NMR Analysis of Pharmaceuticals X: Determination of Methsuximide and Phensuximide in Capsules

JOHN W. TURCZAN▲ and BRUCE A. GOLDWITZ

Abstract □ A method for the quantitative analysis of methsuximide and phensuximide using NMR is reported. For samples of the pure drugs, results were accurate to 0.3% or less with standard deviations of 0.6% or less. Analysis of capsules of each drug by NMR and NF XIII procedures indicated a maximum difference of 1.5%, but generally the difference was less than 1.0%. This procedure is recommended for the analysis of these drugs since it provides good quantitative results together with a unique spectrum as confirmatory identification.

Keyphrases □ Methsuximide and phensuximide capsules—NMR analysis □ Phensuximide and methsuximide capsules—NMR analysis □ NMR spectroscopy—analysis, methsuximide and phensuximide capsules

Methsuximide (*N*,2-dimethyl-2-phenylsuccinimide, I) and phensuximide (*N*-methyl-2-phenylsuccinimide, II) are two succinimide derivatives which are pharmacologically active anticonvulsants. Their use is primarily in the control of petit mal epilepsy.

Several analytical approaches have been successfully applied to the isolation and determination of I and II in biological media. A quantitative procedure for the determination of both I and II in serum was developed by Huisman (1). The method involves nitration of the phenyl rings and separation of the products by TLC, followed by subsequent diazotization and coupling to produce a color measured at 550 nm. Gardner-Thorpe *et al.* (2) used TLC and examination under UV light to estimate the presence of some anticonvulsant succinimides in blood.

Other properties have been exploited to analyze for both I and II in pharmaceutical systems and as pure chemical entities. The assay procedures for II studied by Mativa (3) include titration, reaction in buffered medium to obtain a fluorescent product, and reaction with fuming nitric acid to form a colored product whose color intensity is read in an alkaline acetone solution. The extension of Mativa's technique to I was investigated (4) with satisfactory results.

The methods adopted by NF XIII (5) for the determination of both I and II in capsule dosage forms involve a chloroform extraction and subsequent UV light absorption measurement.

This paper describes a method involving NMR spectrometry[1] to determine I and II in capsule dosage forms. The method utilizes carbon tetrachloride[2] as the solvent for I and 10% methylene chloride[2] in carbon tetrachloride as the solvent for II, and hexamethylcyclotrisiloxane[3] (III) is employed as the internal standard for both drugs. Known mixtures and commercial capsules were analyzed by this technique. Quantitative analysis using NMR offers the advantages of speed, simplicity, and specificity for the active ingredients.

Table I—Determination of Methsuximide and Phensuximide in Standard Mixtures by NMR

Standard Mixture	Internal Standard[a], mg.	Methsuximide and Phensuximide Added, mg.	Found, mg.	Recovery, %
Methsuximide				
1	102.7	320.8	319.5	99.6
2	101.9	319.9	321.8	100.6
3	100.5	321.6	321.3	99.9
4	102.9	320.4	317.8	99.2
5	103.1	321.1	324.0	100.9
6	103.5	319.8	324.6	101.5
7	200.3	320.1	320.4	100.1
				100.3
				SD 0.6
Phensuximide				
1	105.6	319.4	322.4	100.9
2	104.9	321.5	319.6	99.4
3	105.8	321.0	320.7	99.9
4	104.5	319.9	322.5	100.8
5	103.9	320.5	319.9	99.8
6	185.0	325.0	324.4	99.8
				100.1
				SD 0.4

[a] Hexamethylcyclotrisiloxane.

EXPERIMENTAL

Standards and Samples—Methsuximide and phensuximide reference standards[4] and commercial methsuximide and phensuximide capsule preparations were used.

Procedure—Place a counted number of capsules into a 125-ml. glass-stoppered conical flask. Carefully crack the outer shell of each capsule with the end of a glass rod. Using a calculated amount of carbon tetrachloride for I or 10% methylene chloride in carbon tetrachloride for II, so that the final volume will contain the solute to be measured in a concentration of about 80 mg./ml., first wash down the end of the stirring rod to ensure quantitative retention of the sample powder and then add the remainder of the solvent to the flask. Add an accurately weighed amount of III, the internal standard, to the sample solution so that its final concentration is about 25 mg./ml. Stopper the flask and swirl, gently at first, to effect solution. Allow the outer shells and insoluble excipients to rise to the top and then transfer about 0.4 ml. of the bottom solution to an analytical NMR tube. Place this tube in an NMR spectrometer and obtain the spectrum, adjusting the spin rate so that no spinning side bands occur between 0.4 and 0.6 p.p.m. and between 6.8 and 7.7 p.p.m. using the δ-scale to express magnetic field strength. All peak field positions are referenced to tetramethylsilane (IV) at 0 p.p.m. Integrate the peaks of interest at least five times.

