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Pharmacokinetics and Distribution of [^{35}S]Methylsulfonylmethane following Oral Administration to Rats

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Methylsulfonylmethane (MSM) is a sulfur-containing compound found in a wide range of human foods including fruits, vegetables, grains, and beverages. More recently, it has been marketed as a dietary supplement worldwide. The objective of this study was to evaluate the pharmacokinetic profile and distribution of radiolabeled MSM in rats. Male Sprague−Dawley rats were administered a single oral dose of [^{35}S]MSM (500 mg/kg), and blood levels of radioactivity were determined at different time points for up to 48 h. Tissue levels of radioactivity at 48 and 120 h and urine and fecal radioactivity levels were measured at different time points for up to 120 h following [^{35}S]MSM administration to rats. Oral [^{35}S]MSM was rapidly and efficiently absorbed with a mean t_{max} of 2.1 h, C_{max} of 622 μg equiv/mL, and AUC_{0-inf} of 15124 h·μg equiv/mL. The $t_{1/2}$ was 12.2 h. Soft tissue distribution of radioactivity indicated a fairly homogeneous distribution throughout the body with relatively lower concentrations in skin and bone. Approximately 85.8% of the dose was recovered in the urine after 120 h, whereas only 3% was found in the feces. No quantifiable levels of radioactivity were found in any tissues after 120 h, indicating complete elimination of [^{35}S]MSM. The results of this study suggest that [^{35}S]MSM is rapidly absorbed, well distributed, and completely excreted from the body.

KEYWORDS: Methylsulfonylmethane; absorption; pharmacokinetics; distribution

INTRODUCTION

Methylsulfonylmethane (MSM) is an organic sulfur-containing compound that occurs naturally in a variety of fruits, vegetables, grains, animals, and humans, as well as certain species of algae. The most abundant source of MSM is cow's milk, which contains approximately 6.1−8.2 ppm of MSM (*1*). In recent years, MSM has been extensively used as a dietary supplement for its potential to improve human health and to reduce arthritic and rheumatic pain (*2*, *3*). Use of MSM as a cancer preventive agent (*4*, *5*) and treatment for seasonal allergies (*6*) has also been reported. The biological role and action of MSM remain to be fully explored (*7*, *8*). MSM is considered to be a bioactive compound and a source of sulfur for production of the sulfur-containing amino acids, cysteine and methionine (*8*, *9*). The overall goal of our ongoing research is to further the understanding of the bioactivity and safety of MSM. As the available information on pharmacokinetics of MSM is incomplete, the objective of the present study was to further investigate the fate of orally consumed MSM.

Human and animal tissue concentrations of MSM have been reported. In plasma and cerebrospinal fluid from healthy individuals, the concentration of MSM ranged between 0 and 25 μmol/L (*10*, *11*). MSM has also been detected by magnetic resonance spectroscopy in brain tissues of individuals consuming MSM supplements but not in humans not consuming MSM, suggesting that MSM can cross the blood−brain barrier (*12*−*14*). By employing a GC-MS technique, Imanaka et al. (*15*) identified the presence of MSM in cow's milk and in chicken meat and liver. Approximately 5−10 mg of MSM is normally excreted in human urine every day (*1*). MSM was also recently identified in the urine of cheetahs (*16*).

Otsuki et al. (*17*) investigated the distribution of oral MSM using a ^{35}S radioisotope tracer method in rats of different ages fed standardized diets. [^{35}S]MSM was administered daily for 7 days by gavage at a dose level of 470 mg/kg/day. Urine and feces were collected daily for 7 days, and at the end of dosing, tissues were collected for the determination of radioactivity. Levels of radioactivity tended to be highest in blood, spleen, and hair. The majority of the ^{35}S radioactivity was excreted into the urine (∼70%) and feces (∼10%), but not all of the radioactivity was recovered. Therefore, as there is little available information on the pharmacokinetics of MSM, the objective of the present study was to investigate the pharmacokinetics, distribution, and excretion of [^{35}S]MSM in rats. We report that

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Table 1. Protocol for the Pharmacokinetic Study of MSM in Rats

collection group	matrix	*N*	collection times	route	dose (mg/kg)	dose volume (mL/kg)
1	blood	5	0, 15, and 30 min; 1, 2, 4, 8, 12, 24, and 48 h	oral	500	5
	tissues	3[a]	48 h			
2	urine/feces	3	−24 to 0, 0–24, 24–48, 48–72, 72–96, and 96–120 h	oral	500	5
	tissues	3[a]	120 h			

[a] Three rats each from collection group were used for collection of tissues at the specified times; *N* = number of rats.

