

## A Randomized Prospective Comparative Pharmacokinetic and Pharmacodynamic Dose-Escalation Study of Oral Methylsulfonylmethane in Healthy Male Volunteers

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### Abstract

The purpose of this study was to characterize pharmacokinetics of 3 doses of Methylsulfonylmethane (MSM). Six males received a dose of 1, 2, 3 grams of OptiMSM<sup>®</sup>. Blood was tested at 0, 45, 90, 135, 180 and 240 minutes post.  $C_{Max}$  (1 gm =  $100 \pm 36$  uM/ml, 2 gm dose =  $152 \pm 51$  uM/ml, 3 gm =  $202 \pm 52$  uM/ml).  $t_{Max}$  1 gm =  $68 \pm 25$  min, 2 gm =  $90 \pm 49$  minutes and 3 gm =  $115 \pm 73$  minutes. The four-hour AUC score was 1 gm =  $346 \pm 141$  uM/ml\*hours, 2 gm =  $496 \pm 170$  uM/ml\*hours and 3 gm =  $653 \pm 135$  uM/ml\*hours. 24 hour urinary excretion was 1 gm =  $116 \pm 74$  mM, 2 gm =  $164 \pm 81$  mM, and 3 gm =  $140 \pm 173$  mM. MSM had a dose effect for MSM concentrations, by the  $C_{Max}$  value and AUC score but not  $t_{Max}$ , the 24-hour urinary excretion shows no dose dependence. The impacts on sulfate was  $C_{Max}$  1 gm =  $344 \pm 53$ , 2 gm =  $333 \pm 62$  and 3 gm =  $354 \pm 60$  uM/L, the  $t_{Max}$  for 1 gm =  $38 \pm 53$  minutes, 2 gm =  $60 \pm 79$  minutes and 3 gm =  $40 \pm 98$  minutes, with the AUC score of 1 gm =  $1286 \pm 207$  uM/L\*hours, 2 gm =  $1219 \pm 244$  uM/L\*hours, and 3 gm =  $1293 \pm 219$  uM/L\*hours. 24 hour urinary sulfate values were 1 gm =  $57 \pm 53$  uM, 2 gm =  $40 \pm 36$  uM and 3 gm =  $29 \pm 43$  uM. No sulfate PK parameters were dose-dependent. MSM absorption appears to be dose-dependent with rapid uptake with less predictable impacts on sulfate metabolism.

**Keywords:** Pharmacokinetic; Pharmacodynamic; Methylsulfonylmethane; Sulfate; Osteoarthritis; Supplement

### Abbreviations

MSM: Methylsulfonylmethane; GRAS: Generally Recognized as Safe; OA: Osteoarthritis; RONS: Reactive Oxygen and Nitrogen Species; TAC: Total Antioxidant Capacity; CK: Creatine Kinase; KOOS: Knee Osteoarthritis Outcome Score; POMS: Profile of Moods States; PK: Pharmacokinetic; PD: Pharmacodynamic;  $C_{Max}$ : Maximum Concentration;  $t_{Max}$ : Time to Maximum Concentration; AUC: Area Under the Curve; BW: Body Weight; (AUCBL): AUC of MSM Above Baseline; VD: Volume of Distribution

### Introduction

Methylsulfonylmethane (MSM) is composed of sulfur, oxygen, and methyl groups [1]. MSM is naturally found in a variety of foods, such as milk, fruits, tomatoes, corn, coffee, and tea [2]. Because the amount found in foods can significantly decrease during processing, there has been increased interest in the usefulness or utility of supplementing the diet with MSM. OptiMSM<sup>®</sup> is one such commercial MSM product sold in the marketplace. OptiMSM<sup>®</sup> is a branded form of MSM manufactured by Bergstrom Nutrition and is Generally Recognized as Safe (GRAS) [3]. Earlier pharmacokinetic and metabolic research with oral MSM demonstrates it is rapidly absorbed, well distributed and completely excreted from the body [4].

The pharmacodynamics and impacts of MSM as related to dose are not yet well-defined. However, MSM is sold on the commercial dietary supplement market and often utilized or promoted for joint health. Research has suggested that MSM, alone or along with glucosamine, reduces osteoarthritis (OA) related pain, swelling, and improves function [5-8]. Improved function includes quality of life scores [5-8]. This improved quality of life may be explained by results of animal studies that have demonstrated that sulfur-depleted joints affected by OA showed signs of decreased joint degeneration when supplemented with MSM, perhaps due to the abundance of sulfur found in MSM [9,10]. In a study performed on mice, pretreatment with MSM doses of 200 and 400 mg/kg significantly decreased ethanol/HCl-induced increase in NF- $\kappa$ B mRNA expression, a key regulator of inflammation in gastric mucosa [11]. The decrease in severity of ethanol/HCl-induced gastric mucosal injury upon supplementation of MSM has been explained by the inhibition of oxidative stress and inflammation (anti-oxidant and anti-inflammatory activity), which may be of interest to prevent peptic ulcer disease as well as other gastrointestinal disorders [11]. MSM may also be effective in suppressing seasonal allergic rhinitis, interstitial cystitis, autoimmune diseases, and supporting cancer chemoprevention [12].

