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METABOLISM AND EXCRETION OF THE DPP-4 INHIBITOR [^{14}C]SITAGLIPTIN IN HUMANS

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Running title: [^{14}C]Sitaglitptin Human ADME

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Abbreviations: C_{max}, maximum concentration; DPP-4, didpeptidyl peptidase-4; GLP-1, glucagons like peptide-1; LC-MS/MS, liquid chromatography- tandem mass spectrometry; MRL, Merck Research Laboratories; sitagliptin, 2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine).

ABSTRACT

The metabolism and excretion of [^{14}C]sitagliptin, an orally active, potent and selective DPP-4 inhibitor, were investigated in humans following a single oral dose of 83 mg/193 μCi. Urine, feces, and plasma were collected at regular intervals for up to 7 days. The primary route of excretion of radioactivity was via the kidneys, with a mean value of 87% of the administered dose recovered in urine. Mean fecal excretion was 13% of the administered dose, for a total recovery of 100%. Parent drug was the major radioactive component in plasma, urine and feces, with only 16% of the dose excreted as metabolites (13% in urine and 3% in feces), indicating that sitagliptin was eliminated primarily by renal excretion. Approximately 74% of plasma AUC of total radioactivity was accounted by parent drug. Six metabolites were detected at trace levels, each representing <1 to 7% of the radioactivity in plasma. These metabolites were the *N*-sulfate and *N*-carbamoyl glucuronic acid conjugates of parent drug, a mixture of hydroxylated derivatives, an ether glucuronide of a hydroxylated metabolite, and two metabolites formed by oxidative desaturation of the piperazine ring followed by cyclization. These metabolites were detected also in urine, at low levels. Metabolite profiles in feces were similar to those in urine and plasma, except that the glucuronides were not detected in feces. CYP3A4 was the major CYP isozyme responsible for the limited oxidative metabolism of sitagliptin, with some minor contribution from CYP2C8.

INTRODUCTION

Dipeptidyl-peptidase-4 (DPP-4) is a ubiquitous proline-specific serine protease responsible for the rapid inactivation of incretins, including glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (Gorrell, 2005; Mentlein et al., 1993). GLP-1, which is released upon nutrient ingestion, stimulates meal-induced insulin secretion and contributes to glucose homeostasis (Kieffer and Habener, 1999). Stabilization of GLP-1 via DPP-4 inhibition is a new therapeutic approach for Type 2 diabetes (Drucker, 2003; Holst, 2004; Mest and Mentlein, 2005; Nielsen, 2005).

Sitagliptin (Januvia™), also known as MK-0431 (Figure 1) is an orally active, potent and selective DPP-4 inhibitor with an IC_{50} value of 18 nM (Kim et al., 2005). Sitagliptin has been shown to dose-dependently inhibit plasma DPP-4 activity, and enhance active GLP-1 levels in normal volunteers (Bergman 2005, 2006; Herman et al., 2005a) and patients with type 2 diabetes (Herman 2004). Furthermore, in patients with type 2 diabetes, single doses of sitagliptin enhanced insulin and C-peptide release, decreased glucagon secretion, and reduced plasma glucose levels following an oral glucose tolerance test (Herman et al., 2004), while 12-week treatment with sitagliptin significantly reduced HbA_{1c} and fasting plasma glucose (Herman 2005b; Scott et al., 2005).

The metabolism and excretion of [^{14}C]sitagliptin were studied in male human volunteers following oral administration of 83 mg/193 μCi. In preclinical species, [^{14}C]sitagliptin was shown to be eliminated by biliary and/or renal excretion of parent drug (Beconi et al. and Liu et al., 2006). Metabolism was minimal, and it involved *N*-sulfation (M1), *N*-carbamoyl glucuronidation (M4), hydroxylation (M6) followed by ether glucuronidation (M3), and oxidative desaturation followed by cyclization (M2 and M5) (Fig. 1). Synthetic standards of

metabolites M1, M2 and M5 were tested for DPP-4 inhibition and shown to be ~300-, 1000- and 1000-fold less active, respectively, than parent drug.

