Nateglinide Controlled Release Tablet Containing Compressionable Enteric Coated Granules

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We designed a single unit type controlled release tablet containing nateglinide to decrease both postprandial blood glucose level (PBG) and fasting blood glucose level (FBG) in normal beagle dogs. The tablet contains 60 mg of nateglinide in an immediate release portion, and 90 mg of nateglinide in a controlled release portion. Compressionable enteric coated granules were selected as the controlled release portion to primarily decrease FBG, and they were prepared by an aqueous coating with Eudragit®. Three types of nateglinide controlled release tablets were obtained, and their weights were 418.1—425.1 mg/tablet containing the above compressionable enteric coated granules. Even after tableting, the dissolution behavior of enteric coated granules was maintained approximately. *In vivo* single oral administration studies using normal male beagle dogs demonstrated that these tablets were able to decrease both PBG and FBG. The relative bioavailability values of the obtained tablets containing enteric coated granules having a dissolution pH of 6.0 and 6.8 were estimated at about 57.2 and 60.8% respectively against nateglinide immediate release tablets. In an *in vivo* repeated administration study with the tablets containing enteric coated granules having a dissolution pH of 6.8 (an interval: 8 h), decreases in both PBG and FBG were observed continuously twice. On the basis of the above results, it is expected to enable control of both PBG and FBG for moderate and severe diabetes patients with a controlled release formulation containing a short-acting type oral blood glucose regulator, not only nateglinide but also meglitinides (repaglinide, mitiglinide, *etc.*).

Key words nateglinide; compressionable enteric coated granule; repeated administration

Ordinary antidiabetics for oral administration are classified into two types. 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. However, currently there is no oral antidiabetic capable of sufficiently controlling both PBG and FBG, and such an antidiabetic is believed to be the most useful in the treatment of diabetes. The D-phenylalanine derivative, nateglinide ((−)-*N*-(*trans*-4-isopropylcyclohexanecarbonyl)-D-phenylalanine, Fig. 1) is a new short-acting type oral blood glucose regulator, and stimulates insulin secretion.[1,2] Nateglinide immediate release tablets under the trade name of Fastic® tablets are used for patients with mild diabetes, and are used primarily to control PBG.[3] In our previous study, we confirmed that both PBG and FBG are decreased with both immediate release tablets and enteric coated granules containing nateglinide in normal beagle dogs.[4] In this study, we designed a single unit type nateglinide controlled release tablet using compressionable enteric coated granules. Then we evaluated whether PBG and FBG were able to be decreased with the nateglinide controlled release tablet in both a single and a repeated oral administration studies.

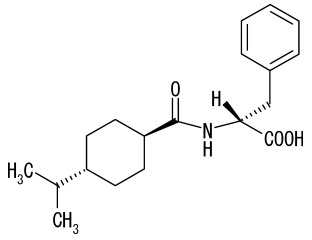

Fig. 1. Chemical Structure of Nateglinide

Experimental

Materials Nateglinide (Ajinomoto Co., Inc., Japan), lactose mono-hydrate (DMV, Japan), hydroxypropylcellulose (Nihon Soda, Japan), low-substituted hydroxypropyl cellulose (Shin-etsu Chemical Co., Ltd., Japan), magnesium stearate (Mg-St, Taiheikagakusangyo, Japan), methacrylic acid copolymer LD (Eudragit® L30D-55, Röhm GmbH, Germany), poly(methyl acrylate-*co*-methyl methacrylate-*co*-methacrylic acid) (Eudragit® FS30D, Röhm GmbH, Germany), ethylacrylate methylmethacrylate copolymer dispersion (Eudragit® NE30D, Röhm GmbH, Germany), croscarmellose sodium (Ac-Di-Sol®, Asahikasei Co., Ltd., Japan), triethyl citrate (CBC, Japan), polysorbate 80 (Wako Pure Chemical Co., Ltd., Japan), glycelyl monostearate (Higuchi Shoukai, Co., Ltd., Japan), sodium hydroxide (JIS K8576, reagent grade, Junseikagaku, Japan), citric acid (JIS K8283, reagent grade, Junseikagaku, Japan) were used in the study.