*In vivo* studies have shown it has an antioxidative effect by reducing the production of reactive oxygen and nitrogen species (RONS) [13]. MSM supplementation may reduce exercise-induced oxidative stress and muscle damage in humans. In untrained males, supplementation of 50 mg/kg/day reduced markers of oxidative stress after an acute bout of exercise, when compared to placebo [14], and also increased the total antioxidant capacity (TAC) and reduced creatine kinase (CK), a marker of muscle damage and bilirubin levels (an antioxidant substrate, a surrogate marker of oxidative stress) after exhaustive exercise compared to placebo [15]. Another study reported reduced muscle soreness and fatigue and increased antioxidant activity in moderately-trained men with an increased MSM dose of 3.0 g/day [16]. Similarly, MSM has been shown to decrease inflammatory molecules in response to strenuous exercise [17]. When physically active men were supplemented with either placebo or MSM (3 g/day), MSM not only dampened IL-1 $\beta$  and IL-6 in response to an intense bout of exercise (suggesting that MSM works as an antioxidant) but also increased IL-10 levels in response to exercise [17]. As IL-10 is increased in response to exercised-induced muscle damage and acts as an anti-inflammatory mediator by downregulating proinflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ , supplementation with MSM reflects anti-inflammatory mechanisms [17]. However, supplementation of 3 g/day of MSM over 8 weeks in active individuals performing high impact activities, did not show significant improvements in Knee Osteoarthritis Outcome Score (KOOS) and the Profile of Moods States (POMS) compared to placebo [18]. The conflicting literature indicates the need for further research. Therefore, the proposed mechanisms of action for MSM are most likely related to its anti-inflammatory [19] and anti-oxidative activity [13]. Dosages of MSM between 1.5 and 6 g/day taken for several weeks to months have been used in human clinical studies with no significant adverse events reported [5,6,20].

## **Materials and Methods**

This was a prospective, randomized, open-label, crossover, pharmacokinetic trial. The purpose of this study was to investigate the pharmacokinetic (PK) and pharmacodynamic (PD) behavior of MSM along with impacts on sulfate following a single oral dose of 1, 2 or 3 grams of OptiMSM<sup>®</sup> in healthy male volunteers. The primary objective of this dose-escalation study was to assess the PK parameters of serum MSM, maximum concentration ( $C_{Max}$ ) and time to maximum concentration ( $t_{Max}$ ), rate of appearance, area under the curve (AUC, terminal elimination half-life) and urinary MSM excretion. Secondary objectives were to determine the effects of oral MSM on sulfate using the same PK parameters, if possible, and to correlate sulfate changes with MSM levels. The safety objective was to assess the effects of acute MSM (OptiMSM<sup>®</sup>) supplementation on blood pressure, heart rate, ECG, adverse events, and subjective remarks.

A total of six (6) participants were enrolled, with each subject receiving all three doses of OptiMSM<sup>®</sup> (branded and patented version of MSM) in a randomly-assigned sequence at three acute test visits spaced seven (7) days apart. Capsules contained 1g MSM. Dosing was 1g, 2g or 3g. Subjects were monitored for four hours post-dose, with PK/PD blood draws at 0, 45, 90, 135, 180 and 240 minutes post-dosing. Subjects also provided a 24-hour post-dose urine collection as part of each acute test visit.

All study procedures were executed after subjects signed an Informed Consent and the study executed under Good Clinical Practices consistent with the Declaration of Helsinki and the World Health Organization guidelines for human research. This study was approved by the Aspire IRB, July 28, 2008 [<http://aspire-irb.com>] and had the Study Code “MSM-2008”.

### Pharmacokinetic Analysis

Blood specimens were drawn on each testing visit, at six-time points (pre-dose, and 45, 90, 135, 180 and 240 minutes post-dose). A pooled 24-hour post-dose urine collection was also taken. Blood and urine specimens were analyzed for MSM and sulfate. Serum concentrations of MSM and sulfate were summarized descriptively and graphed by time point for each dosing level. Changes in concentration from baseline to each subsequent sampling time point were also calculated and graphed. Concentration as a function of time was summarized, graphed, and analyzed by compartmental and noncompartmental pharmacokinetic methods. These changes were adjusted where appropriate for body weight (serum concentrations and AUCs were scaled inversely according to body weight, to give the concentrations and AUCs that might have been expected for a 100 kg subject), and these quantities were summarized and graphed. Maximum concentration ( $C_{Max}$ ) and time to maximum concentration ( $t_{Max}$ ) were recorded, summarized and graphed by dosing level. When possible, the terminal elimination rate constant and half-life were estimated. Area under the curve from 0 to 4 hours (AUC<sub>0-4hr</sub>, or “AUC” was calculated by trapezoidal-rule integration of the concentration-vs-time curve for MSM, and sulfate. AUC above baseline and body-weight-scaled AUC above baseline was also calculated. All AUCs were summarized by dosing level and were graphed to illustrate the relationship to dose. An exploratory compartmental PK analysis of the MSM data was undertaken, in which a simple two-compartment (upper gastrointestinal tract and circulation) model, with first-order transfer from the upper gastrointestinal tract to the circulation, and first-order elimination from circulation, was fitted to the observed MSM concentrations. This permitted rough estimates of the two rate constants and half-times - one for absorption from the upper gastrointestinal tract, and one for terminal elimination from circulation, along with their standard errors. The dose-response behavior of these parameters was examined. The relationship between body weight (BW) and the AUC of MSM above baseline (AUCBL) was investigated. If MSM was quickly and uniformly distributed throughout the body, we would expect the AUCBL to be inversely proportional to BW:  $AUCBL \sim 1/BW$ . If the volume of distribution (VD) was directly proportional to total body weight, we would expect the same inverse proportionality. However, if VD varied with BW to some power law:  $VD \sim BW^h$ , then we would expect AUCBL to vary with BW according to  $AUCBL \sim BW^{-h}$ . Therefore, we tested for compliance with this model, for each of the three dose levels. We also evaluated an overall value of h across all three dose levels by a mixed-effects model. The data were examined for the presence of an order effect by plotting each subject’s baseline MSM concentration by chronological visit. This effect was tested for significance by a linear mixed-effects model (equivalent to a repeated-measures ANOVA). The effect of carry-over from one visit to the next was also examined by summarizing the baseline value for each visit by the dose level at the preceding visit. This effect was also tested for significance by a mixed-effects model.