MATERIALS AND METHODS

Chemicals and Dose Preparation. [^{14}C]sitagliptin was synthesized as the phosphate salt with a specific activity of 2.36 μCi/mg of free base (1.9 μCi/mg of salt) by the Labeled Compound Synthesis Group (Merck Research Laboratories (MRL), Rahway, NJ). The chemical purity was 99.7%, as determined by HPLC. The dose was prepared as a capsule formulation containing 20 mg/48.3 μCi of [^{14}C]sitagliptin (25 mg of phosphate salt). The 2,5-difluoro analog of sitagliptin used to saturate non-specific binding sites on the solid phase extraction cartridges was provided by Process Research (MRL, Rahway, NJ). The synthetic standard of metabolite M1 was synthesized by the Labeled Compound Synthesis Group (MRL, Rahway, NJ), and M2 and M5 were synthesized by Basic Chemistry (MRL, Rahway, NJ). The solid phase extraction cartridges, Varian C_{18} Bond Elute® columns, were purchased from Varian Inc. (Harbor City, CA).

Subjects and Dose Administration. The study was conducted at Clinical Pharmacology Associates in Miami, FL, in six healthy male volunteers, 27 to 43 years old, weighing 60 to 95 kg, Subjects were admitted to the clinical research unit the evening prior to dosing, and remained in the unit until the completion of all laboratory collections for the duration of the study (approximately 7 days). Subjects abstained from food and drink except water from 12 midnight the evening before dosing, and consumed approximately 240 ml of water approximately 2 hr prior to drug administration. Water was restricted 1 hr prior to and 1 hr after drug administration. Each subject ingested 4 capsules containing a total of 83 mg/193 μCi of [14C]sitagliptin with approximately 240 ml of water. A standardized lunch was given at approximately 4 hr post dose, a standardized dinner was given at approximately 10 hr, and a snack was allowed in the evening. Blood was collected in EDTA-coated tubes at selected time

points up to and including 7 days post dose, and spun in a centrifuge to obtain plasma. Urine and feces were collected daily for 7 days. Plasma was stored at -70°C, and urine and feces at -20°C. Safety and tolerability was assessed by clinical and laboratory evaluations pre-study, pre-dose, post dose, and post study. Vital signs and ECGs were also evaluated at selected intervals.

Radioactivity excretion data from one subject (AN 803) showed that there was substantially lower overall recovery compared to the other 5 subjects, suggesting incomplete collection of radioactivity. This subject was subsequently re-dosed with a non-labeled 100 mg dose of sitagliptin, followed by collection of blood and urine samples for 72 hr postdose.

Determination of Radioactivity and Sample Processing for Metabolite Profiling. The concentration of radioactivity in aliquots (0.5 ml) of plasma taken at 0, 0.5, 1.5, 2, 3, 5, 6, 10, 15, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hr after dosing was determined by liquid scintillation counting. For metabolite profiling, approximately 4 ml of plasma taken at 1, 4, 8, 12, and 18 hr from the six subjects were pooled for each time point. The resulting pools were mixed with 4 ml of 8M urea and applied to 20 g Varian C_{18} Bond Elute columns, using the following procedure: 1) two washes with 15 ml methanol; 2) two washes with 15 ml water; 3) equilibration with 30 ml of 50 μM 2,5-difluoro analog of sitagliptin (in order to saturate sites of non-specific adsorption); 4) washes with methanol (2 x 15 ml) and water (2 x 15 ml); 5) loading of the plasma; 6) three washes with 15 ml of water; 7) elution with 12 ml of methanol containing 10% formic acid. Previous studies had shown that sitagliptin and its metabolites were stable under acidic conditions (5% $HClO_4$). The column eluates were evaporated under N_2 and the samples were reconstituted in 0.3 ml of water: methanol: acetic acid (90/10/0.1, by volume) and analyzed by LC-MS/MS and radiometric detection.

Concentrations of radioactivity and percent of radioactive dose excreted into the urine and feces were determined at Charles River Laboratories. Feces were homogenized with water (4 ml/g feces) and weighed aliquots were analyzed by combustion followed by liquid scintillation counting of the trapped $^{14}CO_2$. Radioactivity in weighed aliquots of urine was determined directly by liquid scintillation counting.

For metabolite profiling, 0-168 hr pools of urine and 0-96 hr pools of fecal homogenates were prepared for each subject based on the volume recovered at each time point. Aliquots from each urine or feces pool were treated with an equal volume of acetonitrile. The mixtures were placed on melting ice for 10 min and centrifuged at 3,000 rpm for 10 min. The resulting supernatants were dried under N_2 at 30^{o}C overnight, reconstituted in 350 µl (urine) or 600 to 750 µl (feces) of water: methanol: acetic acid (90:10:0.1, by volume), and analyzed by LC-MS/MS coupled with radiometric detection. Also, representative metabolite profiles were generated by analyzing samples consisting of equal volumes of urine or feces extracts from 5 subjects (excluding Subject 803) or all 6 subjects. For confirmation of metabolites by MRM transition monitoring and MS/MS fragmentation, fecal samples were subjected to solid-phase extraction, using a procedure similar to the method described for plasma.

