Design of Nateglinide Controlled Release Tablet Containing Erosion Matrix Tablet and Multiple Administration Study in Normal Beagle Dogs

Chisato Makino,* Hidetoshi Sakai, Akira Okano, and Akira Yabuki


Received August 18, 2008; accepted June 20, 2009; published online June 22, 2009

We designed a single unit type tablet formulation containing nateglinide to decrease both postprandial blood glucose level (PBG) and fasting blood glucose level (FBG) in normal beagle dogs. The tablet was a dry coated tablet comprising both a core tablet (an erosion matrix tablet: a controlled release portion (nateglinide: 90 mg)) and an outer shell (an immediate release portion (nateglinide: 60 mg)). The weight, the diameter and the hardness of the obtained tablet were 416.1 mg, 10 mm, and about 60 N, respectively. The dissolution study of the obtained tablet in pH 1.2 or 6.8 showed that the nateglinide in the immediate release portion dissolved in almost 30 min., and that 30 min after the dissolution test started, the nateglinide in the controlled release portion had dissolved slowly. An in vivo single oral administration study using normal beagle dogs showed the bioavailability value of the obtained nateglinide dry coated tablets against nateglinide immediate release tablets was 73.6%, although the bioavailability of nateglinide controlled release tablets containing enteric coated granules was 57.2—60.8%. An in vivo multiple oral administration study (b.i.d. (interval: 12 h), 8 d) using normal beagle dogs showed the reproducibility of nateglinide absorption. In addition, decreases in both PBG and FBG were observed. The ability to decrease the blood glucose level did not weaken during a multiple administration. On the basis of the above results, a controlled release formulation containing a short-acting type oral blood glucose regulator, not only nateglinide but meglitinides (repaglinide, mitiglinide, etc.) was suggested to enable control of both PBG and FBG for moderate and severe diabetes patients.

Key words nateglinide; erosion matrix tablet; dry coated tablet

There are two types of ordinary antidiabetics for oral administration. The first type controls primarily postprandial blood glucose level (PBG), while the other type controls primarily fasting blood glucose level (FBG).1,2) It is important to control FBG in patients with moderate and severe diabetes who exhibit elevated FBG levels. Although there is currently no oral antidiabetic capable of controlling both PBG and FBG, such an antidiabetic would be most useful for the treatment of diabetes.

The ω-phenylalanine derivative, nateglinide ((−)-N-(cis-4-isopropylcyclo-hexanecarbonyl)-ω-phenylalanine) was developed by Ajinomoto Co., Inc. for use as an antidiabetic (Fig. 1). Nateglinide demonstrates a short-acting effect,1—3) and its effect is believed to effectively control PBG. Nateglinide immediate release tablets are currently available commercially in the form of Fastic® tablets, and are used primarily for patients with mild diabetes.4)

In our previous studies, it was confirmed that both PBG and FBG can be decreased through controlled release of nateglinide using normal beagle dogs.5) and that both PBG and FBG can be decreased with a controlled release tablet containing tabletable enteric coated granules in a single oral administration or a twice (an interval: 8 h) repeated oral administration study using normal beagle dogs (unpublished data).

However, there were problems regarding the above-mentioned nateglinide controlled release tablet. First, the oral bioavailability of the nateglinide controlled release tablet containing tabletable enteric coated granules was low; area under curve (AUC) values of the tablet against nateglinide immediate release tablet were 57.2—60.8% (unpublished data). It was considered necessary to improve the oral bioavailability of nateglinide.

The average diameter of the used immediate release granules was about 250 μm and that of the used enteric coated granules was about 1 mm. In order to manufacture this nateglinide controlled release tablet, tableting is conducted after mixing immediate release granules and enteric coated granules. As each average diameter is different, it is difficult to secure a content uniformity of nateglinide. Generally, in the case of a tablet containing more than 2 types of granules with different average diameters, it is difficult to secure a content uniformity of the drug substance. It is necessary to design and manufacture an excellent drug product.

In the case of a multiple oral administration of a nateglinide controlled release tablet, the blood glucose lowering action may be weakened, because nateglinide is an insulin secretion stimulator.1,5) A multiple oral administration study using a nateglinide controlled release tablet must be conducted in order to confirm whether this tablet is able to control both PBG and FBG.

In this regard, we considered an erosion matrix tablet as the controlled release portion, and a dry coated tablet as the nateglinide controlled release tablet comprising both immediate release granules and an erosion matrix tablet. This was because a dry coated tablet is easier to manufacture than a tablet containing enteric coated granules from the view point of a drug content uniformity.
The thus-obtained granular product was mixed with magnesium stearate, and the mixture was tabletted to obtain erosion matrix tablets using a tablet press.

