Determination of DMSO in Solutions and Ointments by NMR

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An NMR method for the determination of DMSO in ointments and solutions is presented, using methanol as an internal standard. Samples containing from 20 to 0.05 percent (v/v) DMSO were successfully analyzed with this technique.

DIMETHYL SULFOXIDE (DMSO) is readily analyzed by NMR because it produces a single absorption peak of relatively great intensity and is miscible with a wide variety of solvents. NMR spectroscopy has been used to determine DMSO in a mixture with glycerol and water by measuring total hydrogen in the sample and in that fraction due to DMSO (1). This report discusses the determination of DMSO in solutions and ointments with methanol as an internal standard.

Although volatile liquids are not generally recommended as internal standards, methanol was found to be useful because of the chemical shift of its methyl peak, its low equivalent weight, and its wide miscibility range. Its use simplifies sample preparation and calculation of results for a series of determinations.

Sample and standard were mixed with suitable solvent, NMR spectra were obtained, and the amount of DMSO in the sample was calculated from the integration of the sample and standard peaks of interest (2–4).

Serial dilutions of a mixture of DMSO standard and methanol were similarly analyzed. The use of peak heights (5) as a means of estimation was investigated for solutions too dilute to produce integral presentations of any reasonable reproducibility.

PROCEDURE

Sample Preparation—Liquid—Pipet sample equivalent to 4–5 ml. of DMSO into a 50-ml. glass-stoppered conical flask. If the sample is too viscous to be pipeted accurately, accurately weigh a portion, determine the density of the material, and calculate the volume of the weighed portion ($V = W/d$). Add 5.0 ml. of methanol. Dilute with 10 ml. of water, stopper, and mix thoroughly.

Semi-Solid—Weigh sample equivalent to 4–5 Gm. of DMSO into a 50-ml. glass-stoppered conical flask, add 5.0 ml. of methanol and 15 ml. of water stopper, and mix thoroughly. If material is not soluble in water, use chloroform as diluent.

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Transfer approximately 0.4 ml. of solution to an analytical NMR tube. Prepare an NMR spectrum on the Varian A-60, adjusting settings for optimum integration. Each sample is integrated 10 times.

Calculations:

$$\% \text{ DMSO in sample (v/v)} = \frac{A \text{ DMSO}}{A \text{ CH}_3\text{OH}} \times \frac{E \text{ DMSO}}{E \text{ CH}_3\text{OH}} \times \frac{d \text{ CH}_3\text{OH}}{d \text{ DMSO}} \times \frac{V \text{ CH}_3\text{OH}}{V \text{ sample}} \times 100$$

$$\% \text{ DMSO in sample (w/w)} = \frac{A \text{ DMSO}}{A \text{ CH}_3\text{OH}} \times \frac{E \text{ DMSO}}{E \text{ CH}_3\text{OH}} \times \frac{d \text{ CH}_3\text{OH}}{W \text{ sample}} \times V \text{ CH}_3\text{OH} \times 100$$

in which:

A DMSO = area of DMSO peak (2.7 p.p.m. δ)
A CH_3OH = area of methanol CH_3 peak (3.3 p.p.m. δ)
d = density (Gm./ml.)
V = volume (ml.)

$$E \text{ DMSO} = \text{equivalent weight of DMSO} = \frac{78.13}{6} = 13.02$$

$$E \text{ CH}_3\text{OH} = \text{equivalent weight of methanol} = \frac{32.04}{3} = 10.68$$

W sample = weight of sample in Gm.

If a series of determinations is made, the combination of repeated values will greatly simplify the calculations; *e.g.*, in determining % DMSO (v/v) in various solutions, equal volumes of methanol and sample were taken; the densities of methanol and DMSO at room temperature, 74° F., were determined to be 0.7863 and 1.0915, respectively. Combining terms, the calculation becomes:

$$\% \text{ DMSO (v/v)} = 87.83 \times \frac{A \text{ DMSO}}{A \text{ CH}_3\text{OH}}$$

DISCUSSION

A solution containing known amounts of DMSO and methanol in water was prepared. Aliquots were diluted to obtain concentrations ranging from 20% to 0.05% (v/v) DMSO. Table I shows recoveries obtained for concentrations of 2–20% DMSO.