Qualitative LC-MS/MS Analysis. LC-MS analysis was conducted on a PE Sciex API 3000 mass spectrometer (PerkinElmerSciex Instruments, Boston, MA), which was interfaced with a PerkinElmer HPLC system (PerkinElmer Life and Analytical Sciences, Boston, MA) equipped with two Series 200 micro pumps and a PerkinElmer Series 200 autosampler. A ThermoHypersil Fluophase PFP column (3.0 x 150 mm, 5 µm; Thermo Electron Corporation) was used for chromatographic separation. The column was eluted with a mixture of 5 mM ammonium acetate in water plus 0.05% acetic acid (mobile phase A) and 5 mM ammonium acetate in methanol plus 0.05% acetic acid (mobile phase B). The gradient was begun with 18% B for 2 min, increased

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linearly to 80% B over 33 min, and then to 95% B in 5 min, followed by a hold at 95% B for 5 min. The effluent from the HPLC, pumped at a rate of 0.6 ml/min, was diverted at a 5:1 ratio into the radiometric flow detector and into the mass spectrometer, respectively. Scintillation cocktail (Packard Ultima Flo-M, Downers Grove, IL) was pumped at a rate of 1.2 ml/min in the radiometric detector. The contributions of parent drug and metabolites were calculated from the amount of radioactivity eluting in each peak relative to the total radioactivity in the HPLC chromatogram. LC-MS and LC-MS/MS experiments were carried out using the Turbo-Ionspray interface operated in the positive ion mode. The source voltage was 3,500 V, and the probe temperature 300^{o}C. Metabolites were identified by selective ion monitoring of the following precursor→product transitions (MRM monitoring): M1, *m/z* 488.2→408.2 and *m/z* 488.2→193.0; M2, M3, and M5, *m/z* 406.2→174 and *m/z* 406→191; M4, *m/z* 628.2→408 and *m/z* 628.2→452; and M6, *m/z* 424.2→406.1 and *m/z* 424.2→191. The presence of parent drug and metabolites was confirmed by a signal of the MRM transition for each metabolite at least 2- to 3-fold above background at the correct retention time. Also, product ion scan experiments were carried out to compare the MS/MS fragmentation of M1 with that of the synthetic standard.

Identification of CYP Isozymes Involved in the Metabolism of Sitagliptin. Sitagliptin (25 μM) was incubated with cell membranes containing singly expressed CYP isoforms (CYP2A6, 2B6, C8, C9, C19, 2D6, and 3A4), cytochrome b5, and an NADPH-regenerating system in 0.05 M potassium phosphate buffer. The final concentration of the CYP isoforms and cytochrome b5 in the incubation mixture was 0.5 μM. The relative contribution of individual CYPs to the metabolism of sitagliptin was determined by pre-incubating human liver microsomes (2 mg protein/ml) with monoclonal antibodies against human CYP3A4 and 2C8 for 1 hr at room temperature, followed by the addition of 10 μM sitagliptin. Control incubations were carried out

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using a control antibody. The mixtures were incubated at 37˚C for 5 min, NADPH was added and incubations continued for another 30 min. The reactions from both sets of incubations were quenched by the addition of acetonitrile containing 2% formic acid, and supernatants were analyzed by LC-MS/MS, for the formation of metabolites M2, M5 and M6 using MRM monitoring.

Quantitative LC-MS/MS Analysis. Concentrations of sitagliptin in plasma were determined by direct on-line LC-MS/MS analysis using a Cohesive Technologies High Turbulence Liquid Chromatography (HTLC) system, as described in more detail elsewhere (Bergman et al. 2006). Analyte and internal standard were detected using selected reaction monitoring (SRM) with turbo-ionspray interface in the positive ion mode. The lower limit of quantification (LLOQ) for the plasma assay was 0.5 ng/mL (1.23 nM) and the linear calibration range was 0.5 to 1000 ng/mL (1.23 to 2455 nM).

Pharmacokinetic Calculations. Plasma concentrations of sitagliptin and radioactivity were converted into molar units (nM or nM eq.) using the molecular weight of 407.321 prior to pharmacokinetic analysis. Area under the plasma concentration-time curve to the last time point where radioactivity was above the lower limit of quantitation ($AUC_{0\text{-last}}$) was calculated for both sitagliptin concentrations and radioactivity using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. Sitagliptin and radioactivity plasma C_{max} and T_{max} were obtained by inspection of the plasma concentration data.