Preparation of Nateglinide Immediate Release Granules (an Immediate Release Portion) Three-hundred-and-seventy-five grams of nateglinide, 637.5 g of lactose monohydrate and 450.0 g of hydroxypropylcellulose having a low degree of substitution were mixed with a high shear mixer (FS-10JD, Fukae Powtec, Japan), a rotating cutter type mill (New speed mill, Okadaseiko, Japan), a tabletting machine (HT-AP, Hata Machinery, Japan), and a pan type coating machine (Freund Industry Co., Japan). The hardness of the obtained tablets was evaluated with a tablet tester (TS-50N, Okada Seiko, Japan).

Preparation of Nateglinide Erosion Matrix Tablets and HPMC2910 Coated Erosion Matrix Tablets (a Controlled Release Portion) The compositions are shown in Table 1. In the case of Erosion Matrix Tablet A, nateglinide and hydroxypropylmethylcellulose were charged in a high shear mixer (MINI), and mixed. In the case of Erosion Matrix Tablets B and C, nateglinide, hydroxypropylmethylcellulose and microcrystalline cellulose were charged in a high shear mixer (MINI), and mixed. Then, water was added, and granulation was conducted for 1.5 min.

Preparation of Nateglinide Controlled Release Tablet; a Dry Coated Tablet Containing Erosion Matrix Tablet A and the immediate release granules (Fig. 2, Table 2, tablet diameter: 10 mm).

Dissolution Profiles of Nateglinide Preparations The dissolution profiles of nateglinide preparations were evaluated (JP15, paddle method, 50 rpm, test fluid: 900 mL, nateglinide: 90 or 150 mg/vessel) with a dissolution tester (NTR-VS6P, Toyama Sangyo Co., Ltd., Japan). Each test fluid was JP1 fluid (JP15, Dissolution Test Fluid No. 1) containing 0.6 w/v% of nateglinide (90 mg/vessel), 1.2 w/v% of nateglinide (150 mg/vessel) polysorbate 80 for pH 1.2, and Clark–Lubs buffer for pH 6.8 (JP2 fluid: JP15, Dissolution Test Fluid No. 2).

Dissolution rates were determined with a reversed phase HPLC system consisting of an L-6000 constant flow pump and an L-4000 UV detector operating at 210 nm (Hitachi Corp., Japan). Separations were performed with a reversed phase C-18 column (4.5×150 mm, GL Science, Japan). The mobile phase consisted of an acetonitrile–pH 2.5 phosphate buffer (55:45, v/v) at a flow rate of 1.5 mL/min.

Oral Administration Study; Plasma Nateglinide Concentration and Blood Glucose Level In the case of a single administration study with an erosion matrix tablet (nateglinide: 90 mg) or a dry coated tablet (immediate release portion: 60 mg of nateglinide, controlled release portion: 90 mg of nateglinide), one tablet was administered to normal male beagle dogs (body weight: ca. 10 kg) just before feeding. One-hundred-and-fifty grams of dry DS meal suspended in 600 g of hot water was forcibly administered to the beagle dogs with a syringe. Feeding was conducted within 12 min. Blood samples were taken before and at 15, 30, 45, 60, 120, 240, 360, 540, 720 and 1440 min (n=3).

Table 1. Composition of Erosion Matrix Tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>A [w/w%]</th>
<th>B [w/w%]</th>
<th>C [w/w%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core tablet Nateglinide</td>
<td>65.3</td>
<td>59.1</td>
<td>51.1</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose 2910</td>
<td>32.7</td>
<td>—</td>
<td>12.8</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose 2208</td>
<td>—</td>
<td>14.8</td>
<td>—</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>—</td>
<td>24.6</td>
<td>21.3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.0</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Coating film</td>
<td>—</td>
<td>—</td>
<td>10.9</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose 2910</td>
<td>—</td>
<td>—</td>
<td>10.9</td>
</tr>
<tr>
<td>Macrogol 6000</td>
<td>—</td>
<td>—</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2. Composition of the Dry Coated Tablet Containing Erosion Matrix Tablet C [mg]

<table>
<thead>
<tr>
<th>Weight [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core tablet Erosion Matrix Tablet C</td>
</tr>
<tr>
<td>Outer shell Immediate release granules</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
Three types of nateglinide erosion matrix tablets as Table

<table>
<thead>
<tr>
<th>Tablet</th>
<th>09:00</th>
<th>12:00</th>
<th>15:00</th>
<th>18:00</th>
<th>21:00</th>
<th>00:00</th>
<th>03:00</th>
<th>06:00</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 1st day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 2nd day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 3rd day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 4th day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 5th day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 6th day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 7th day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
<tr>
<td>The 8th day</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
<td>1 tablet/feeding</td>
</tr>
</tbody>
</table>