### Pharmacodynamic Analysis

In addition to the pharmacokinetic analyses on serum sulfate, additional analyses were carried out to investigate the pharmacodynamic effect of MSM on sulfate itself:

- The change in Sulfate over the 4-hour post-dose period was calculated and tested
- For a significance, and for correlation with dose level;
- Overall MSM, Sulfate levels (as assessed by  $C_{Max}$  and AUC over BL) were tested for significant correlation; and
- The concentrations of Sulfate at specific time points were tested for correlation with the concentration of MSM at the corresponding time points;

All statistical analyses in this study were conducted at the 0.05 alpha level ( $p \leq 0.05$  was considered nominally significant). For this exploratory clinical trial, no adjustments for multiple comparisons were made. Each pharmacokinetic parameter was considered to be a distinct, independent endpoint of interest, and we were willing to incur a 5% chance of drawing a false inference regarding each of these endpoints. When interpreting p-values for other statistical comparisons performed on this data, the increased chance of random fluctuations leading to a conclusion of significance when no real effect was present needs to be taken into consideration.

## Results and Discussion

### Baseline study characteristics

This study enrolled six males aged  $42.5 \pm 17.5$  years, with a height of  $182.6 \pm 5.5$  cm, and a weight of  $90.1 \pm 18.3$  kg. Subjects also had mean glucose of  $100.2 \pm 17.7$  mg/dl, with renal function as denoted by blood urea nitrogen (BUN)  $17.7 \pm 6.7$  mg/dl and a creatinine of  $1.13 \pm 0.203$  mg/dl. In addition, mean baseline heart rate was  $62.0 \pm 10.5$  beats per minute with a systolic blood pressure of  $119. \pm 6.5$  mm Hg and diastolic blood pressure of  $75.7 \pm 6.0$  mm Hg. No adverse events were reported.

### Pharmacokinetic analysis

MSM concentration shows the expected rise-and the beginning of a decline, with larger doses producing higher MSM levels. Sulfate levels seem to decline, but not in a dose-dependent way (See figure 1). For more specific examination of the dose-dependent impact of oral MSM, please see table 1.