RESULTS

Excretion of Radioactivity. The excretion of radioactivity in human urine and feces following a single 83-mg/193 μCi oral dose of [^{14}C]sitagliptin is summarized in Table 1. The results indicated that most of the radioactive dose was excreted via the kidneys, with a mean value of ~87% of the administered dose recovered within 7 days in urine (range: ~83 to 94%) in 5 of 6 subjects who participated in this study. Fecal excretion averaged ~13% (n=5) of the administered dose (range: ~9 to 20%), with a mean total recovery of radioactivity in urine and feces of ~100% (range: ~94 to 105%).

The recovery of radioactivity in one of the subjects (subject 803) was much lower than the average recovery in the other 5 subjects (30 versus 100% of the dose). The data from this subject were not used in the calculation of the mean and standard deviation values reported in Table 1 and Figure 2. In a subsequent study with non-radiolabeled sitagliptin (100 mg), it was determined that the pharmacokinetics and renal excretion of sitagliptin in this subject were similar to historical data. Pharmacokinetic analysis of the plasma and urine samples following this dosing revealed that approximately 66% of the sitagliptin dose was excreted unchanged in urine over the 72 hour collection period (data not shown). Also, the renal clearance of MK-0431 was generally similar to that observed in other subjects (439 mL/min). These results suggested that the results obtained for this subject following the 83.04 mg [^{14}C]sitagliptin were very likely spurious, and therefore this subject was excluded from the primary analysis. .

Radioactivity and Sitagliptin Levels in Plasma. Concentrations of radioactivity (expressed as [^{14}C]sitagliptin nM eq) and sitagliptin (nM) in human plasma following oral dosing of [^{14}C]sitagliptin are depicted in Figure 2, and pharmacokinetic parameters are summarized in Table 2. The highest concentrations in plasma (C_{max}) were achieved at 2 to 4 hr post dose and ranged from 706 to 993 nM eq (total radioactivity) and 523 to 930 nM

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(sitagliptin) in 5 of the 6 subjects (excluding subject AN 803). Radioactivity levels at 60 to 168 hr post dose were below the limit of quantification, ~25 nM eq. Plasma $AUC_{0\text{-last}}$ values in the 5 subjects ranged from 7.19 to 9.21 µM eq.•hr, with a mean value of 8.20 µM eq•hr for total radioactivity, and from 5.12 to 6.83 (mean 6.04) µM•hr for sitagliptin. The mean $AUC_{0\text{-last}}$ of radioactivity was 74% of the $AUC_{0\text{-last}}$ of sitagliptin. Data from Subject AN803 were not used in the calculation of mean and standard deviation values, because of the low recovery of the radioactive dose in this subject.

Metabolite Profiles in Plasma. Metabolite profiles in plasma pooled across subjects at 1 and 8 hr are illustrated in Figure 3. Similar profiles were observed at 4, 12, and 18 hr. Due to the low levels of radioactivity and the limited volume of plasma, it was not possible to obtain individual metabolite profiles. Radioactivity in plasma was comprised primarily of parent drug at all time points examined, with approximately 90% of circulating radioactivity detected at 1 hour, approximately 80% detected at 4, 8, and 18 hr, and approximately 78% detected at 12 hr. Six known metabolites were detected, each accounting for <1 to 8% of the circulating radioactivity between 1 and 18 hr post dose (Table 3). The most abundant metabolites in plasma were M5 (4 to 7% of radioactivity) and M2 (1 to 6%), both of which are formed by oxidative desaturation of the piperazine ring followed by cyclization (Figure 1). Other metabolites include M6 (a group of hydroxylated derivatives; 1 to 4%), M1 (*N*-sulfate conjugate; 2 to 4%), M4 (*N*-carbamoyl glucuronide conjugate; 1%) and M3 (ether glucuronide conjugate of a hydroxylated derivative; <1%).

Metabolite Profiles in Urine and Feces. The metabolite profile of a pooled sample of urine collected at 0-168 hr post dose is shown in Figure 4. Similar profiles were obtained for urine collected from individual subjects, including subject AN0803. Parent drug was the major radioactive component, comprising ~84 to 88% of the urinary radioactivity. All six metabolites

detected in plasma were excreted in small amounts into urine (<1 to 5% of the urinary radioactivity, <1 to ~4% of the dose, each).