Equipment A high shear mixer (FS-10JD, Fukae Powtec, Japan), an extrusion granulator (DG-L1, Fuji Paudal, Japan), a cutter mill(New Speed Mill (ND-10), Okadaseiko, Japan), a spherized granulator (Q-230, Fuji Paudal, Japan), a fluidized bed granulator/dryer (FLO-1, Freund Industry Co., Japan), a V-blender (VFS, Tsutsuirikakagaku, Japan), a tableting machine (HT-AP15SSII, Hata Machinery, Japan), and a microfluidizer (Nanomizer Inc., Japan) were used.

Preparation of Nateglinide Immediate Release Granules (Immediate Release Granules) Three-hundred-seventy-five grams of nateglinide, 637.5 g of lactose monohydrate and 450.0 g of low-substituted hydroxypropyl cellulose were mixed in a high shear mixer for 10 min. Subsequently, 1035 g of a binding solution of 15 g of hydroxypropyl cellulose in water was added, and granulation was conducted for 2.5 min (agitator: 400 rpm, chopper: 3600 rpm). The total amount of the resulting product was uniformly granulated with a cutter mill (2000 rpm, screen: 1×10 mm), and dried with a fluidized bed drier (FLO-1) (inlet air temperature: 80 °C). The obtained granules were screened through a sieve of 850 μm. The granular product remaining on the sieve of 850 μm was forcibly passed through the sieve, and both products were mixed to form immediate release granules.

Preparation of Compressionable Enteric Coated Granules Composition of core granules is shown in Table 1. Five-hundred grams of nateglinide, 5 g of hydroxypropylcellulose, and 10 g of polysorbate 80 were suspended and dissolved in 800 g of water with a microfluidizer (pressure:

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1200 kgf/cm^2). After mixing this suspension with the mixture of 22.1 g of lactose monohydrate and 252.8 g of croscarmellose sodium, extrusion granulation was conducted (diameter: 1.0 mmϕ). The resulting granules were rounded by a spherical granulator (rotor agitation: 450 rpm), and then dried in a fluidized bed dryer (inlet temperature: 80 °C). Fractions of 850—1400 μm granules were obtained by grading, and then they were used for coating. Table 2 shows the compositions of the used enteric coating suspensions. The resulting core granules were coated with the coating solutions using a fluidized bed coating machine (outlet temperature during coating: 26—31 °C (Enteric Coated Granules (a)), 18—26 °C (Enteric Coated Granules (b)), 20—26 °C (Enteric Coated Granules (c)). After drying, these enteric coated granules were annealed at 35 °C over night. Particle diameter was evaluated by sieving method. Loss on drying test was conducted at 80 °C with an infrared moisture determination balance (AD-230, KETT ELECTRIC LABORATORY, Japan).

Preparation of Nateglinide Controlled Release Tablet Containing Compressionable Enteric Coated Granules The obtained enteric coated granules and immediate release granules were mixed with a V-blender (38 rpm, 10 min). Then the obtained granules and magnesium stearate were mixed (38 rpm, 5 min). The granular product was tabletted to obtain the nateglinide controlled release tablets (target hardness: *ca.* 30 N). Hardness of the obtained tablets was evaluated with tablet tester (TS-50N, Okada Seiko, Japan).

Dissolution Behaviors of Nateglinide Preparations The dissolution behaviors 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% (nateglinide: 90 mg/vessel), 1.2 w/v% (nateglinide: 150 mg/vessel) of polysorbate 80 for pH=1.2, and Clark–Lubs buffer for pH=5.5—6.8. 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 acetonitrile–pH=2.5 phosphate buffer (55 : 45, v/v). Nateglinide eluted at about 10 min at 40 °C (at a flow rate of 1.5 ml/min).

Plasma Nateglinide Concentration[4,5] and Blood Glucose Level *In vivo* studies were conducted according to the guidelines of Ethical Committee in INA Research Co., Ltd. (Japan). Nateglinide preparations were administered to normal male beagle dogs (body weight: *ca.* 10 kg) just before feeding. One-hundred-and-fifty grams of dry DS meal (Oriental Yeast Co., Ltd., Japan) suspended in 600 g of hot water was forcibly administered to the beagle dogs with a syringe. Feeding was conducted within 12 min. Fastic® tablet was used as an immediate release tablet. In the case of a single oral administration of enteric coated granules (nateglinide: 9 mg/kg), blood samples were taken before and at 15, 30, 45, 60, 120, 180, 240, 360, 540, 720 and 1440 min (n=3). In the case of a single oral administration of nateglinide controlled release tablet containing compressionable enteric coated granules, blood samples were taken before and at 15, 30, 45, 60, 120, 240, 360, 540, 720 and 1440 min after oral administration (n=3). In the case of a repeated oral administration, the nateglinide controlled release tablet was administered at certain intervals for 8 h. Blood samples were taken before and at 15, 30, 45, 60, 120, 240, 360, 480, 495, 510, 525, 540, 600, 720, 840, 960, 1020, 1200 and 1440 min after the first oral administration (n=3). 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 pH=6.0 0.05 mol/l 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 pH=6.0 0.05 mol/l 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-6A 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, Kagakubushitsukenkyukikou, 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 column switching pattern was according to the method described in ref. 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). Statistical analyses were performed using Student's t-test or Tukey test.