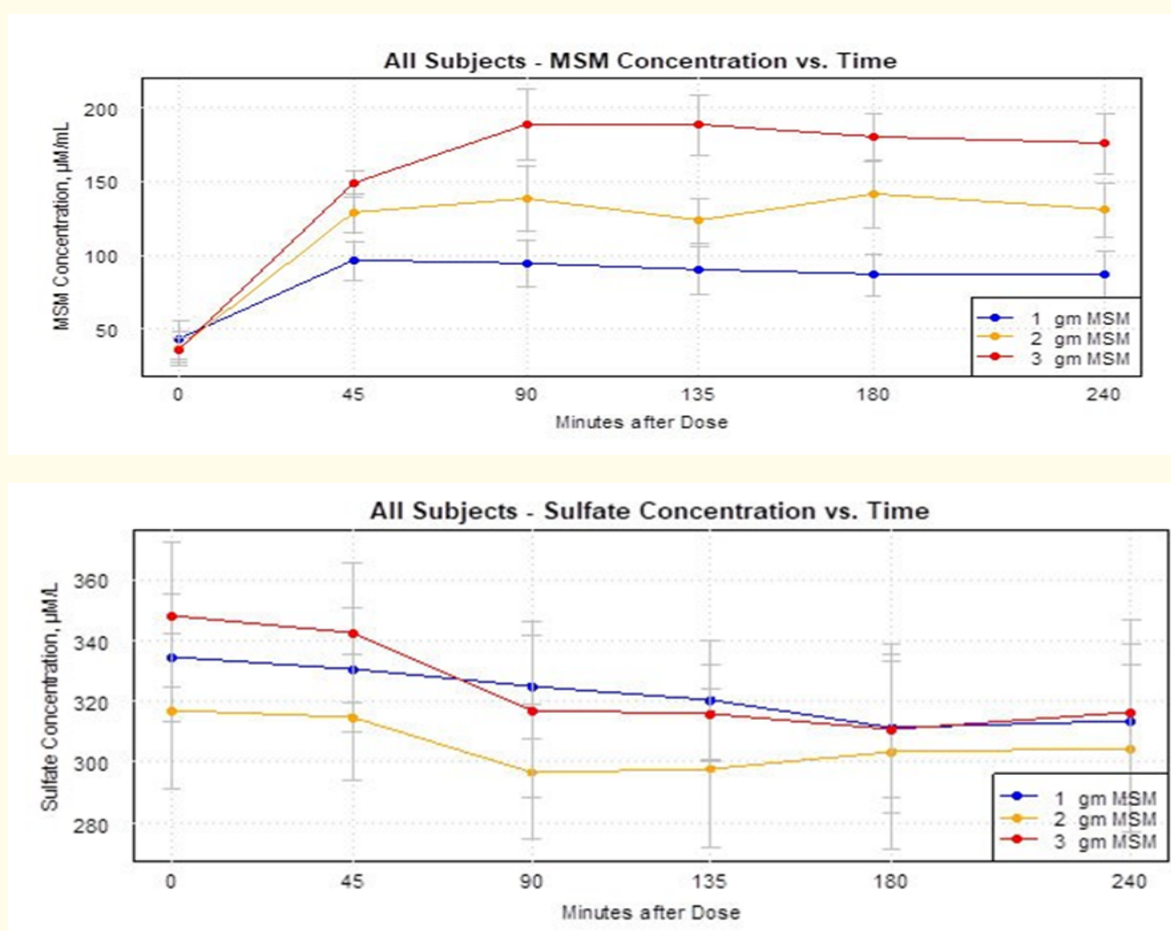


Figure 1: MSM, and sulfate concentration vs time average of all subjects for each dose.

MSM AUCs show clear dose-dependent behavior; Sulfate AUCs do not (see figure 2).

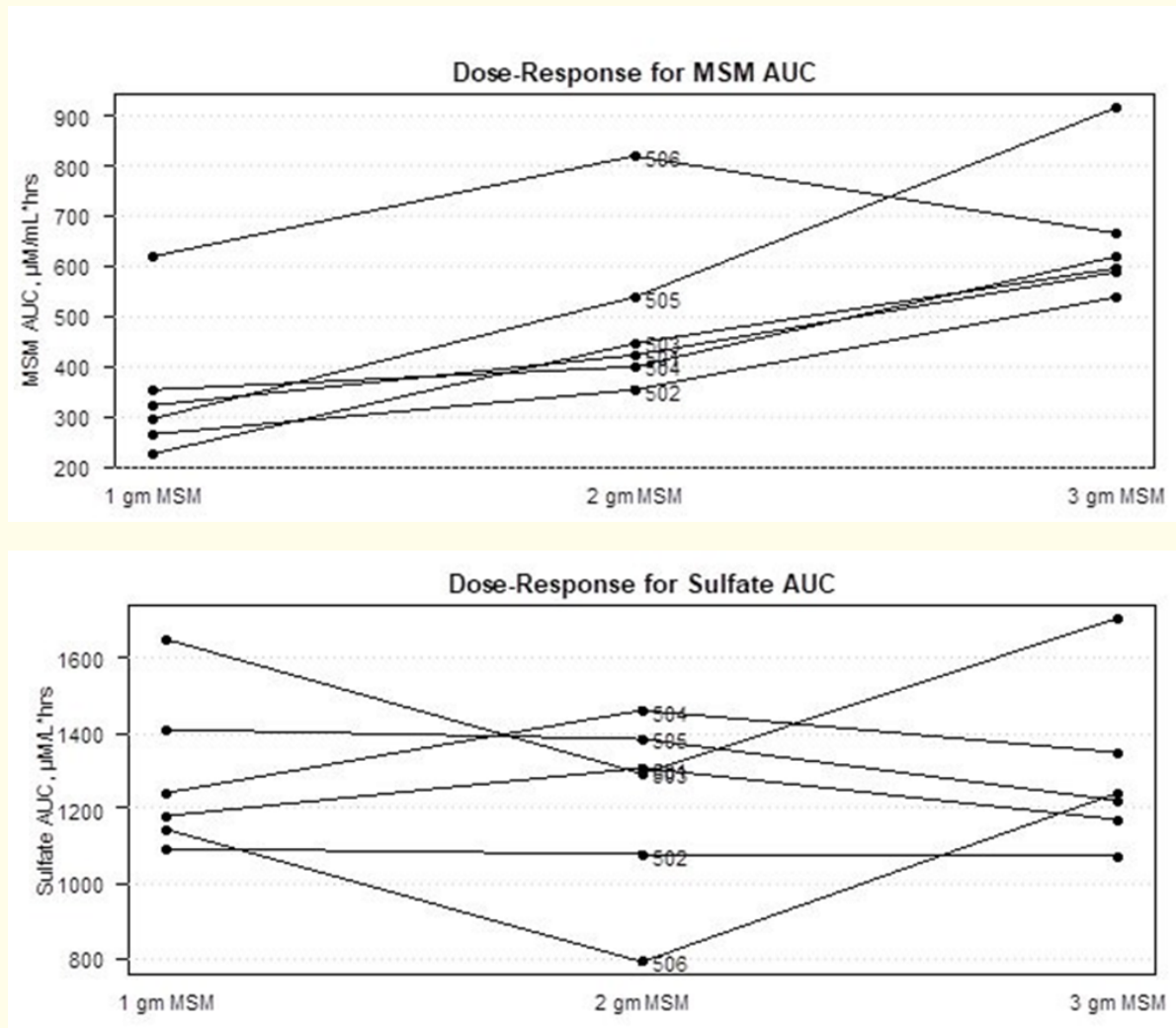


Figure 2: Dose response for MSM and sulfate.