Since integration was not feasible for the more dilute solutions, peak heights of CH_3 (DMSO) and

TABLE I—DMSO DETERMINATION OF STANDARD PREPARATIONS[a]

Solution	DMSO Added, ml.	DMSO Found, ml.	Relative Error, %
1	20.00	20.14	0.7
2	10.00	9.99	0.1
3	5.00	4.94	1.2
4	2.00	1.98	1.0

[a] Equal volumes of DMSO and methanol were diluted to approximately 100 ml. in each case.

TABLE II—EFFECT OF CONCENTRATION OF PEAK HEIGHT RATIO OF DMSO/CH_3OH[a]

Solution	Concn. DMSO, % (v/v)	Mean $\frac{H \text{ DMSO}}{H \text{ } CH_3OH}$	Standard Deviation	Relative Standard Deviation, %
1	20	1.494	0.019	1.3
2	10	1.313	0.009	0.7
3	5	1.226	0.015	1.2
4	2	1.164	0.011	0.9
5	1	1.177	0.016	1.4
6	0.2	1.234	0.040	3.2
7	0.05	1.235	0.066	5.4

[a] H DMSO = height of DMSO peak. H CH_3OH = height of CH_3 peak in methanol. Results are based on 5 scans per solution.

$CH_3(CH_3OH)$ were measured on spectra of the aforementioned solutions, and the ratio of the two peaks was calculated for each spectrum. Table II shows mean ratios and standard deviations for 5 scans of each dilution. Reproducibilities of the mean peak height ratios for concentrations of 2% down to 0.05% were deemed adequate to suggest this procedure for estimating DMSO present as a contaminant in human and veterinary drugs. If any of the usual components of the drug produce an interfering spectrum, they may possibly be kept out of solution by a change of solvent.

As may be noted, there is a marked trend in peak height ratios of DMSO to the methyl in methanol as the concentrations increase from 2% up to 20%. This may be due to differential line broadening effects on the CH_3 peaks of methanol and DMSO resulting from increased viscosity. However, the importance of this phenomenon is only academic, as solutions of greater concentration may be determined satisfactorily by integration.

The DMSO peak is prominent down to a concentration of 0.01%; at this level the signal-to-noise ratio was found to be approximately 7:1 at a spectrum amplitude of 100 and a filter band width of 0.4 Hz.

Water is the solvent of choice; nearly all commercial DMSO preparations analyzed in this laboratory were found to be soluble in it, and its chemical shift (4.6–4.7 p.p.m. δ) is far removed from those of DMSO (2.7 p.p.m. δ) and the methyl peak of methanol (3.3 p.p.m. δ). Certain preparations produced a heavy precipitate upon the addition of water but were soluble in chloroform (7.3 p.p.m. δ). In these cases the addition of a small amount of hydrochloric acid eliminated spin-spin coupling between the methyl and hydroxyl groups of methanol. In either case, the use of a deuterated solvent is unnecessary.

In a series of commercial samples analyzed recently, results were in good agreement with the declared values (Table III).

TABLE III—DMSO CONTENT OF COMMERCIAL PREPARATIONS

Nature of Product	DMSO Declared, %	DMSO Found, %	Found/ Declared, %
Liquid	90 (v/v)	91.3	101.4
Liquid	90 (v/v)	90.9	101.0
Liquid	90 (v/v)	88.5	98.3
Liquid	90 (v/v)	86.1	95.1
Semi-solid	70 (w/w)	68.3	97.6
Semi-solid	70 (w/w)	69.8	99.7
Semi-solid	70 (w/w)	70.5	100.7
Semi-solid	70 (w/w)	69.8	99.7

REFERENCES

(1) Alexander, T. G., private communication, Food and Drug Administration.
(2) Barcza, S., *J. Org. Chem.*, **28**, 1914(1963).
(3) Williams, R. B., *Ann. N. Y. Acad. Sci.*, **70**, 890(1958).
(4) Paulsen, P. J., and Cooke, W. D., *Anal. Chem.*, **36**, 1713(1964).
(5) Slomp, G., Baker, R. H., Jr., and MacKellar, F. A., *Anal. Chem.*, **36**, 375(1964).

Keyphrases

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