Table 1. Composition of Core Granules for Enteric Coating

	w/w%
Nateglinide	63.3
Lactose monohydrate	2.8
Croscarmellose sodium	32.0
Hydroxypropylcellulose	0.6
Polysorbate 80	1.3

Results and Discussion

Design of Compressionable Enteric Coated Granules Nateglinide is rapidly absorbed and disappears from the blood stream after oral administration. Therefore, nateglinide

Table 2. Composition of Enteric Coating Suspension

	Enteric coated granules					
	(a)		(b)		(c)	
	Weight (g)	Solid content (g)	Weight (g)	Solid content (g)	Weight (g)	Solid content (g)
Methacrylic acid copolymer LD	208.0	62.40	70.0	21.00		
Poly(methyl acrylate-*co*-methyl methacrylate-*co*-methacrylic acid)			630.0	189.00	700.0	210.00
2 w/w% NaOH aq.	3.5	0.07				
Ethylacrylate methylmethacrylate copolymer dispersion	104.0	31.20				
20 w/w% citric acid aq.	1.0	0.20				
Glycelyl monostearate	2.9	2.90	6.3	6.30	6.3	6.30
Polysorbate 80			1.1	1.10	1.1	1.10
33 w/w% polysorbate 80 aq.	1.5	0.50				
Triethyl citrate	9.8	9.80	10.3	10.30	10.5	10.50
Water	624.0		1812.3		1400.0	
Total	954.7	107.07	2530.0	227.70	2117.9	227.90

Table 3. Composition of Nateglinide Controlled Release Tablet Containing Compressionable Enteric Coated Granules

Natglinide controlled release tablet	Immediate release granules (nateglinide: 60 mg) (mg)	Enteric coated granules (nateglinide: 90 mg) (mg)		Mg-St (mg)	Total weight (mg)
Tablet A	226.4	(a)	192.3	6.4	425.1
Tablet B	226.4	(b)	187.5	4.2	418.1
Tablet C	226.4	(c)	187.9	4.2	418.5

immediate release formulation controls PBG primarily.[1,2,4] In order to decrease FBG with nateglinide, it is necessary to conduct a sustained release of nateglinide.[4] When administering enteric coated granules with meal, it was reported that a sustained release of the drug was achieved.[4,6—10] Moreover, it was reported that nateglinide was only partially absorbed in the stomach, but was well absorbed in the whole area of the intestines, according to the *in situ* experiment in rats using a ligated loop method.[11] As in the above mentioned results, focusing the enteric coated granule, the authors aimed to design compressionable enteric coated granules as a controlled release portion to primarily decrease FBG, and a single unit type nateglinide controlled release tablet containing the enteric coated granules.

Nateglinide core granules were coated using the coating suspensions shown in Table 2 to prepare 3 types of compressionable enteric coated granules. It was thought to be necessary to coat 15 w/w% or more of enteric coating material on core granules to obtain acid resistance.[4] Therefore, 15 w/w% or more of enteric coating materials were coated on the core granules (Enteric Coated Granules (a): 22 w/w% of methacrylic acid copolymer LD (Eudragit® L30D-55), Enteric Coated Granules (b): 31.4 w/w% of methacrylic acid copolymer LD+poly(methyl acrylate-*co*-methyl methacrylate-*co*-methacrylic acid) (Eudragit® FS30D) (1 : 9 dry substance weight ratio), Enteric Coated Granules (c): 31.6 w/w% of poly(methyl acrylate-*co*-methyl methacrylate-*co*-methacrylic acid)). The loss on drying values were 3.6 w/w% (Enteric Coated Granules (a)), 3.4 w/w% (Enteric Coated Granules (b)), 3.2 w/w% (Enteric Coated Granules (c)) respectively. The average diameter of the obtained compressionable enteric coated granules was about 1 mm.