Subtracting the pre-dose baseline reduces inter-subject and inter-visit variability, shortening the lengths of the error-bars and making the patterns clearer to see. There appear to be a slight decrease in Sulfate over time with increasing dose levels (see figure 3).

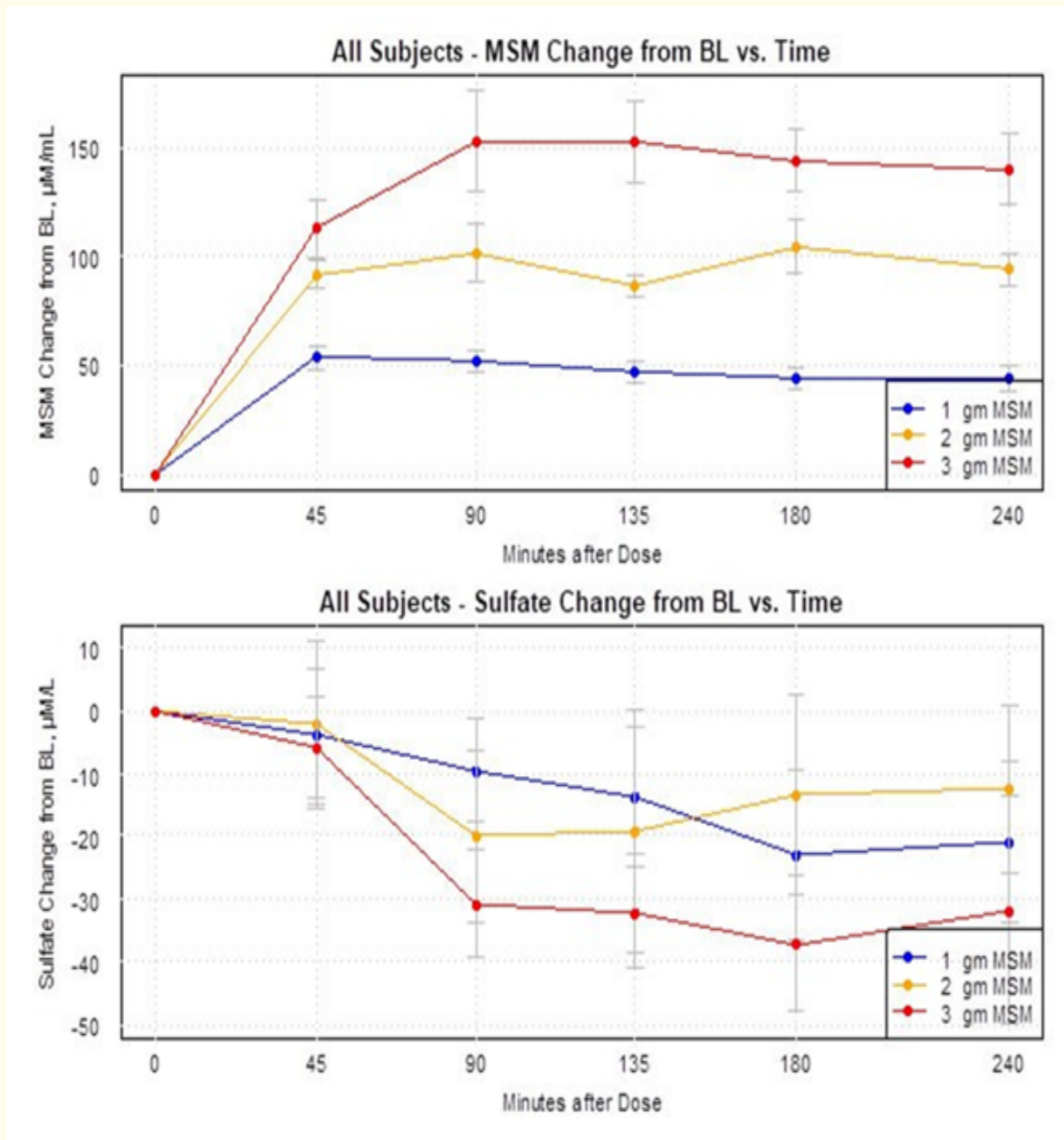


Figure 3: All subjects MSM, sulfate change from baseline vs time.

The linearity of the MSM dose-response relationship is clearer with baseline-adjusted AUCs. The error-bars are shorter because baseline adjustment removes most within-subject and within-visit variability. There is still no visibly evident effect for Sulfate (see figure 4).