Day Night

An 8-d multiple administration study with dry coated tablets was conducted according to Table 3. Blood samples were taken at 09:00, 09:15, 09:30, 09:45, 10:00, 11:00, 13:00, 15:00, 18:00, 21:00, 21:15, 21:30, 21:45, 22:00 and 23:00 on the 1st day, 01:00, 05:00, 06:00 and 09:00 on the 2nd day, 09:00 on the 3rd, 4th, 5th, 6th and 7th day, 09:00, 09:15, 09:30, 09:45, 10:00, 11:00, 13:00, 15:00, 18:00, 21:00, 21:15, 21:30, 21:45, 22:00 and 23:00 on the 8th day, 01:00, 05:00, 06:00 and 09:00 on the 9th day after the 1st oral administration (n=3). Plasma nateglinide concentration was evaluated for samples of the 1st, 2nd, 8th and 9th day. Blood glucose level was evaluated for all blood samples. The feeding method was the same as in a single administration.

Blood was sampled from a leg vein. Whole blood was centrifuged at 1700 g for 15 min. at 5 °C and plasma was collected for analysis. A 50 μl portion of internal standard solution was spiked into 0.5 ml plasma in an Eppendorf tube, followed by the addition of 0.5 ml of 0.05 M pH 6.0 phosphate buffer. The mixture was vortex-mixed for 10 s and applied to a Sep-Pak Vac tC18 cartridge that was pre-equilibrated with 5 ml of 0.05M pH 6.0 phosphate buffer. The cartridge was washed with 2 ml of water and finally eluted with 2 ml of ethanol. The elute was evaporated to dryness in vacuo at 30 °C. The residue was dissolved in 0.2 ml of mobile phase and 20 μl of this solution was used for the HPLC sample.

Plasma nateglinide concentration was determined with a two-column switching HPLC system consisting of a 600E multi solvent pump system, 515 HPLC pump (Waters, Japan), 2487 UV detector (Waters, Japan) operating at 210 nm, and SPV-N-A column switching apparatus (GL Science, Japan). Separations were performed with an Inertsil ODS-3 reversed phase C-18 column (4.0×20 mm, GL Science, Japan) and L-column ODS (4.6×250 mm, Kagakubushitsukan Kenkyukikou, Japan).

Three types of mobile phases were used consisting of acetonitrile: pH 6.6 0.05 mol/l phosphate buffer (3:7, v/v) (Mobile Phase A), acetonitrile: pH 6.6 0.05 mol/l phosphate buffer (45:55, v/v) (Mobile Phase B), and acetonitrile: pH 6.6 0.05 mol/l phosphate buffer (6:4, v/v) (Mobile Phase C). The timetable of the column switching pattern is shown in Table 4. At a flow rate of 1.0 ml/min., nateglinide eluted in about 7.5 min at 40 °C.

Blood glucose level was determined with the Fuji DRICHEM 3500S (FUJIFILM Co., Japan).

Results and Discussion

Dissolution Profiles of Nateglinide Erosion Matrix Tablet Three types of nateglinide erosion matrix tablets as controlled release portions were prepared according to Table 1 (Erosion Matrix Tablet A, B, C). The amount of nateglinide in one erosion matrix tablet was determined to be 90 mg according to the results of our previous study.5) Tablet hardness values of the Erosion Matrix Tablet A and B were about 50 N. The value of the Erosion Matrix Tablet C was about 300 N, due to coating with HPMC2910.

Dissolution profiles of the obtained erosion matrix tablets were evaluated in JP1 fluid containing 0.6 w/v% Polysorbate 80 or JP2 fluid. Nateglinide is a poorly water-soluble drug. Polysorbate 80 was added to acid pH testing fluid to satisfy the sink condition.5) The results are shown in Figs. 3 and 4.

The dissolution rate at pH 1.2 decreased in the order of nateglinide Erosion Matrix Tablet A, B and finally C. The dissolution rate at pH 6.8 also decreased in the order of nateglinide Erosion Matrix Tablet A, B and finally C. In the case of Tablet C, the lag time of dissolution was observed. It was assumed to be due to the HPMC2910 coating.