Design of Nateglinide Controlled Release Tablet Containing Compressionable Enteric Coated Granules Three types of nateglinide controlled release tablets were prepared with the composition shown in Table 3 (Tablet A, B, C, concave shape, diameter: 10 mmϕ). The amounts of nateglinide in both an immediate release portion and a controlled release portion were decided according to ref. 4 (the immediate release portion: 60 mg of nateglinide, the controlled release portion: 90 mg of nateglinide). The average diameter of used immediate release granules was about 250 μm. The hardness values of the obtained tablets were about 30 N. These are lower than those of conventional film coated tablets in the market, but are similar to those of orally disintegrated tablets.[12] Further process studies are required to make the above tablets commercially produced for the market.

Dissolution Behaviors of Nateglinide Preparations Nateglinide is a poorly water-soluble drug in JP1 fluid (pH 1.2). Polysorbate 80 was added to JP1 fluid to satisfy the sink condition.[4] The acid resistance of the compressionable enteric coated granules was evaluated in JP1 fluid (Table 4). The dissolution rates at 120 min in JP1 fluid of Enteric Coated Granules (a), (b) and (c) were 6.4%, 0.4%, 0.4% respectively, demonstrating sufficient acid resistance. Then, the dissolution behavior in neutral pH region was also evaluated (Fig. 2). In this study, dissolution pH[4] is defined as the pH at which the 60 min dissolution rate reaches 10% or more. Enteric Coated Granules (a), (b) and (c) were confirmed to have a different dissolution pH, demonstrating values of 6.0, 6.5 and 6.8, respectively. The dissolution rate of nateglinide became slower in the order of Enteric Coated Granules (a), (b) and finally (c). Furthermore it was possible to control the dissolution pH value of enteric coated granules by mixing more than 2 kinds of enteric coating materials. The dissolution rate of nateglinide from immediate release tablet (Fastic® tablet) or of immediate release granules is nearly 100% in both an acid and neutral pH. It is suggested that these compression-

Table 4. Dissolution Rate at 120 min of Compressionable Enteric Coated Granules in JP1 Fluid[a)]

	% Dissolved in JP1 fluid[a)] at 120 min (%)
Enteric coated granules (a)	6.4±0.0
Enteric coated granules (b)	0.4±0.0
Enteric coated granules (c)	0.4±0.2

Nateglinide: 90 mg/vessel, $n=3$, mean±S.D. *a*) JP1 fluid containing 0.6 w/w% polysorbate 80.

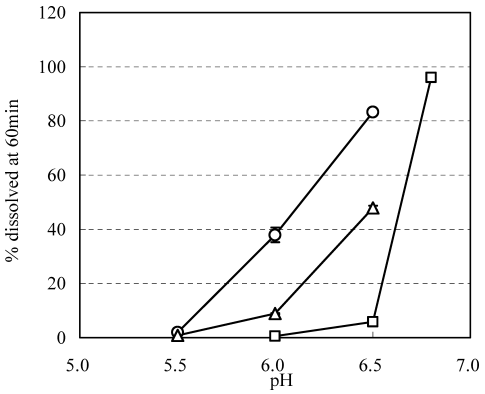

Fig. 2. pH Relationship of Dissolution Rate at 60 min of Enteric Coated Granules

JP15 paddle method (50 rpm), nateglinide: 90 mg/vessel, $n=3$, mean±S.D., medium: Clark–Lubs buffer (KH_2PO_4+NaOH). ○: Enteric Coated Granules (a). △: Enteric Coated Granules (b). □: Enteric Coated Granules (c).

Table 5. Dissolution Rate at 120 min of Nateglinide Controlled Release Tablets in JP1 Fluid[a)]

	% Dissolved in JP1 fluid[a)] at 120 min (%)
Tablet A	43.3±1.3
Tablet B	40.0±1.8
Tablet C	37.3±1.5

Nateglinide: 150 mg/vessel, n=3, mean±S.D. *a*) JP1 fluid containing 1.2 w/w% polysorbate 80.

