatin. In addition, CIB could be prepared by the general wet granulated method using a fluidized bed.

References

1) Aoki S., Okamoto A., Mizutani T., Danjo K., Sunada H., Otuka A., *Drug Dev. Ind. Pharm.*, **23**, 561—565 (1997); Aoki S., Ito Y., Danjo K., Sunada H., *Yakugaku Zasshi*, **118**, 72—77 (1998); *idem*, *ibid.*, **118**, 287—293 (1998); Aoki S., Danjo K., *ibid.*, **118**, 511—518 (1998).
2) *a*) Simmons D. L., Legore A. A.,. Picotte P, Cesari F., *Can. J. Pharm. Sci.*, **15**, 26—29 (1980); *b*) Herzfeldt C. D., Kummel R., *Drug Dev. Ind. Pharm.*, **9**, 767—793 (1983); *c*) Gillespie W. R., Disanto A. R., Monovich R.E., Albert K. S., *J. Pharm. Sci.*, **71**, 1034—1038 (1982); *d*) Stead J. A., Freeman M., Jhone E. G., Ward G. T., Whiting B., *Int. J. Pharm.*, **14**, 59—72 (1983); *e*) Fini A., Zecchi V., Tartarini A., *Pharm. Acta Helv.*, **59**, 106—108 (1984).
3) Albert K. S., Gernaat C. M., *The American Journal of Medicine*, **13**, 40 (1984).
4) Najib N. M., Suleiman M., Malakh A., *Int. J. Pharm.*, **32**, 229—236 (1986); El-Hinnawi M. A., Najib N. M., *ibid.*, **37**, 175—177 (1987); NajibN. M., El-Hinnawi M. A., Suleiman M. S., *ibid.*, **45**, 139—144 (1988).
5) Mura P., Liguori A., Bramanti G., *Il Farmaco*, **41**, 377—387 (1986).
6) *a*) Imai T., Kimura S., Iijima T., Miyoshi T., M Otagiri., *J. Pharm. Pharmacol.*, **42**, 615—619 (1990); *b*) Kimura S., Imai T., Otagiri M., *Chem. Pharm. Bull.*, **39**, 1328—1329 (1991); *c*) F. Acarturk, S. Takka, I. Agabeyoglu, Y. Yalim, R. Simsek, *Parmazie*, **48**, 761—763 (1993).
7) Saano V., Paronen P., Peura P., Vidgren M., *Drug Dev. Ind. Pharm.*, **18**, 491—497 (1992).