The dissolution rate of nateglinide immediate release tablets (Fastix® tablets) under the same conditions is nearly 100% within 30 min.5)
for Erosion Matrix Tablet A, 7.70±1.32 μg/ml ($T_{\text{max}}$: 2.0 h) for Erosion Matrix Tablet B, 5.69±1.58 μg/ml ($T_{\text{max}}$: 4.0 h) for Erosion Matrix Tablet C, and 23.44±1.61 μg/ml ($T_{\text{max}}$: 0.75 h) for immediate release tablets (90 mg of nateglinide). The $C_{\text{max}}$ values and AUC values of the erosion matrix tablets were lower than those of an immediate release tablet. However, an increasing trend was observed in plasma nateglinide concentrations of Erosion Matrix Tablet C starting at 4 h after administration as compared with that of the immediate release tablet.

Blood glucose level profiles are shown in Fig. 6. Blood glucose level decreased to a maximum of about 74% (2 h) for Erosion Matrix Tablet A, about 80% (2 h) for Erosion Matrix Tablet B, and about 75% (4 h) for Erosion Matrix Tablet C as compared with blood glucose levels immediately before administration. In the case of immediate release tablets (90 mg of nateglinide), FBG at 8 h after administration did not decrease, although PBG decreased to a maximum of about 79% as compared with blood glucose levels immediately before administration.5) PBG is defined as a blood glucose level from 0 to 3 h after feeding in this study. There appears to be a correlation between plasma nateglinide concentration and blood glucose level. Erosion Matrix Tablet C was thought to be the most suitable to decrease FBG according to the blood glucose level profile.

Preparation of Nateglinide Dry Coated Tablet Containing Erosion Matrix Tablet and Dissolution Profiles After deciding to focus on Erosion Matrix Tablet C (HPMC2910 coated erosion matrix tablet), which effectively lowered FBG with hardly any decrease in PBG, a nateglinide controlled release tablet was designed with both Erosion Matrix Tablet C (90 mg of nateglinide) and immediate release granules (60 mg of nateglinide), resulting in a dry coated tablet. The amount of nateglinide in the immediate release portion and in the controlled release portion was determined according to the results of our previous study.5) The diameter of the obtained dry coated tablet was 10 mm, and the hardness values of the tablets were about 60 N originating in the outer shell of the tablet.

Dissolution profiles of the obtained dry coated tablets were evaluated in JP1 fluid containing 1.2 w/v% Polysorbate 80 or JP2 fluid. The results are shown in Fig. 7. About 35% of the total dose was dissolved in 30 min at both pH 1.2 and 6.8. This indicated that most of the nateglinide contained in the immediate release portion was dissolved in 30 min. The dissolution rate of nateglinide immediate release tablets (Fastic® tablets) under the same conditions is nearly 100% within 30 min. Thirty minutes after the test started, nateglinide was dissolved slowly at both pH 1.2 and 6.8. These behaviors were the same as those of Erosion Matrix Tablet C.

Plasma Nateglinide Concentration after in Vivo Single
Oral Administration of Nateglinide Dry Coated Tablet

Plasma nateglinide concentration profiles are shown in Fig. 8. Results are also shown for nateglinide immediate release tablets only (nateglinide: 60 mg, 150 mg) used as controls. The nateglinide C_{max} values were 13.10±3.05 μg/ml (T_{max}: 0.75 h) for nateglinide Dry Coated Tablets, 15.63±1.08 μg/ml (T_{max}: 0.75 h) for the immediate release tablets (nateglinide: 60 mg), and 34.80±5.15 μg/ml (T_{max}: 0.5 h) for the immediate release tablets (nateglinide: 150 mg). There were no significant differences of the C_{max} values observed between the immediate release tablets (nateglinide: 60 mg) and the nateglinide dry coated tablets (Student’s t-test). This is because the C_{max} values are based on the immediate release portion. This result confirms the above dissolution results. On the other hand, plasma nateglinide concentrations from 4 to 12 h after administration demonstrated an increasing trend due to the nateglinide erosion matrix tablet, and there was a significant difference of plasma nateglinide concentrations at 6 h after administration between the immediate release tablets (nateglinide: 60 mg) and nateglinide dry coated tablets(Student’s t-test, p<0.05). It was considered possible to decrease both PBG and FBG with this nateglinide dry coated tablet according to the plasma nateglinide concentration profiles.

The bioavailability value of the dry coated tablets against nateglinide immediate release tablets was 73.6%, although the value was 57.2—60.8% in the case of the nateglinide controlled release tablet containing enteric coated granules (unpublished data). This means that the bioavailability value of the controlled release portion was improved by using an erosion matrix tablet. It is not obvious why the bioavailability value of administration of the tablet containing the erosion matrix tablet was higher than that of administration of the tablet containing enteric coated granules. Further study is necessary.