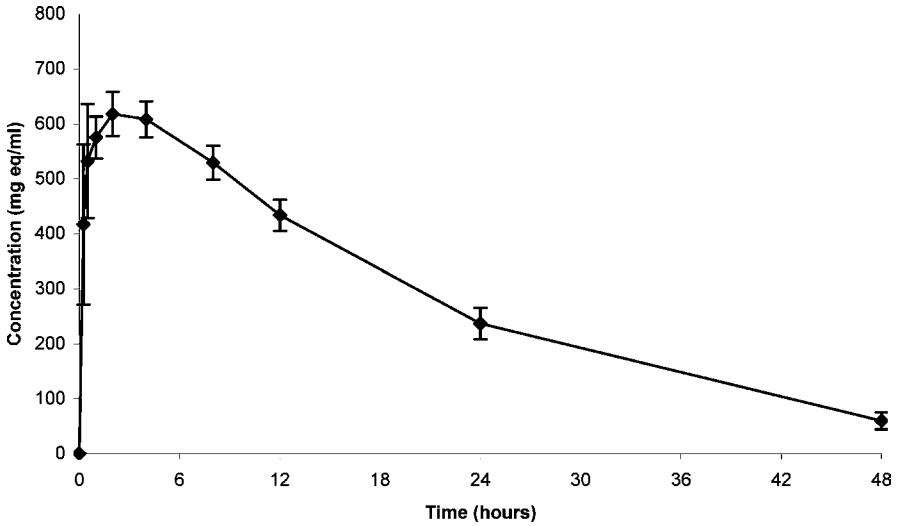

Figure 1. Blood concentrations of ^{35}S in male Sprague–Dawley rats following administration of a single oral dose of [^{35}S]MSM. At 0, 15, and 30 min and 1, 2, 4, 8, 12, 24, and 48 h following MSM administration, blood samples were collected and processed for radioactivity determination. Values are presented as mean ± SD.

Table 2. Pharmacokinetic Parameters of Total Radioactivity following [^{35}S]MSM Administration to Rats[a]

parameter	units	mean ± SD
dose	mg/kg	583 ± 11
C_{max}	μg equiv/mL	622 ± 37
C_{max}/D	kg μg equiv/mL/mg	1.07 ± 0.06
t_{max}	h	2.1 ± 1.2
$AUC_{(0-48)}$	h μg equiv/mL	14052 ± 835
$AUC_{(0-48)}/D$	h kg μg equiv/mL/mg	24.1 ± 1.0
$AUC_{(0-inf)}$	h μg equiv/mL	15124 ± 1082
$AUC_{(0-inf)}/D$	h kg μg equiv/mL/mg	25.9 ± 1.4
kel	1/h	0.0575 ± 0.0069
$t_{1/2}$	h	12.2 ± 1.4
CL/*F*	mL/h/kg	38.7 ± 2.2

[a] AUC, area under the plasma concentration–time curve; CL/F, clearance divided by the fraction of dose absorbed; C_{max}, maximum observed plasma concentration; *D*, dose; kel, elimination rate constant; $t_{1/2}$, half-life of terminal phase; t_{max}, time of C_{max}.

MSM is rapidly and efficiently absorbed into the bloodstream, reaching maximum blood concentrations within 2 h after dosing. MSM radioactivity is distributed fairly homogeneously in soft tissues, is undetectable in tissues after 120 h, and is eliminated via the urine and feces in rats given an oral dose of 500 mg/kg. These data support the overall evidence for the safety in use of oral MSM.

MATERIALS AND METHODS

Test Animals. Eight male Sprague−Dawley rats approximately 7−8 weeks old were obtained from Taconic Farms (Germantown, NY). Animals were acclimatized for >1 week, prior to dose initiation. Animals were fasted overnight and for approximately 4 h postdose and were provided water ad libitum. After dosing, Harlan Teklad Certified Rodent Diet 8728C was supplied ad libitum to each rat. The study was conducted in accordance with U.S. FDA Good Laboratory Practice Regulations as set forth in 21 CFR 58.