The metabolite profile of a pooled human fecal sample collected at 0-96 hr is illustrated in Figure 4. Feces collected between 4 and 7 days post dose contained negligible amounts of radioactivity and were not analyzed. Parent drug was the major radioactive component in feces, comprising ~51 to 86% of the radioactivity. The metabolites profiles in feces were similar in all subjects (not shown), and also similar to the profiles in urine and plasma, with the exception that the conjugates M3 and M4 were not detected in feces, presumably because they had been hydrolyzed to their corresponding aglycones, M6 and sitagliptin, respectively. Metabolites M1, M2, M5, and M6 were detected in small amounts (~1 to 12% of the fecal radioactivity, <1 to ~1.6% of the dose, each).

Safety Evaluation. There were no clinical or laboratory adverse experiences reported in this study. In addition, there were no apparent treatment-related clinically relevant changes in vital signs, ECG or laboratory safety parameters.

Identification of Cytochrome P450 Involved in Sitagliptin Metabolism. Following one-hour incubations of 10 μM [^{14}C]sitagliptin with NADPH-enriched human liver microsomes, ~2% turnover was observed. The only metabolites detected by LC-MS/MS were a hydroxylated derivative (M6), and the cyclized products M2 and M5 (Beconi et al., submitted). Incubations with recombinant CYPs indicated that CYP3A4 and, to a much smaller extent, CYP2C8 were capable of catalyzing the formation of the oxidative metabolites M2, M5 and M6. Due to the low turnover, the relative contribution of these CYPs could not be determined accurately. However, based on LC-MS/MS analysis, it could be discerned that the formation of M2 and M5 in human liver microsomes could be inhibited to a much larger extent by anti-CYP3A4 than anti-CYP2C8 antibody. Also, the formation of M6 could be inhibited by anti-CYP3A4 only.

Discussion

Following oral administration [^{14}C]sitagliptin to healthy volunteers, the total recovery of radioactivity was approximately 100%. The results of this study demonstrate that the primary route of elimination of sitagliptin in healthy subjects is via renal excretion of intact drug. Approximately 16% of the oral radioactive dose was excreted as metabolites (13% in urine, 3% in feces), and ~10% of the radioactivity dose was excreted unchanged in feces. The unchanged sitagliptin found in feces may represent unabsorbed material, drug cleared by biliary excretion, or back-converted M1 (*N*-sulfate) and/or M4 (*N*-carbomoyl glucuronide). Nonetheless, these results indicated that sitagliptin was well-absorbed following oral administration, as ~87% of the radioactivity was recovered in urine. This data is corroborated by the high bioavailability (Bergman et al., 2005) and high recovery of parent drug in urine following the administration of unlabeled sitagliptin to healthy subjects (Bergman et al., 2006, Herman et al., 2005).

Examination of the sitagliptin and radioactivity pharmacokinetic data indicate that sitagliptin makes up the majority (74%) of the radioactivity in plasma following an oral dose (as determined by the ratio of sitagliptin AUC and radioactivity AUC), with the remaining radioactivity accounted for by the metabolites shown in Figure 1. Due to their low affinity for the DPP-4 enzyme (M1, M2, and M5) and their low levels in plasma, these metabolites would not be expected to contribute to the pharmacological activity of sitagliptin.

Similar observations were made in rats and dogs (Beconi et al., 2006), where, as in humans, sitagliptin was eliminated primarily unchanged into urine (dog) or urine and bile (rat). Also, all the metabolites observed in human plasma, urine and feces were observed also in rat and/or dog plasma, urine, bile and feces, as well as in incubations in vitro with rat, dog, and human liver preparations (Beconi et al., 2006). Results from in vitro experiments with recombinant CYPs and monoclonal anti-CYP antibodies indicated that the oxidative metabolism of sitagliptin in

human liver microsomes is catalyzed primarily by CYP3A4 with some minor contribution from CYP2C8. Because sitagliptin is eliminated primarily unchanged into urine, it is not expected to be a victim of metabolism-based drug interactions.

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Figure Legends

FIG. 1. Main biotransformation pathways for [^{14}C]sitagliptin in humans

FIG. 2. Mean concentration-time profiles of sitagliptin and total radioactivity in plasma following oral administration of [^{14}C]sitagliptin in healthy young men.

Healthy volunteers received 83 mg/193 μCi of [^{14}C]sitagliptin in 4 dry-filled capsules. Radioactivity in plasma was determined by liquid scintillation counting; mean ± standard deviation values (N=5) are shown.

FIG. 3. HPLC radiochromatograms of human plasma following oral administration of [^{14}C]sitagliptin.

Healthy volunteers received 83 mg/193 μCi of [^{14}C]sitagliptin. Plasma pooled across subjects was subjected to solid-phase extraction followed by LC-MS/MS analysis coupled with radiometric detection.