It is assumed that not only the dry coated tablets (immediate release portion: 60 mg of nateglinide, controlled release portion: 90 mg of nateglinide), but also the immediate release tablets (nateglinide: 150 mg) might decrease both PBG and FBG according to nateglinide plasma concentration profile. However, nateglinide dry coated tablets are believed to be more useful than the immediate release tablets (nateglinide: 150 mg), because the ability to control both PBG and FBG without side effect, is easier.

Plasma Nateglinide Concentration and Blood Glucose Level during in Vivo Multiple Oral Administration (b.i.d. (Interval: 12 h), 8 d) of Nateglinide Dry Coated Tablet

Plasma nateglinide concentration profiles are shown in Fig. 9. The nateglinide C_{max} values were 12.65±0.92 μg/ml (T_{max}: 2 h (11:00, the 1st day)), 19.54±1.25 μg/ml (T_{max}: 13 h (22:00, the 1st day)), 16.12±2.84 μg/ml (T_{max}: 2 h (11:00, the 8th day)), and 16.63±1.72 μg/ml (T_{max}: 12.75 h (21:45, the 8th day)). There were no significant difference of the C_{max} values observed among 13 h (22:00, the 1st day) and 2 h (11:00, the 8th day) and 12.75 h (21:45, the 8th day) (Student’s t-test). However, there were significant differences of the C_{max} values observed between 2 h (11:00, the 1st day) and 13 h (22:00, the 1st day) (Student’s t-test, p<0.05). C_{max} values at 13 h (22:00, the 1st day) and 2 h (11:00, the 8th day) and 12.75 h (21:45, the 8th day) demonstrated an increasing trend against that at 2 h (11:00, the 1st day). This is because plasma nateglinide concentration just before administration was not zero (about 4 μg/ml, Fig. 8) except at the first administration. It was found that nateglinide absorption during a multiple administration was reproducible.

Blood glucose level profiles are shown in Fig. 10. Blood glucose level decreased to about 76.3% (1 h, 10:00, the 1st day), 71.2% (6 h, 15:00, the 1st day), 75.1% (12.25 h, 21:15, the 1st day), 83.3% (14 h, 23:00, the 1st day), 81.4% (1 h, 10:00, the 8th day), 78% (6 h, 15:00, the 8th day), 80.8%
stimulator. It is expected that a commercially available formulation will be evaluated in clinical trials.

**Conclusion**

A single unit type tablet formulation containing nateglinide was designed to decrease both PBG and FBG in normal beagle dogs, using an erosion matrix tablet as a controlled release portion. The tablet was a dry coated tablet comprising both a core tablet (an erosion matrix tablet: a controlled release portion) and an outer shell (an immediate release portion), and contained 60 mg of nateglinide in the immediate release portion and 90 mg of nateglinide in the controlled release portion. The weight, the diameter and the hardness of the obtained tablet were 416.1 mg, 10 mmφ and about 60 N, respectively.

In a dissolution study of the obtained tablet in pH 1.2 or 6.8, nateglinide in the immediate release portion was almost dissolved in 30 min. Thirty minutes after the test starts, nateglinide in the controlled release portion was dissolved slowly.

An in vivo single oral administration study with the nateglinide dry coated tablet containing HPMC2910 coated erosion matrix tablet using normal beagle dogs showed that it was possible to improve bioavailability, as compared with nateglinide controlled release tablet containing enteric coated granules. The bioavailability value of the dry coated tablet against nateglinide immediate release tablet was 73.6%, although the value of the nateglinide controlled release tablet containing enteric coated granules was 57.2—60.8%.

An in vivo multiple oral administration study (b.i.d. (interval: 12 h), 8 d) with the nateglinide dry coated tablets using normal beagle dogs showed reproducibility of nateglinide absorption during this study. It was found that decreases in both PBG and FBG were observed. It was considered that the ability to decrease blood glucose level did not weaken during a multiple oral administration using the nateglinide controlled release formulation.

These results suggest that a controlled release formulation containing a short-acting type oral blood glucose regulator, not only nateglinide but meglitinides (repaglinide, mitiglinide, etc.) enables control of both PBG and FBG for moderate and severe diabetes patients. It is expected that a formulation will be available commercially, and further evaluation of the effect on blood glucose level of moderate and severe diabetes patients using nateglinide controlled release formulation in
clinical trials will be completed.

Acknowledgement  In vivo studies using normal male beagle dogs were in collaboration with Mr. T. Sawada and coworkers at INA Research (Japan). The authors gratefully thank Mr. A. Gonsho, Ajinomoto Pharmaceutical Research Laboratory for his suggestions and discussion concerning in vivo pharmacokinetic study.

References