Test Materials. The MSM used in this study was OptiMSM distilled microprill provided by Cardinal Nutrition, Inc. (Vancouver, WA). Labeled [^{35}S]MSM was prepared by Perkin-Elmer Life Sciences (Boston, MA) as an aqueous solution (5 mCi/mL, 500 mCi/mmol). The dose solution (100 mg/mL; 30 μCi/mL) was prepared by adding appropriate amounts of radiolabeled [^{35}S]MSM and unlabeled MSM.

Experimental Design. Each rat received a single oral (gavage) dose of [^{35}S]MSM formulation at 5 mL/kg to deliver approximately 500 mg/kg MSM and 50 μCi/rat. The dose represented 3 times the maximum reported dose in humans of 182 mg/kg (*14*) and approximately 5 times the dose of 6000 mg/day used in adults in a recent clinical study (*2*). Five rats were designated group 1 (blood group), and three rats were designated group 2 (urine and feces group). Samples of blood were collected at 0, 15, and 30 min and 1, 2, 4, 8, 12, 24, and 48 h from group 1. Tissues were collected from group 1 and 2 animals after 48 and 120 h, respectively. Urine and feces were collected during the following time intervals: −24 to 0 (prestudy initiation), 0−24, 24−48, 48−72, 72−96, and 96−120 h after dosing. The protocol is summarized in **Table 1**.

Blood Collection. Approximately 0.25−0.30 mL of whole blood was collected via venipuncture from the jugular vein into syringes containing heparin at 0 (predose) and the specified times postdose administration of MSM. Approximately 2 mL of blood was collected via the abdominal aorta from animals at the 48 h collection time, immediately prior to the harvesting of tissues. All blood samples were stored at approximately −70 °C until analyzed for total ^{35}S radioactivity concentrations.

Tissue Collection. Three animals from group 1 were euthanized after the blood collection at 48 h postdose and three animals from group 2 at 120 h postdose using CO_2. The following tissues were collected for radioactivity determinations: liver, heart, kidneys, spleen, brain, testes, eyes, scapular skin (shaved), and knee joints (bone and cartilage). The same tissues were collected from three untreated control animals

Table 3. Tissue Concentrations of Radioactivity and Tissue/Blood Ratios following [^{35}S]MSM Administration to Rats

		concentration[a] (μg equiv/g)		tissue/blood ratio	
tissue	*N*	48 h	120 h	48 h	120 h
blood[b]	3	63.7 ± 12.3	N/A	N/A	N/A
liver	3	54.7 ± 11.4	BLQ	0.856	N/A
heart	3	59.4 ± 11.7	BLQ	0.932	N/A
kidney	3	71.1 ± 15.7	BLQ	1.11	N/A
spleen	3	58.2 ± 14.4	BLQ	0.909	N/A
testes	3	69.4 ± 16.2	BLQ	1.08	N/A
brain	3	58.7 ± 11.8	BLQ	0.921	N/A
eye	3	66.7 ± 12.9	BLQ	1.05	N/A
skin	3	51.8 ± 13.7	BLQ	0.807	N/A
bone	3	35.2 ± 0.9	BLQ	0.563	N/A

[a] Values are expressed as means ± SD. BLQ, below the limit of quantification; *N*, number; N/A, not applicable. [b] This mean blood concentration uses only the same three animals utilized for tissue analysis.

as matrix blanks for background determination during total radioactivity analysis. The tissue samples were stored at approximately −70 °C until analysis.

Urine and Feces Collection. Urine and fecal samples were collected at daily intervals of −24 to 0 (matrix controls used for radioactive background determination), 0−24, 24−48, 48−72, 72−96, and 96−120 h after dose administration. The samples (urine and feces) were stored at −20 °C or lower until analysis. The cages (pan and mesh floor) were rinsed with deionized water after the end of the collection period, and the rinsewater was collected for analysis. The cage contents (mostly ground food) were also collected and stored for future analysis.