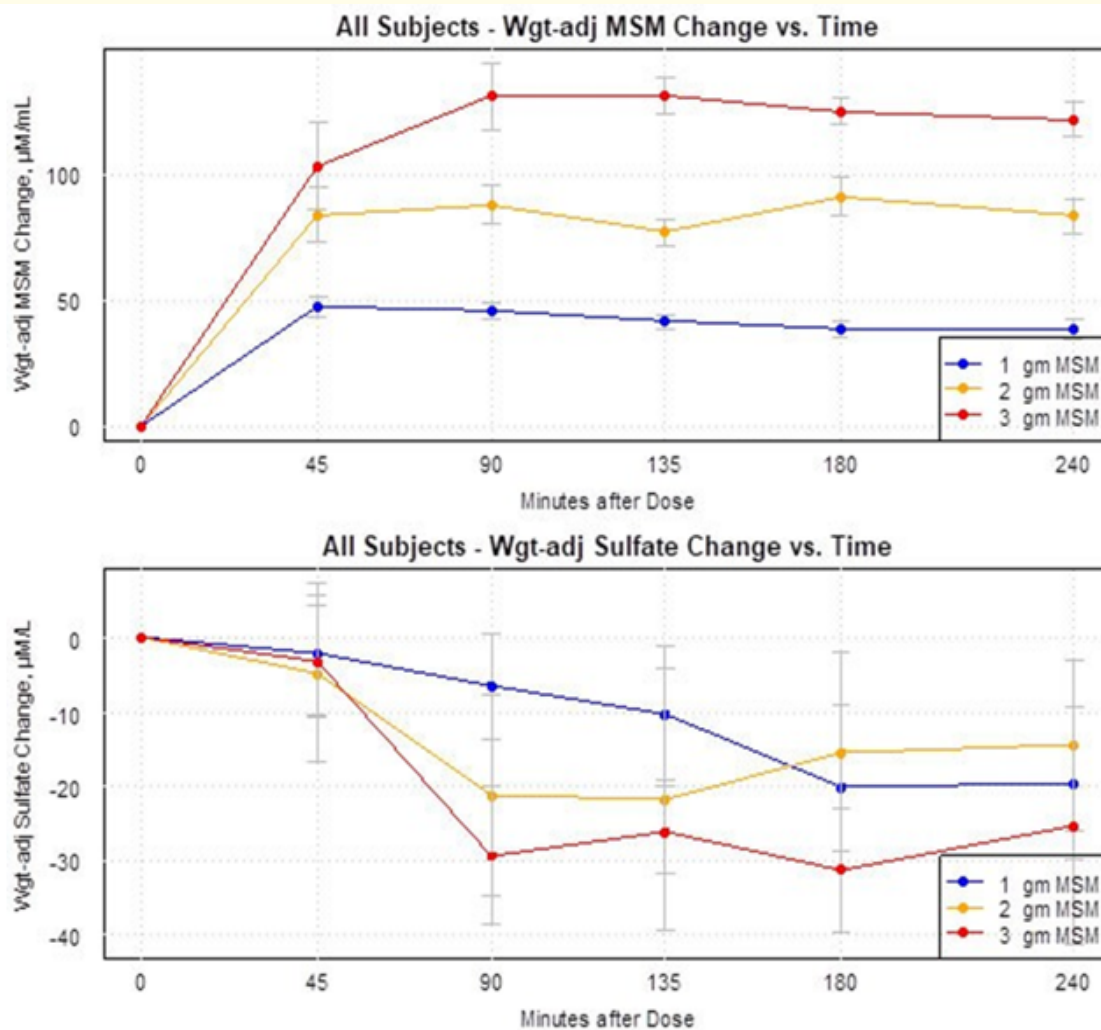


Figure 4: All subjects weight adjusted change vs time for MSM and sulfate.

Scaling for body-weight removes another source of random variability and makes the error bars even shorter (see figure 4).

MSM concentration is now seen to be very consistently proportional to MSM dose. There are still no consistent dose-response relationships for Sulfate (see figure 4).

No clear dose-effect patterns are evident in the 24-hour urinary excretion of MSM or Sulfate.

MSM concentrations, AUCs and  $C_{Max}$  values tend to be dose-proportional;  $t_{Max}$  and 24-hour urinary excretion values show no clear dose dependence (see table 1).

Dose:	1 gm MSM	2 gms MSM	3 gms MSM
Concentration, Pre-dose µM/mL	45.0 ± 36.1 (6) 31.8 (16.2 - 112.7)	36.7 ± 27.2 (6) 30.9 (9.9 - 89.6)	30.2 ± 13.5 (6) 26.3 (19.4 - 55.3)
Concentration, 45 minutes post-dose µM/mL	97 ± 37 (6) 90 (61 - 162)	127 ± 31 (6) 129 (90 - 171)	152 ± 20 (6) 151 (120 - 179)
Concentration, 90 minutes post-dose µM/mL	96 ± 42 (6) 85 (60 - 177)	137 ± 50 (6) 117 (98 - 230)	187 ± 64 (6) 168 (131 - 307)
Concentration, 135 minutes post-dose µM/mL	93 ± 43 (6) 81 (59 - 177)	120 ± 45 (6) 107 (79 - 207)	190 ± 59 (6) 170 (129 - 292)
Concentration, 180 minutes post-dose µM/mL	87 ± 34 (6) 86 (51 - 147)	144 ± 59 (6) 126 (84 - 250)	179 ± 48 (6) 166 (130 - 264)
Concentration, 240 minutes post-dose µM/mL	92 ± 42 (6) 88 (52 - 169)	127 ± 58 (6) 119 (80 - 240)	173 ± 57 (6) 166 (120 - 263)
Maximum Concentration (C <sub>Max</sub> ) µM/mL	100 ± 42 (6) 90 (61 - 177)	156 ± 52 (6) 141 (98 - 250)	203 ± 56 (6) 188 (151 - 307)
Time of Max. Conc. (t <sub>Max</sub> ) minutes	108 ± 78 (6) 90 (45 - 240)	120 ± 68 (6) 135 (45 - 180)	122 ± 67 (6) 112 (45 - 240)
Area Under the Curve (AUC <sub>0-4 hrs</sub> ) µM/mL*hours	353 ± 154 (6) 322 (213 - 642)	491 ± 174 (6) 446 (317 - 828)	651 ± 161 (6) 618 (491 - 946)
AUC Above Pre-dose Baseline µM/mL*hours	173 ± 46 (6) 170 (122 - 232)	345 ± 68 (6) 332 (277 - 470)	530 ± 111 (6) 509 (403 - 725)
Weight-adjusted AUC Over BL µM/mL*hours	153 ± 38 (6) 157 (96 - 214)	307 ± 66 (6) 314 (219 - 386)	467 ± 71 (6) 481 (337 - 542)
24-hour Urinary Excretion mM	116 ± 74 (6) 96 (41 - 253)	164 ± 81 (6) 162 (37 - 257)	140 ± 173 (6) 75 (33 - 491)