FIG 4. HPLC radiochromatogram of pooled human urine (0-168 hr) and feces (0-96 hr) following oral administration of [^{14}C]sitagliptin.

Healthy volunteers received 83 mg/193 μCi of [^{14}C]sitagliptin. Urine and fecal homogenates extracts pooled across subjects were analyzed by LC-MS/MS coupled with radiometric detection.

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Table 1

Excretion of radioactivity in human urine and feces following an oral dose of [^{14}C]sitagliptin[a]

Time/ Subject	Percent of Dose							
	0800	0801	0802	0803 [b]	0804	0805	Mean	SD
Urine							N=5	
0-6 hr	43	38	44	16	46	47	44	3.7
6-12 hr	17	17	26	4.2	18	21	20	3.9
12-24 hr	13	16	14	3.4	12	14	14	1.5
24-168 hr	9.4	11	9.4	1.4	8.3	7.7	9.2	1.4
0-168 hr	82	82	93	25	85	90	87	5.2
Feces								
0-24 hr	2.1	0.1	0.3	4.4	0.3	0.3	0.6	0.9
24-48 hr	15	18.2	3.1	0.5	5.4	6.9	9.8	6.6
48-168 hr	0.4	1.4	6.9	<0.1	3.0	1.6	2.7	2.6
0-168 hr [b]	18	20	10	4.9	8.9	8.7	13	5.3
Total	100	102	103	30	94	99	100	4.1

[a] Six healthy volunteers received 83 mg/193 μCi of [^{14}C]sitagliptin in 4 dry-filled capsules. Radioactivity in fecal homogenates and urine was determined and expressed as percent of administered dose. Subject 0803 was considered an outlier and data from this subject were not used for the calculation of the mean and standard deviation values. SD = standard deviation.

[b] Includes radioactivity on fecal wipes.

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Table 2

Individual plasma pharmacokinetic parameters of sitagliptin and radioactivity following administration of a single oral 83-mg dose of [^{14}C]sitagliptin to healthy young men [a]

Subject	Sitagliptin			Radioactivity			Sitagliptin /Radioactivity	
	$AUC_{0\text{-last}}$ [b] (μM•hr)	C_{max} (nM)	T_{max} (hr)	$AUC_{0\text{-last}}$ (μM eq.•hr)	C_{max} (nM eq.)	T_{max} (hr)	$AUC_{0\text{-last}}$ Ratio	C_{max} Ratio
800	5.27	869	2	7.30	955	2	0.72	0.91
801	6.83	771	2	8.55	833	2	0.80	0.93
802	6.67	702	5	9.21	888	5	0.72	0.79
803 [b]	3.45	447	1.5	4.64	572	1.5	0.74	0.78
804	6.31	930	1.5	8.73	993	2	0.72	0.94
805	5.12	523	4	7.19	706	3	0.71	0.74
AM [c]	6.04	759	2 [d]	8.20	875	2 [d]	NC	NC
SD [c]	0.80	158	NC [e]	0.90	113	NC	NC	NC
GM [c]	6.00	745	NC	8.16	869	NC	0.74	0.86

[a] Six healthy volunteers received 83 mg/193 μCi of [^{14}C]sitagliptin in 4 dry-filled capsules. Concentrations of radioactivity and sitagliptin in plasma were determined by liquid scintillation counting and LC-MS/MS, respectively.

[b] last = last time point where plasma radioactivity is above the lower limit of quantitation.

[c] Subject 0803 was considered an outlier and data from this subject were not used for the calculation of the arithmetic mean (AM), geometric mean (GM) or standard deviation (SD) values.

[d] Median

[e] NC = not calculated.

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Table 3

Relative contribution of [^{14}C]sitagliptin and metabolites to the radioactivity in human plasma following oral administration

Compound	Contribution (Percent of Radioactivity)				
	1 hr	4 hr	8 hr	12 hr	18 hr
Sitagliptin	90	81	80	78	81
M1	3	4	3	3	2
M2	1	3	4	6	6
M3	<1	<1	<1	<1	<1
M4	<1	1	1	<1	<1
M5	4	6	7	7	6
M6	1	4	3	2	2