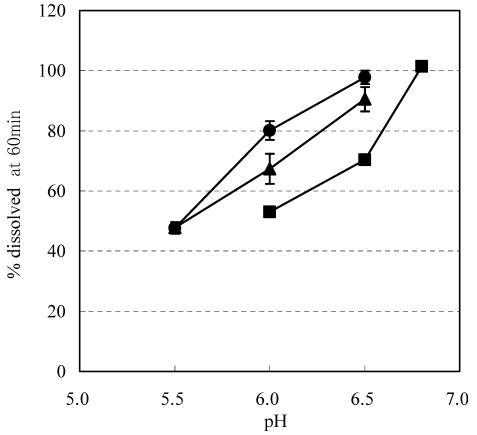

Fig. 3. pH Relationship of Dissolution Rate at 60 min of Nateglinide Controlled Release Tablets

JP15 paddle method (50 rpm), nateglinide: 150 mg/vessel, n=3, mean±S.D., medium: Clark Lubs buffer (KH_2PO_4+NaOH). ●: Tablet A. ▲: Tablet B. ■: Tablet C. Immediate release portion: 60 mg of nateglinide. Controlled release portion: 90 mg of nateglinide.

able enteric coated granules effectively lowered FBG with hardly any decrease in PBG according to our previous study.[4)]

Dissolution behaviors were also evaluated for the obtained Tablet A, B and C (Table 5, Fig. 3). In JP1 fluid, dissolution rates at 120 min of the obtained Tablets A, B and C were around 40%. This means that only nateglinide contained in the immediate release portion was dissolved under this dissolution testing condition (60 mg/150 mg=40%), and that acid resistance of enteric coated granules was maintained even after tableting.[13)] In neutral pH (pH=5.5—6.8), although the little change in pH relationship of dissolution rate was observed when compared with those shown in Fig. 2, the dissolution behavior of enteric coated granules was maintained approximately even after tableting. It is thought that further process control studies are required for enteric coating process and tableting process in order to precisely control the dissolution behavior. The content uniformity of both immediate release granules and enteric coated granules in the obtained tablets was not evaluated. However, it was thought that both immediate release granules and enteric coated granules were mixed uniformly according to the deviations of dissolution rates (Table 5).

Plasma Nateglinide Concentration and Blood Glucose Level after Single Oral Administration of Nateglinide Controlled Release Tablets Tablets A and C were orally administered (nateglinide: 150 mg/head) to normal beagle dogs just before feeding followed by measurement of plasma nateglinide concentrations and blood glucose levels (Figs. 4, 5). Results are also shown for a control (feeding only) and immediate release tablets (nateglinide: 60, 150 mg/body).

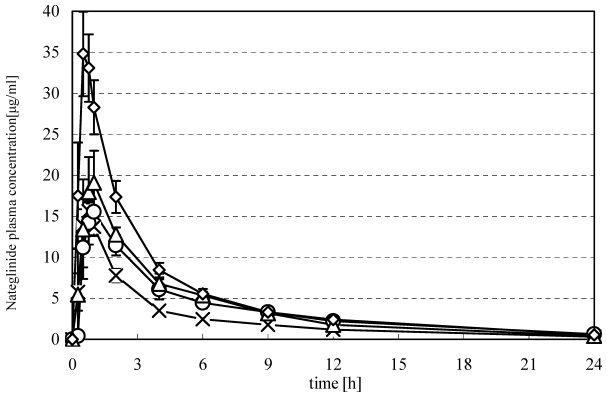

Fig. 4. Plasma Nateglinide Concentration Profiles after Oral Administration of Nateglinide Controlled Release Tablets in Fasted Beagle Dogs Just before Feeding

Each point and vertical bar represents mean±S.E.M. ×: Immediate release tablets (60 mg of nateglinide), n=6. ◇: Immediate release tablets (150 mg of nateglinide), n=6. ○: Tablet A, n=3. △: Tablet C, n=3.