Blood Analysis. Whole blood samples were analyzed by digestion and liquid scintillation counting according to the method of Thompson (*18*). The samples were thawed and mixed, and a 100 μL aliquot of each was placed in a scintillation vial with 1 mL of Soluene-350/isopropyl alcohol (1:1, v/v, Perkin-Elmer), swirled, and processed for determination of radioactivity following treatment with hydrogen peroxide (Fisher Chemicals, Fair Lawn, NJ) and Ultima Gold (Perkin-Elmer) scintillation cocktail. Samples were counted for ^{35}S using a Beckman LS6500 (Beckman Coulter, Fullerton, CA) with internal quench correction.

Urine, Cage Wash, and Cage Contents Analysis. Urine samples were thawed, and the total volume in each sample was measured using a graduated cylinder and recorded. Duplicate 200 μL aliquots of each sample were combined with 15 mL of Ultima Gold and counted directly by LSC for ^{35}S radioactivity. The concentration and volume were used to calculate the total percent of the dose recovered for each interval. Similarly, cage washes were thawed, the volume was measured, the samples were counted by LSC, and the percent of dose recovered was calculated in the same manner as for urine samples. Cage contents were extracted twice with deionized water and centrifuged, the extract was decanted, and the volume was measured. Duplicate 200 μL aliquots of each extract were counted with 15 mL of Ultima Gold for ^{35}S. The total recovery for both extracts was summed to calculate the percent of dose recovered.

Fecal Analysis. Fecal samples were thawed and homogenized in 5 volumes of deionized water using a Polytron tissue grinder (Kinematica, Newark, NJ). Approximately 0.5 g of each homogenate was weighed into separate scintillation vials in duplicate, and 1 mL of sodium hypochlorite (Clorox bleach) was added to each sample with swirling. The samples were capped and heated in a 60 °C oven for approximately 1 h and allowed to cool for 30 min, followed by the addition of 15 mL of Hionic Fluor scintillation cocktail (Perkin-Elmer). Samples were allowed to light adjust overnight prior to counting by LSC (at 5 min each) for total ^{35}S radioactivity with appropriate half-life correction.

Tissue Analysis. Soft tissues (liver, heart, kidney, spleen, brain, and testes) were all analyzed for radioactivity after digestion. The tissues were thawed and homogenized in deionized water (3−5× w/w) using a Polytron tissue grinder. Approximately 0.5 g of each homogenate was digested by adding 1 mL of Solvable (Perkin-Elmer) and heating in a 60 °C oven for approximately 2 h. Eye and skin samples were diced with fine scissors and digested without homogenization. The samples were allowed to cool, and 0.2 mL of hydrogen peroxide was added (with swirling) for decolorizing, followed by an additional 30 min at 60 °C. Samples were allowed to cool, 15 mL of Hionic Fluor was added, and radioactivity was measured after 24 h.

Bone samples were digested by using the method of "wet oxidation". Bone samples were allowed to thaw, and the knee joint of each sample was separated using scissors. The head (condyle region) of one bone was cut off and cut into smaller pieces; approximately 100 mg of each sample was placed into poly-cone scintillation vials. A nitric/perchloric acid (1:1, v/v) mixture (0.6 mL, Daigger Chemicals, Vernon Hills, IL/Fisher Chemicals, Fair Lawn, NJ) was added to each sample and heated at 60 °C for approximately 1 h. The samples were cooled, and 21 mL of Hionic Fluor was added to each sample before counting by LSC for total ^{35}S at 5 min per sample using the appropriate half-life correction program. All tissue homogenates were analyzed in duplicate, except for eyes and bone, in which the right and left served as duplicates for each animal.

Data Analysis. Mean and standard deviation calculations were performed using Excel Office XP (Microsoft, Redmond, WA). Pharmacokinetic analysis of the total ^{35}S blood concentration−time data was calculated by noncompartmental analyses using WinNonlin, version 4.1. (Pharsight Corp., Mountain View, CA).