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Fig. 1

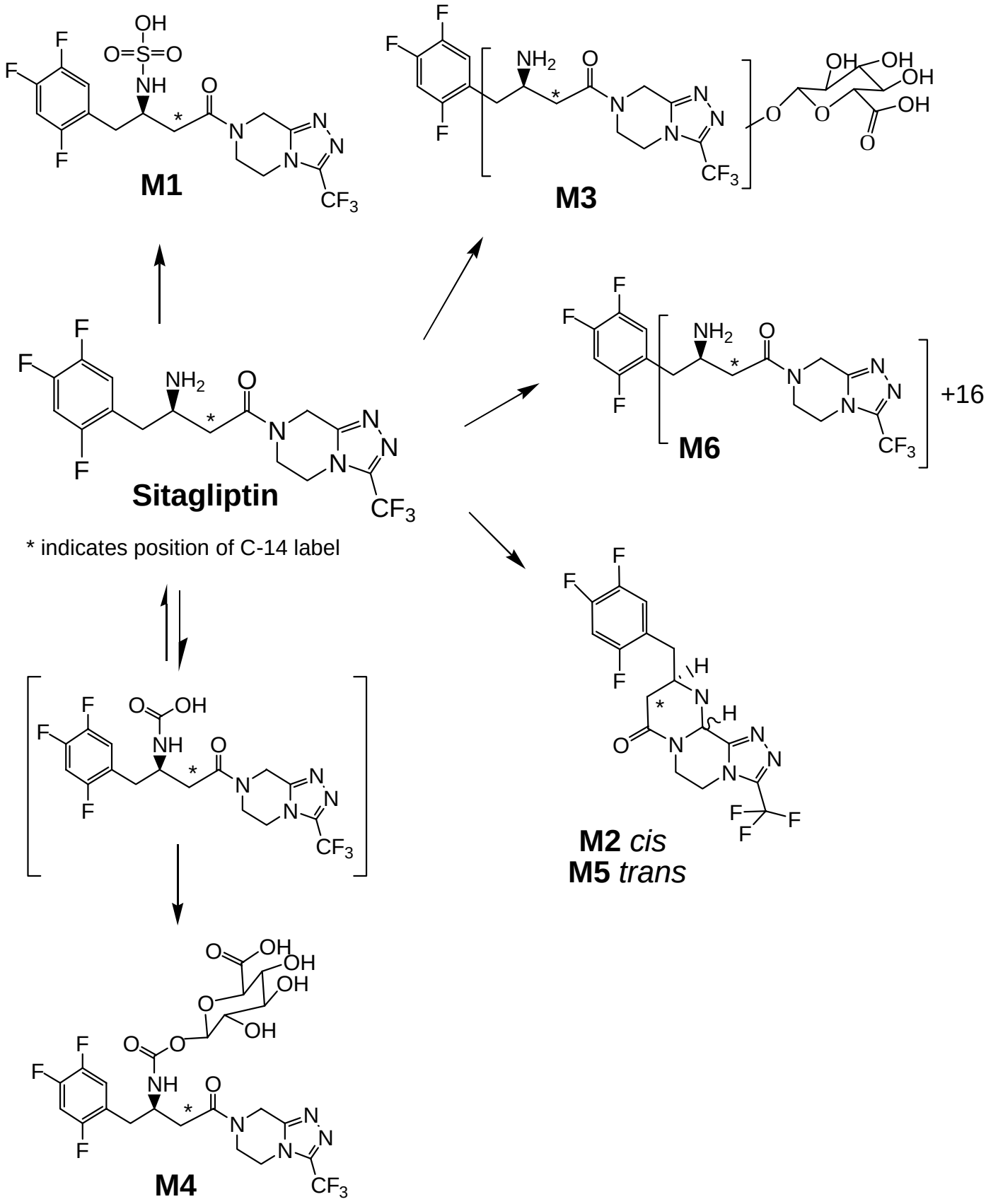

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Fig. 2