According to Fig. 4, the respective nateglinide C_{max} values consisted of 15.56±2.99 μg/ml (T_{max}: 1.0 h) for Tablet A, 19.09±3.89 μg/ml (T_{max}: 1.0 h) for Tablet C, 15.63±1.08 μg/ml (T_{max}: 0.75 h) for immediate release tablets (60 mg of nateglinide), 34.80±5.15 μg/ml (T_{max}: 0.5 h) for immediate release tablets (150 mg of nateglinide). There were no significant differences observed for C_{max} values among the immediate release tablets (60 mg of nateglinide) and Tablet A and Tablet C (Tukey test). This is because C_{max} values are only dependent on the immediate release component. On the other hand, there were significant differences observed at 9 and 12 h between the immediate release tablets (60 mg of nateglinide) and Tablet A, and also observed at 6, 9 and 12 h between the immediate release tablets (60 mg of nateglinide) and Tablet C ($p<0.05$, Student's t-test). It demonstrated an effect of increase in nateglinide plasma concentration by the controlled release portion (Enteric Coated Granules (a) or (c)). Relative bioavailability values of Tablet A and C against immediate release tablets (nateglinide: 150 mg/head) were 57.2% and 60.8% respectively. It was reported that nateglinide was rapidly and almost completely absorbed in the case of an oral administration of nateglinide suspension in normal beagle dogs (bioavailability value: about 90%).[14)] The area under curve (AUC) values and C_{max} values increase linearly in normal beagle dogs (60—150 mg/head of nateglinide, data not shown). It was considered that the enteric coated granules lowered bioavailability values of these tablets, and it is necessary to improve the bioavailability value of the enteric coated granules. According to Fig. 5, in the cases of Tablets A and C, FBG decreased to a maximum of about 84% and about 76%, respectively, as compared with blood glucose levels immediately before administration. In the case of the administration of 60 mg of nateglinide (immediate release tablets), FBG at 8 h after administration did not decrease, although PBG decreased to a maximum of about 79%. PBG is defined as a blood glucose level from 0 to 3 h after feeding in this study. In the case of the administration of 150 mg of nateglinide (immediate release tablets), a decrease in both PBG and FBG was observed. However, Tablets A and C are

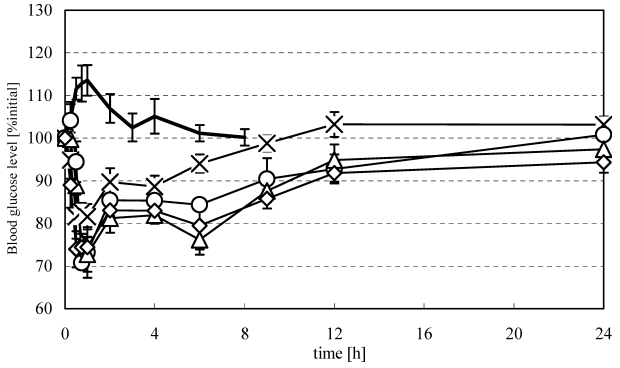

Fig. 5. Blood Glucose Level after Oral Administration of Nateglinide Controlled Release Tablets in Fasted Beagle Dogs Just before Feeding

Each point and vertical bar represents mean±S.E.M. ▬: Only feeding, $n=6$. ×: Immediate release tablets (60 mg of nateglinide), $n=6$. ◇: Immediate release tablets (150 mg of nateglinide), $n=6$. ○: Tablet A, $n=3$. △: Tablet C, $n=3$.

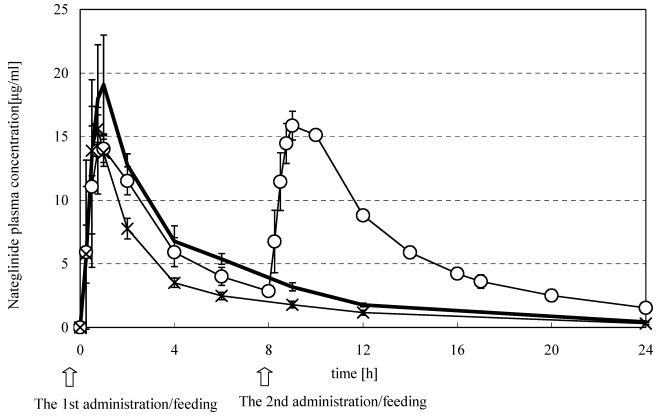

Fig. 6. Plasma Nateglinide Concentration Profiles during Repeated Oral Administration of Nateglinide Controlled Release Tablets in Fasted Beagle Dogs Just before Feeding

Each point and vertical bar represents mean±S.E.M. ×: Immediate release tablets (60 mg of nateglinide), single administration, $n=6$. ▬: Tablet C, single administration, $n=3$. ○: Tablet C, repeated administration, $n=3$.

believed to be more useful than the immediate release tablets (150 mg of nateglinide), because of easy control of both PBG and FBG without a side effect, especially hypoglycemic state due to high nateglinide plasma concentration. In addition, there was no correlation observed between plasma nateglinide concentration and plasma insulin concentration, or between plasma insulin concentration and blood glucose level (data not shown). This is thought to be due to having sampled from a vein in the leg.[4] On the basis of the above results, it was found that both PBG and FBG can be decreased in a single oral administration with either Tablet A, or Tablet C.