**Table 1:** MSM Pharmacokinetic Parameters: summarizes the concentrations over time, and the derived pharmacokinetic parameters, for MSM at each dosing level.

Numeric values are summarized in the format:  
 Mean ± Standard Deviation (Number of Subjects)  
 Median (Minimum - Maximum)

The pharmacokinetics of sulfate derived from MSM does not appear to be dose-dependent (see table 2).

Dose	1 gm MSM	2 gms MSM	3 gms MSM
Concentration, Pre-dose µM/L	334 ± 51 (6) 322 (276 - 400)	317 ± 62 (6) 311 (230 - 393)	348 ± 58 (6) 342 (283 - 454)
Concentration, 45 minutes post-dose µM/L	330 ± 50 (6) 311 (285 - 425)	315 ± 51 (6) 334 (222 - 362)	342 ± 57 (6) 331 (277 - 434)
Concentration, 90 minutes post-dose µM/L	325 ± 42 (6) 308 (288 - 396)	297 ± 53 (6) 320 (197 - 335)	317 ± 70 (6) 292 (256 - 451)
Concentration, 135 minutes post-dose µM/L	320 ± 48 (6) 300 (277 - 408)	298 ± 63 (6) 312 (197 - 363)	316 ± 39 (6) 307 (274 - 386)
Concentration, 180 minutes post-dose µM/L	311 ± 68 (6) 303 (239 - 414)	304 ± 78 (6) 322 (174 - 387)	311 ± 55 (6) 296 (267 - 413)
Concentration, 240 minutes post-dose µM/L	314 ± 62 (6) 300 (247 - 425)	304 ± 67 (6) 326 (188 - 369)	316 ± 74 (6) 284 (256 - 434)
Maximum Concentration (C <sub>Max</sub> ) µM/L	344 ± 53 (6) 322 (293 - 425)	333 ± 62 (6) 352 (230 - 393)	354 ± 60 (6) 348 (283 - 454)
Time of Max. Conc. (t <sub>Max</sub> ) minutes	38 ± 53 (6) 22 (0 - 135)	60 ± 79 (6) 22 (0 - 180)	40 ± 98 (6) 0 (0 - 240)
Area Under the Curve (AUC <sub>0-4 hrs</sub> ) µM/L*hours	1286 ± 207 (6) 1,212 (1,094 - 1,646)	1219 ± 244 (6) 1,300 (794 - 1,460)	1293 ± 219 (6) 1,232 (1,074 - 1,702)
AUC Above Pre-dose Baseline µM/L*hours	-51 ± 83 (6) -30 (-162 - 46)	-49 ± 126 (6) -72 (-215 - 114)	-100 ± 53 (6) -96 (-178 - -34)
Weight-adjusted AUC Over BL µM/L*hours	-41 ± 61 (6) -33 (-112 - 34)	-56 ± 112 (6) -69 (-214 - 83)	-84 ± 36 (6) -80 (-146 - -37)
24-hour Urinary Excretion µM	57 ± 53 (5) 43 (7 - 147)	40 ± 36 (6) 28 (3 - 90)	29 ± 43 (5) 16 (2 - 106)

**Table 2:** Sulfate Pharmacokinetic Parameters summarizes the concentrations over time, and the derived pharmacokinetic parameters, for Sulfate at each dosing level.

Numeric values are summarized in the format:  
 Mean ± Standard Deviation (Number of Subjects)  
 Median (Minimum - Maximum)



The MSM concentration-vs.-time data appeared to be of suitable quality to attempt an exploratory compartmental analysis, using the simplest applicable model - first-order absorption of MSM from the upper gastrointestinal tract into the bloodstream, followed by first-order elimination of MSM from the bloodstream. Each of these two processes is associated with a first-order rate constant ( $k_1$  and  $k_2$ , respectively), and a corresponding half-time ( $\lambda_1$  and  $\lambda_2$ , respectively). The model is:

$$Conc = A X (e^{-k_2 t} - e^{-k_1 t})$$

Or, in terms of half-times:

$$Conc = A X (e^{-\frac{t}{\lambda_2}} - e^{-\frac{t}{\lambda_1}})$$

The fitted models are shown here (data for the 1-gram MSM dose could not be fitted).

Only MSM concentrations from the 3 gms MSM dosing level could be modeled with any degree of confidence.