RESULTS

Blood Concentrations of MSM. Oral administration of [^{35}S]-MSM to rats resulted in the rapid appearance of substantial blood concentrations of ^{35}S at the first time point of 15 min postdose and quantifiable concentrations at all time points up to 48 h (**Figure 1**). Radiolabel concentrations remained close to peak levels for 8 h following dose administration (mean blood levels were >80% of the maximal concentration level from 0.5 to 8 h postdose). The peak mean blood concentration of 618 μg equiv/mL was achieved at 2 h following MSM administration. Significant blood concentrations of radioactivity (>70 times the quantifiable level of 0.816 μg equiv/mL) persisted through the 48 h time point. Examination of the blood concentrations versus time analysis from individual rats revealed that the blood concentration profile was very consistent from rat to rat (data not shown).

Pharmacokinetics Parameters. A summary of the key pharmacokinetic parameters of total ^{35}S in blood is presented in **Table 2**. OptiMSM was well absorbed on the basis of detection of [^{35}S]MSM with a mean maximum concentration (C_{max}) of 622 μg equiv/mL. Absorption was relatively rapid with a mean time to maximal concentration (t_{max}) of 2.1 h. The mean area under the curve from 0 to 48 h (AUC_{0-48}) was 14052 h·μg equiv/mL, and the mean AUC extrapolated to infinity (AUC_{0-inf}) was 15124 h·μg equiv/mL, which was only 7.6% higher than the AUC_{0-48}. Examination of the individual data and the standard deviations indicated that the pharmacokinetics of total ^{35}S were fairly consistent between the animals (data not shown).

Distribution of Radioactivity. Total radioactivity appeared to be widely distributed throughout the body, and measurable levels of total ^{35}S were found in all tissues analyzed at 48 h postdose (**Table 3**). The mean tissue concentrations observed in the soft tissues (liver, heart, kidneys, spleen, testes, brain, and eye) were fairly consistent, ranging from 54.7 to 71.1 μg equiv/g. The highest levels of radiolabel were found in kidney, testes, and eye. These values were comparable (±15%) to the blood concentration (63.7 μg equiv/g) found at the 48 h time point. Radioactivity levels in the skin (51.8 μg equiv/g) and bone (35.2 μg equiv/g) were lower than the ±15% range. No quantifiable levels of radioactivity (values greater than twice background; ranging from 0.76 to 2.43 μg equiv/g depending

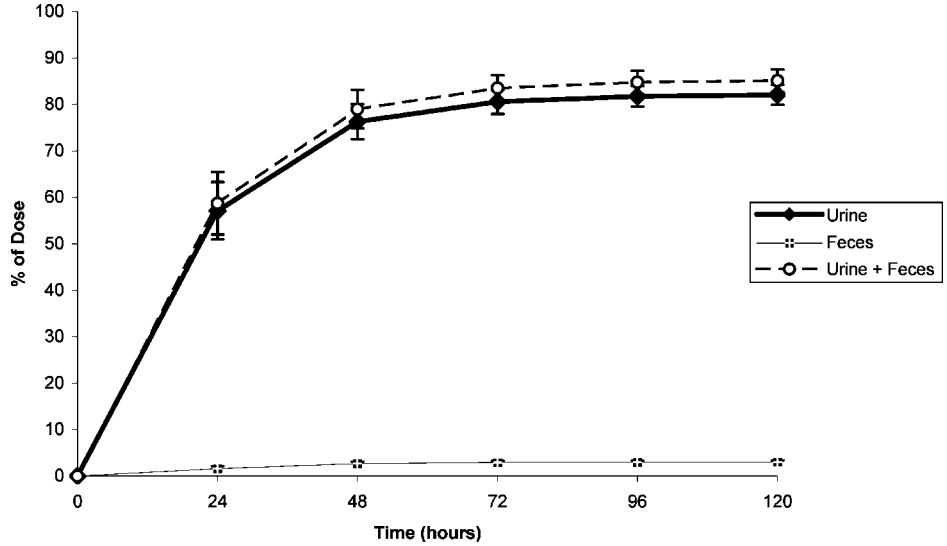

Figure 2. Cumulative percent of dose recovered in urine, feces, and urine + feces following MSM administration. Male Sprague–Dawley rats were administered a single oral dose of [^{35}S]MSM. At 24, 48, 72, 96, and 120 h following MSM administration, urine and feces samples were collected and processed for radioactivity determination. Values are presented as mean ± SD.