The amount of I or II may then be calculated as follows:

$$\frac{\text{mg. I or II}}{\text{capsule}} = \frac{A_s}{A_h} \times \frac{EW_s}{EW_h} \times \frac{\text{mg. III}}{\text{number of capsules}} \quad \text{(Eq. 1)}$$

[1] A Varian A-60 NMR spectrometer, equipped with a V-6031 variable-temperature probe having a six-turn insert, was used.
[2] Fisher Scientific Co., Fair Lawn, N. J.
[3] K & K Labs., Inc., Plainview, N. Y.
[4] Parke, Davis & Co., Detroit, Mich.

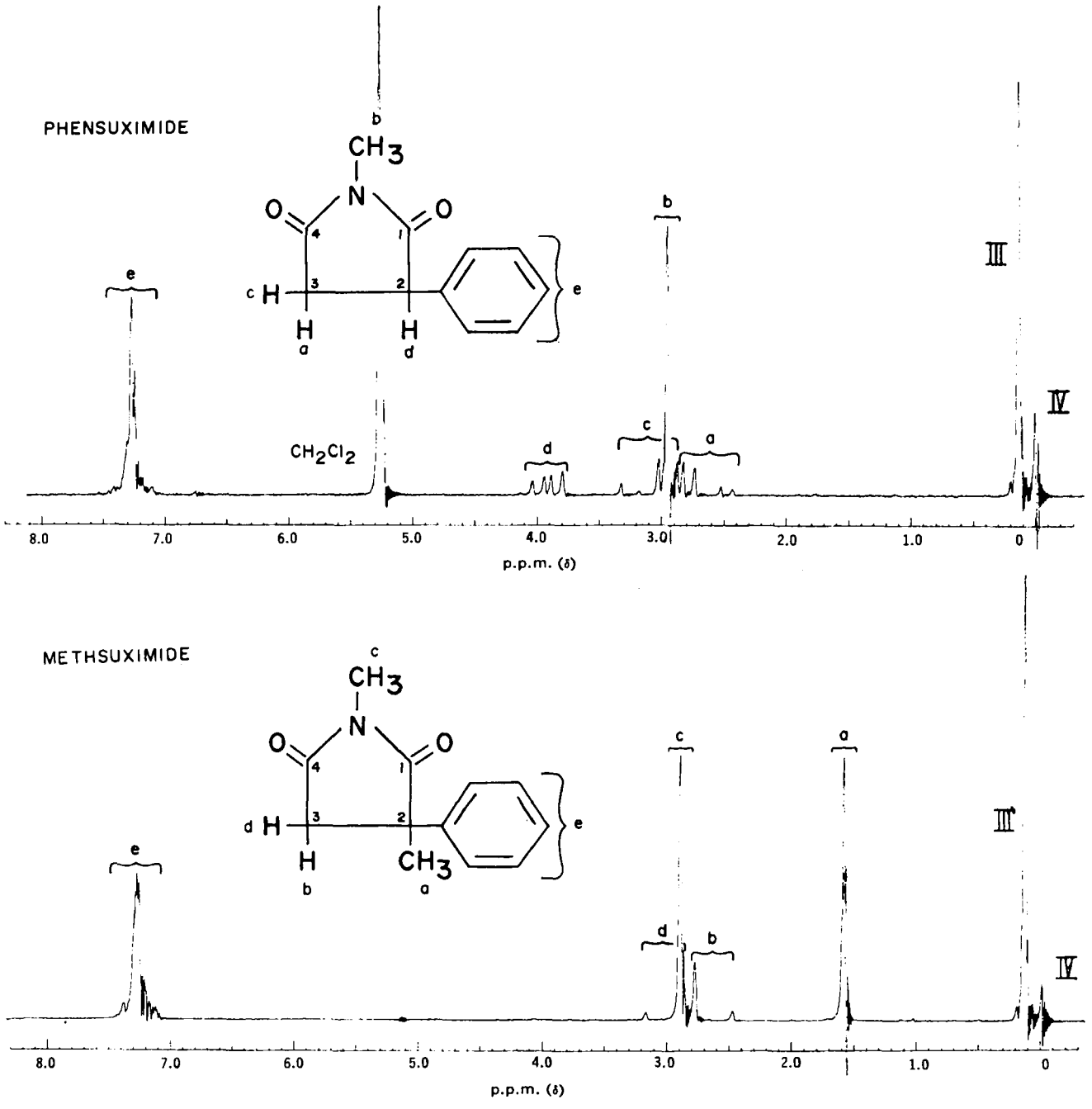

Figure 1—*NMR spectra of phensuximide in 10% methylene chloride in carbon tetrachloride and of methsuximide in carbon tetrachloride (III, hexamethylcyclotrisiloxane; and IV, tetramethylsilane).*

where:

A_s = integral value of the signal representing I or II
A_h = integral value of the signal representing III
EW_s = formula weight of I/5 = 40.65 or formula weight of II/5 = 37.84
EW_h = formula weight of III/18 = 12.35

RESULTS AND DISCUSSION

Although the two succinimide compounds, I and II, are very similar structurally, different solvents were required. The extreme solubility of both I and III in carbon tetrachloride plus the lack of resonance signals makes carbon tetrachloride the obvious choice of solvent for these solutes in this procedure. However, II does not exhibit the same solubility in pure carbon tetrachloride, but a 10% methylene chloride in carbon tetrachloride solvent system was satisfactory. The methylene chloride solvent component introduces no interference since its protons absorb at 5.25 p.p.m., a region not occupied by any other peaks.

The applicability of III as an internal standard has been demonstrated previously (6–8). It appears as a single spectral signal at an extreme upfield position. This combination of solvent system and internal standard provides the opportunity for a clear, interference-free identification of the active ingredient in addition to quantitative results.

The NMR spectra of I and II under the described analytical conditions are depicted in Fig. 1. The amounts of both succinimide derivatives are determined from the integration of the broad resonance pattern at about 7.25 p.p.m. due to the five phenyl protons at position 2 on the succinimide ring and the integration of the singlet at about 0.14 p.p.m. resulting from the 18 methyl protons of the internal standard III.

In addition to quantitative analysis, the hydrogen resonance characteristics are useful for qualitative purposes and are interpretable. In I, the two singlets at about 1.59 and 2.90 p.p.m. are due to

Table II—Determination of Methsuximide and Phensuximide in Commercial Capsules by NMR

Sample	Declared Dosage, mg./Capsule	NMR Procedure, mg./Capsule	Percent	NF XIII Procedure, mg./Capsule	Percent
Methsuximide					
1	300	299.1	99.7	297.9	99.3
2	300	292.2	97.4	293.1	97.7
3	300	298.2	99.4	299.1	99.7
4	150	149.6	99.7	149.1	99.4
5	150	152.1	101.4	149.9	99.9
6	150	148.4	98.9	146.9	97.9
Phensuximide					
1	500	481.0	96.2	484.5	96.9
2	500	497.5	99.5	496.0	99.2
3	500	493.5	98.7	495.5	99.1
4	500	491.0	98.2	493.5	98.7
5	500	496.0	99.2	497.5	99.5

the methyl protons at position 2 and on the nitrogen, respectively, of the succinimide ring. The two methylene protons at position 3 are nonequivalent and exhibit a characteristic *AB* pattern between 2.4 and 3.2 p.p.m. For Compound II, the three protons on the methyl group bonded to the nitrogen appear as a singlet at about 2.95 p.p.m. The methylene protons at position 3 couple with the methine proton at position 2 to form an intricate *ABX* pattern between 2.4 and 4.1 p.p.m.

The analysis of a group of standard I and II mixtures by NMR is summarized in Table I. As noted, the method is accurate and precise for I and II, with a standard deviation of 0.6 and 0.4%, respectively. The relative proportions of III to either I or II show no significant bearing on the accuracy of the determination for the range of proportions shown in Table I.

The potential value of the proposed NMR analysis to dosage forms was established by the measurement of the content of I and II in capsules. Table II summarizes the results of the analysis of six lots of I capsules and five lots of II capsules. For comparative purposes, the same capsules were analyzed by the NF XIII method, a UV spectrophotometric determination using the phenyl group absorption characteristics that occur in a spectral region not unaccustomed to harboring UV-absorbing interferences. The two procedures generally agreed to within 1%. No interference from any capsule excipients was observed.

As demonstrated previously, the use of NMR for quantitative analysis offers a number of advantages, which were experienced in this case as well. The procedure is simple and rapid, an advantage shared by other spectroscopic analyses. However, in the matter of specificity, NMR does stand alone, since the recorded spectrum provides unique field positions of the various protons for unambiguous identification (less complex than IR) and offers specific peaks for integration and subsequent quantitative interpretation. It is to be hoped that the advantages of NMR coupled with the welcome availability of less expensive, reliable instruments will encourage the use of this technique in quantitative analysis.

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Other titles in this series include: J. W. Turczan, B. A. Goldwitz, and J. J. Nelson, *Talanta*, **19**, 1549(1972); B. A. Goldwitz and J. W. Turczan, *J. Pharm. Sci.*, **62**, 115(1973); and J. W. Turczan and B. A. Goldwitz, *J. Ass. Offic. Anal. Chem.*, **56**, 669(1973).

▲ To whom inquiries should be directed.