The results suggest that most of the MSM dose is absorbed from the stomach over the course of an hour or two (absorption half-time = about ½ hour), and then slowly eliminated from the bloodstream over the course of a day or so (terminal elimination half-time = about 8 hours). This suggests the sufficiency of a 7-day washout interval (which represents about 20 half-times, after which negligible amounts of the previous dose would remain in the body). However, there was a significant “order effect” indicating a significant amount of “carry over” of MSM from one visit to the next. This would not be expected if the terminal elimination half-life was as short as 10 or 12 hours, because then the inter-visit washout-period of 6 days would have been more than sufficient to flush virtually all of the MSM out of the body (12 half-lives would have removed 99.97% of the MSM if the elimination were truly first order).

While a model could be fitted to the concentrations from the 2 gms MSM dosing level, and while the fitted curve seems to nicely model the observed data, the parameters have essentially no precision (the standard errors are larger than the estimated values of the parameters). Therefore, no conclusions should be drawn from these numbers.

The two-compartment model could not be fitted to the concentrations from the 1 gm MSM dosing level (the iterative curve-fitting algorithms would not converge).

The “A” parameter in the above table represents an estimate of what the total MSM concentration increase from baseline would have been had there been no elimination of MSM from the bloodstream.

Results and discussion must illustrate and interpret the reliable results of the study.

## Discussion

Serum MSM levels displayed the rise and fall pattern consistent with fairly rapid absorption from the stomach (within an hour), followed by slower elimination from the bloodstream (over the course of one or two days).  $C_{max}$  and AUC tended to be dose-linear. AUC values over pre-dose baseline were found to be dose-proportional. Rough estimates have been obtained for the half times of absorption (1/2 hour) and elimination (8 hours).

This was a small-scale pilot study whose purpose was to provide a general idea of the PK and PD characteristics of oral MSM, and it did serve this purpose. The results provided information that can guide the design of any subsequent PK/PD studies of oral MSM in humans.

First, the rapid absorption of MSM from the stomach appears to indicate the need for two more PK samples in the first 30 minutes post-dose in order to precisely characterize the rate of absorption.

Second, the slow clearance of MSM from the bloodstream requires PK samples beyond 4 hours in order to precisely characterize the rate of clearance. None of the 6 subjects had substantial clearance in the first 4 hours post-dose. Samples at 8, 16, and 24 should provide points far enough “down the curve” to characterize the terminal elimination phase with adequate precision. This is especially important for the lower MSM dosing levels, where almost no noticeable elimination was evident in the first four hours. If it is not convenient to keep the patient for 24 hours, it would still be possible to obtain a blood sample at approximately 24 hours when the patient returned the 24-hour pooled urine specimen.

Third, if an intravenous (IV) administration of MSM could be worked into the protocol, then we would be able to confirm if bioavailability of oral MSM in the human is consistent with animal models, and also estimate the volume of distribution and clearance rates [21]. These parameters cannot be estimated from studies utilizing only oral administration.

Finally, we now have estimates of within-subject and within-visit variability for concentrations, AUCs, and other PK parameters, which can be utilized in power and sample-size calculations for subsequent studies.

Two chemically related nutritional supplements are DMSO (an organic form of Sulphur) and MSM (oxidized form of DMSO) [22]. In a different study, after 3g DMSO/kg B.W. was administered orally to Rhesus monkeys, a peak serum concentration of DMSO was observed four hours after ingestion, then declined rapidly after twenty-four hours. The serum half-life of DMSO was found to be sixteen hours [23]. Therefore, it is relevant to consider comparative clinical studies researching administration of DMSO. Similar to the established topical application of DMSO, a topical application of MSM+EDTA was studied as a possible treatment for pitting edema and oxidative stress [24]. When administered an active lotion containing 5.4 g MSM + 2.6 g EDTA per dL vehicle (vehicle: 0.9 g sodium alginate per dL distilled water), a consistent decrease in lower limb edema was observed compared to placebo. This decrease was primarily due to the combination of the chelating properties of EDTA and the permeability enhancement of MSM [24]. As edema is often a symptom of OA, MSM offers a variety of approaches for OA symptom management.

As well, in a study comparing the benefits of glucosamine-chondroitin sulfate with and without MSM in grade I-II knee osteoarthritis patients, it was determined that combination (1500 mg of glucosamine + 1200 mg of chondroitin sulfate + 500 mg of MSM) showed significant benefits with WOMAC and VAS score analysis compared to glucosamine alone (1500 mg of glucosamine + 1200 mg of chondroitin sulfate + 500 mg of saccharum lactis) or placebo [8]. As a result, it may be advisable to consider exploring samples containing OA patients and evaluating WOMAC and VAS scores. Also, clinical combinations studies should be considered before exploring greater dosing levels of MSM alone, for a combination containing MSM may yield more pronounced benefits compared to MSM alone.

## Conclusion

In all, this study demonstrated the bioavailability of oral MSM and the impacts it also has on sulfate metabolism. Oral MSM appears to be absorbed in a dose-dependent manner without direct dose-dependent impact on sulfate metabolism. The following is recommended if a follow-up MSM PK study is contemplated:

- Obtain two more PK samples in the first 30 minutes post-dose in order to precisely Characterize the rate of absorption.
- Obtain PK samples beyond 4 hours to precisely characterize the rate of clearance.
- Consider adding an IV administration of MSM if estimates of oral MSM bioavailability of oral MSM to IV MSM

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## Conflict of Interest

Douglas S Kalman declares that he worked for a Contract Research Organization (QPS) and as such, has received funding to execute clinical studies which include dietary supplements. "The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results".

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