Table 4. Mean Individual and Cumulative Urine, Feces, and Urine + Feces Percent of [^{35}S]MSM Dose Recovered in Rats[a]

		urine (% of dose)		feces (% of dose)		urine + feces (% of dose)	
time (h)	*N*	individual	cumulative	individual	cumulative	Individual	cumulative
–24 to 0	3	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
0–24	3	57.1 ± 6.2	57.1 ± 6.2	1.6 ± 0.5	1.6 ± 0.5	58.7 ± 6.7	58.7 ± 6.7
24–48	3	19.2 ± 3.9	76.3 ± 3.8	1.1 ± 0.4	2.7 ± 0.4	20.3 ± 4.4	79.0 ± 4.1
48–72	3	4.3 ± 1.3	80.7 ± 2.6	0.2 ± 0.0	2.9 ± 0.3	4.5 ± 1.3	83.5 ± 2.8
72–96	3	1.2 ± 0.3	81.8 ± 2.2	0.1 ± 0.0	3.0 ± 0.3	1.3 ± 0.3	84.7 ± 2.5
96–120	3	0.3 ± 0.1	82.1 ± 2.2	0.0 ± 0.0	3.0 ± 0.3	0.44 ± 0.1	85.1 ± 2.4
cage wash	2	0.2 ± 0.0	82.2 ± 2.3	N/A	N/A	0.2 ± 0.0	85.2 ± 2.5
cage contents	3	3.6 ± 3.0	85.8 ± 4.8	N/A	N/A	3.6 ± 3.0	88.9 ± 5.1
total			85.8 ± 4.8		3.0 ± 0.3		88.9 ± 5.1

[a] Values are expressed as means ± SD; BLQ, below the limit of quantification; *N*, number; N/A, not applicable.

on the tissue) were found in any of the tissues analyzed at the 120 h time point, suggesting that all radioactivity was eliminated by 120 h.

Excretion in Urine and Feces. Following a single administration of [^{35}S]MSM, the majority of the radioactivity (85.8%) was excreted in the urine (**Table 4**). Only a relatively minor amount of the radioactive dose (3.03%) was excreted in the feces. The majority of the radioactivity (58.7%) was excreted within the first 24 h, with 79.0% excreted by 48 h on the basis of radioactivity in urine and feces. Less than 1% of the radioactivity was found in the cage wash (**Table 4**). Approximately 4% of the radioactivity was recovered from the cage contents; this was most likely residual urine absorbed into ground feed in the pan and so was included with the urinary excretion data. The overall recovery of total radioactivity from urine and feces was 88.9% of the administered radioactive dose. The cumulative percents of dose (±SD) excreted in urine, feces, and urine + feces are given in **Figure 2**.

DISCUSSION

The results from the present study suggest that MSM is rapidly absorbed and distributed throughout the body following oral administration of a dose of 500 mg/kg of body weight in rats. The majority of the radioactivity (~57%) was excreted in the urine within 24 h. Given the high water solubility of MSM (*19*), a rapid excretion is expected. The results of the present study are similar to those of Hucker et al. (*20*), who reported excretion of ~64% of a dose of [^{35}S]MSM (21 mg/kg) to rats within 24 h following intraperitoneal administration. Although the data were not shown, Richmond (*9*) reported that most of the radioactivity from single oral doses of [^{35}S]MSM ranging from 2 to 200 mg/kg (0.4% radiolabel) was excreted in the urine in male guinea pigs after 24 h. On the basis of previous reports of excretion of MSM in the urine of humans (*1*) and cheetahs (*16*), it is likely that the radioactivity detected in the urine in this study was from unmetabolized MSM, but only total radioactivity was measured.

The radioactivity was distributed evenly over the range of tissues in rats in this study, indicating that MSM or its metabolites permeated all tissues. The tissue concentrations of radioactivity appeared to follow blood concentrations, which is also reasonable considering the high water solubility of MSM and high blood perfusion in these tissues. As a result, the tissue/blood ratios (tissue concentration/blood concentration) for these soft tissues (**Table 4**) are close to unity, ranging from 0.856 to 1.11. The low levels of radioactivity detected in tissues such as skin and bone could be explained by the more lipophilic nature of skin and lower water content in bone.