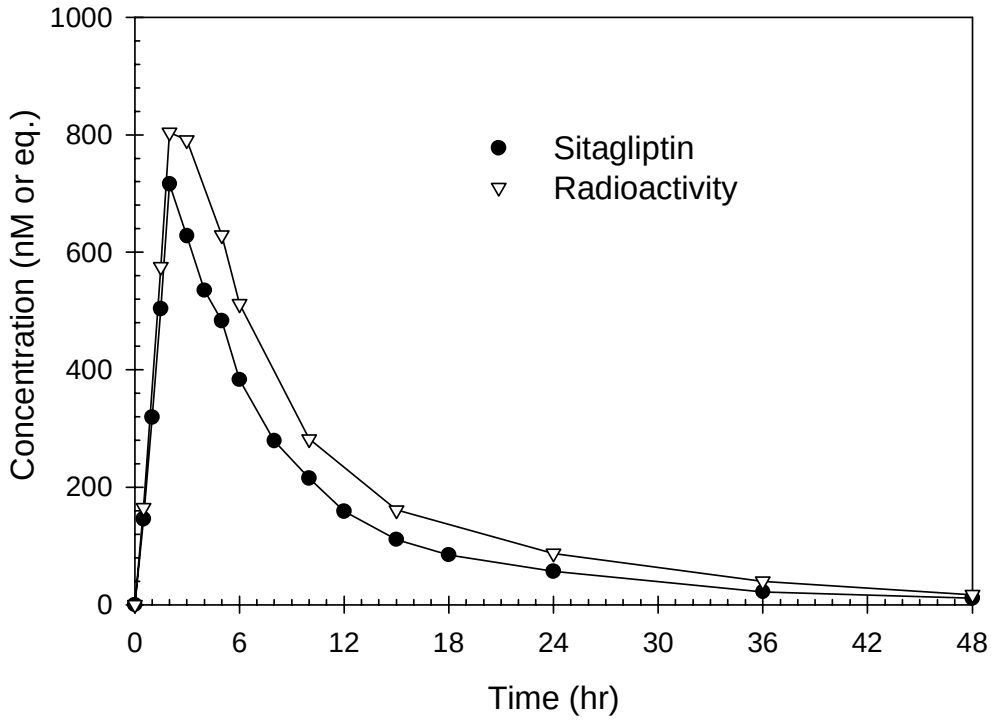

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Fig. 3

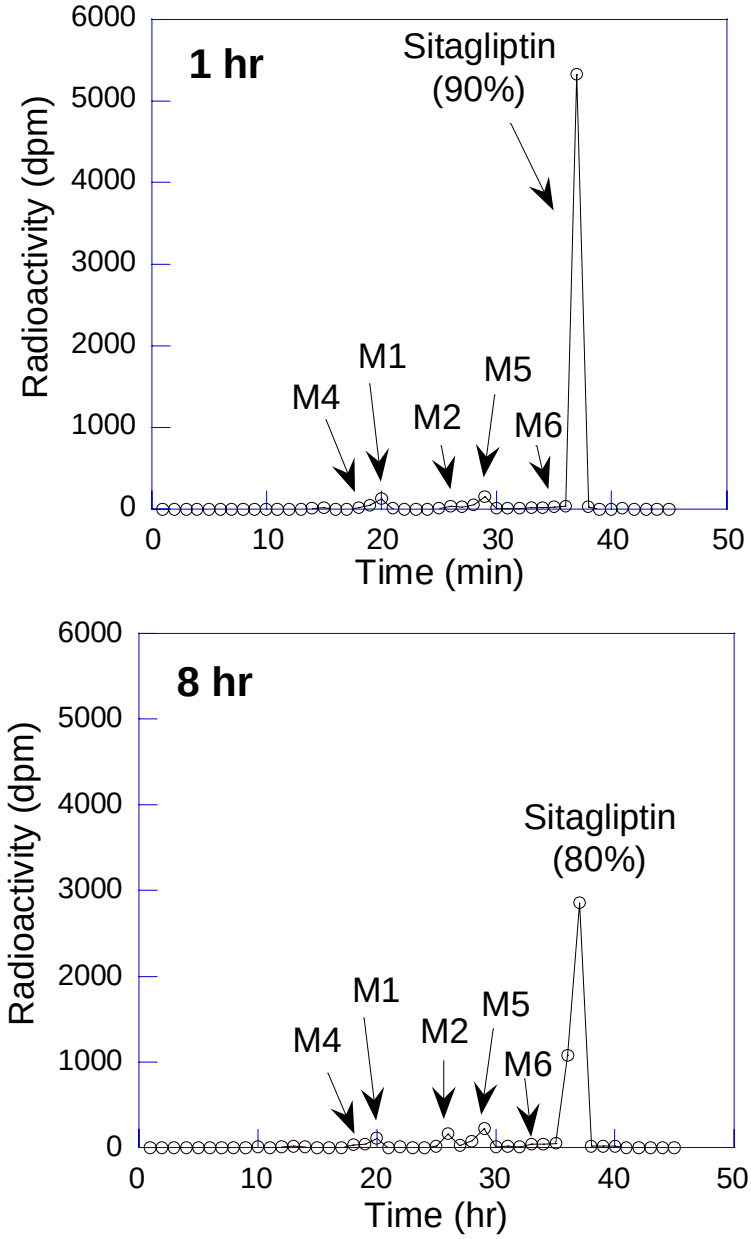

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Fig. 4