Plasma Nateglinide Concentration and Blood Glucose Level during Repeated Oral Administration of Nateglinide Controlled Release Tablets In the case of a repeated oral administration of gliclazide to normal rats, the blood glucose lowering action had been reported to weaken during the second administration.[1] Nateglinide is also an insulin secretion stimulator. It was considered necessary to evaluate the effect on decrease in both PBG and FBG in a repeated oral administration. After deciding to focus on Tablet C, a repeated oral administration study (an interval: 8 h) was conducted to normal beagle dogs just before feeding. According

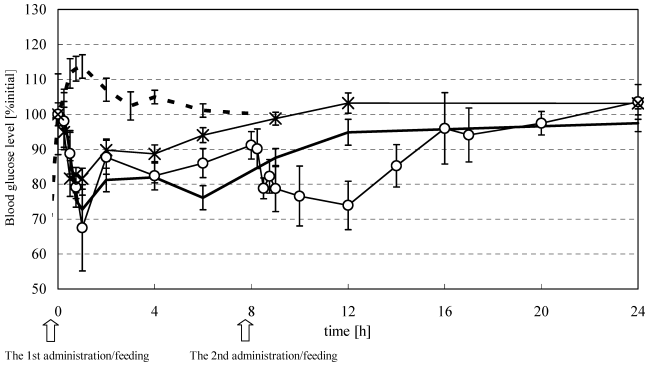

Fig. 7. Blood Glucose Levels during Repeated Oral Administration of Nateglinide Controlled Release Tablets in Fasted Beagle Dogs Just before Feeding

Each point and vertical bar represents mean±S.E.M. ▬▬▬: Only feeding, $n=6$. ×: Immediate release tablets (60 mg of nateglinide), single administration, $n=6$. ▬: Tablet C, single administration, $n=3$. ○: Tablet C, repeated administration, $n=3$.

to Fig. 6, the nateglinide C_{max} values were 14.03±1.05 μg/ml (T_{max}: 1.0 h), 15.87±1.13 μg/ml (T_{max}: 9.0 h) for repeated administration of Tablet C, 15.63±1.08 μg/ml (T_{max}: 0.75 h) for the immediate release tablets (60 mg of nateglinide), and 19.09±3.89 μg/ml (T_{max}: 1.0 h) for single administration of Tablet C. According to Fig. 7, in the case of the repeated administration, PBG decreased to a maximum of about 67.5% for the first administration and about 78.7% for the second administration and FBG decreased to a maximum of about 82.4% for the first administration and about 73.9% for the second administration, as compared with blood glucose levels immediately before the 1st administration. The effect of decrease in both PBG and FBG was not reduced, even in the repeated oral administration. Although it was initially believed that it would be difficult to lower blood glucose levels in the case of a repeated administration, it was confirmed that the effect of decreases in both PBG and FBG were observed continuously twice. These results indicate that there exists a possibility to decrease both PBG and FBG of moderate or severe diabetes by this nateglinide controlled release tablet. Moreover, it appeared to enable control of both PBG and FBG for moderate and severe diabetes patients with a controlled release formulation containing a short-acting type oral blood glucose regulator, not only nateglinide but meglitinides (repaglinide, mitiglinide, *etc.*), because they are all classified as a short acting type insulin secretion stimulators.[15]

However, problems remain, such as low oral bioavailability, productivity of a tablet containing both immediate release granules and enteric coated granules, and determination of the appropriate amounts of nateglinide in both an immediate release portion and a controlled release portion. These problems have to be solved out prior to clinical trials.

Conclusion

A nateglinide controlled release tablet was designed, comprised of both immediate release granules and compressionable enteric coated granules. The tablet contained 60 mg of nateglinide in the immediate release portion and 90 mg of nateglinide in the controlled release portion. It was found that it was able to control both PBG and FBG using the nateglinide controlled release tablets in both a single and a

repeated oral administration studies.

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