It should be noted that in the present study, elimination of total ^{35}S was measured and not the elimination of MSM. The ^{35}S half-life in blood of approximately 12 h from MSM indicates that approximately 75% of the radioactivity from MSM is cleared in 24 h, and almost complete elimination of radiolabel

is expected by 60 h (5 half-lives). The results of the present study indicate that no radioactivity was detected in tissues at 120 h and support the rapid elimination kinetics of MSM. The fact that the administered radioactivity may remain in the animal body for longer periods does not mean it is present as MSM. There are many opportunities for sulfur to incorporate into biological molecules, especially when the animal feed has low sulfur content. Studies have demonstrated that sulfur from MSM can be incorporated into tissue proteins (*9*, *17*).

A previous repeat dose study performed by Otsuki et al. (*17*) investigated the distribution and elimination of MSM in rats using a ^{35}S radioisotope tracer method. In that study, male Wistar rats were fed standardized diets for 2, 43, 83, and 96 days, followed by a daily gavage administration of [^{35}S]MSM at a dose level of 470 mg/kg/day for 7 days. The majority of the daily administered ^{35}S was excreted in the urine (70%) and feces (10%), with excretion rates being fairly level over 7 days, indicating a high excretion rate. The total radioactivity yield in the urine, feces, and tissues for the treatments after 2, 43, 83, and 96 days on the diet were 100.6, 94.9, 89.4, and 68.5%, respectively. These results indicate that total radioactivity in urine, feces, and tissues was greater in younger rats or groups fed standardized diet for shorter periods of time compared to those fed for longer periods. In rats fed standardized diets for longer duration and treated with [^{35}S]MSM, the remaining amount of radioactivity was not accounted for, and the investigators did not comment on this.

Similar to the present study, Otsuki et al. (*17*) also reported an almost even tissue distribution of radioactivity following the administration of [^{35}S]MSM. Relatively high levels of ^{35}S were noted in blood, spleen, and hair tissues, compared to other tissues. In the present study, the concentrations of radioactivity were similar in all soft tissues studied. The relatively higher concentrations in blood, spleen, and hair in the Otsuki et al. (*17*) study may be due to the repeat dose administration of MSM. The high uptake in the spleen following a repeat dose administration may be attributed to the spleen's function as a blood filtering, purifying, and storing organ. It is also possible that MSM might have been metabolized to yield sulfur-containing proteins such as keratin, a component of hair, increasing the sulfur content in the hair.

Richmond (*9*) also reported that administration of [^{35}S]MSM to guinea pigs resulted in incorporation of radiolabel into serum proteins, particularly in the amino acids methionine and cysteine. These observations also indicate that the partial elimination of radiolabel (~59%) by 24 h in the present study may be partly because of the incorporation of ^{35}S from MSM into proteins that may have a half-life of >1 day. For example, proteins with N-terminal methionine, serine, alanine, threonine, valine, or glycine have half-lives of >20 h (*21*). However, radioactivity was undetectable in all tissues tested at 120 h postdose, suggesting complete elimination of [^{35}S]MSM when given as a single dose. Thus, it is likely that chronic administration of MSM would be needed for demonstrable health benefits in chronic conditions as has been reported for relief of arthritic and rheumatic pain (*2*, *3*),

In summary, the results from the present study provide new information on the pharmacokinetic parameters of orally administered MSM and suggest that MSM is rapidly absorbed, well distributed throughout the body, and quickly eliminated primarily through the urine. No evidence of accumulation in specific tissues was noted. These results support the growing body of evidence of safety in the use of MSM as a dietary supplement as the dose used in the study was at least 3 times higher than the highest reported dose, yet was efficiently and quickly eliminated. The rapid elimination of MSM suggests that repeated administration of MSM may be needed to maintain tissue levels and provide demonstrable effects on chronic health conditions. Therefore, additional studies on the safety of chronic administration of oral MSM are in progress.

ABBREVIATIONS USED

MSM, methylsulfonylmethane; AUC, area under the curve; CFR, *U.S. Code of Federal Regulations*; GC-MS, gas chromatography−mass spectrophotometry; BLQ, below the limit of quantification; C_{max}, maximum observed plasma concentration; LSC, liquid scintillation counting; t_{max}, time of C_{max}; N/A, not applicable; $t_{1/2}$, half-life.

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