

## **A New Quantitative Determination Method for Aspirin Phenacetin, Caffeine and Their Mixtures Using NMR Spectrometer**

Aspirin, Fenasetin, Kafein ve Karışımlarının NMR Spektrometri ile Yeni Bir Nicel Saptama Yöntemi

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There are several methods for the determination of aspirin, phenacetin and caffeine quantitatively in their preparations. Connors<sup>1</sup> has given many references for quantitative determination. The method mentioned in the NF XII<sup>2</sup> is an extraction procedure therefore very time consuming and not suitable for routine applications, Parke et al.<sup>3</sup> have used infrared spectrophotometer for the quantitative determination. This method is faster and more accurate than the one mentioned in NF XII. NMR spectrometer has been used by Hollis<sup>4</sup> for the quantitative determination but the known sample used in his method is caffeine which causes the calculations to be long and enough complicated. Therefore we have looked for another reference compound and decided to use succinic acid.

### **EXPERIMENTAL**

In this research the nmr spectrometer is a T- 60 Varian 60 MHz. instrument.

Operation: 10 tablets are weighed accurately and powdered. An accurate quantity of this powder which corresponds to 1/3 of a tablet is weighed. To this powder, 25 mg succinic acid, 2 ml deuterated chloroform and 1 ml deuterated dimethylsulfoxide is added. The

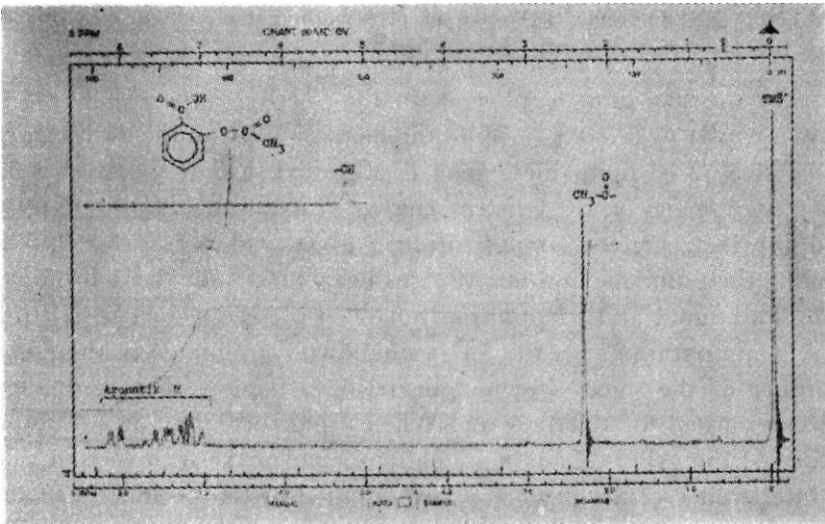
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mixture is well stirred and then filtered through glass wool. 0.4 - 0.5 ml of the filtrate is taken into an nmr tube and the spectrum is drawn. The bands which are to be used for the quantitative determination are chosen and their integrals are scanned repeatedly and the average is found. The proper APC preparations contain cafein less then the others therefore starting with more powder increases the cafein concentration and thus the integral value resulting more accurate determinations. This has not been done in this research and still the results have allways shown an error less then 4 %.

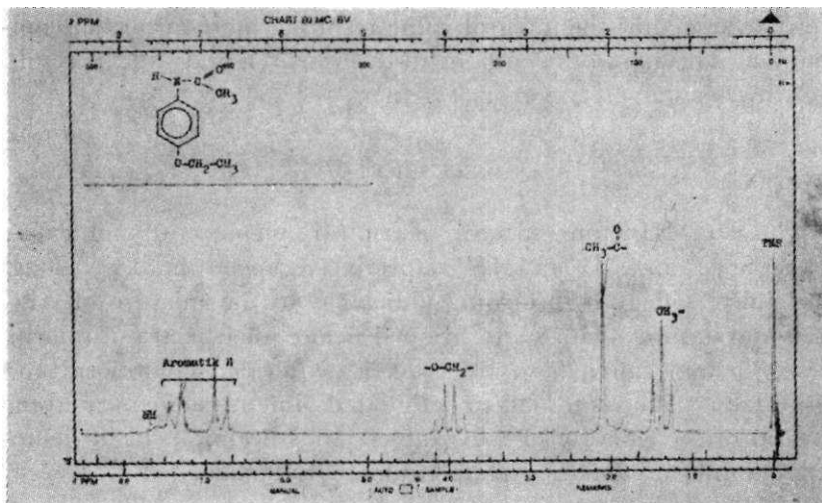
#### DISCUSSION

The 60 MHz nmr spectra of aspirin, phenacetin and cafein are the Spectra. I, II and III respectively. Spectrum. IV belongs to succinic acid and Spectrum. V belongs to the mixture of APC tablets and succinic acid. As mentioned before, the spectra of aspirin, phenacetin and cafein have been taken deuterated chloroform and the spectrum of succinic acid in deuterated dimethylsulfoxide and the spectrum of the mixture of APC tablets and succinic acid in deuterated chloroform and deuterated dimethylsulfoxide.



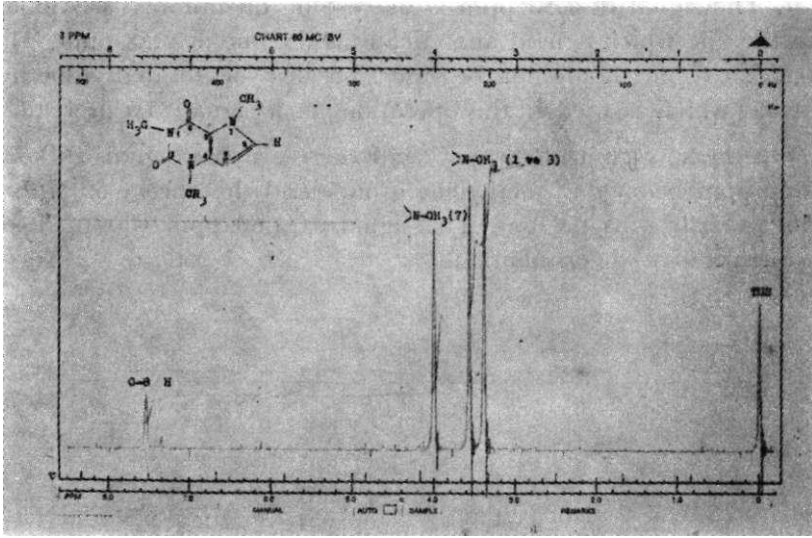
Spectrum. I. Aspirin, 60 MHz nmr spectrum

The sharp signal at 2.33 ppm in the spectrum of Aspirin belongs to methyl group of ester moiety, the signals at 7.00 - 8.17 ppm refer to phenyl hydrogens, the one at 10.47 ppm refers to the proton of carboxyl group. Among these the one at 2.33 ppm which is a sharp signal has been used for the determination.



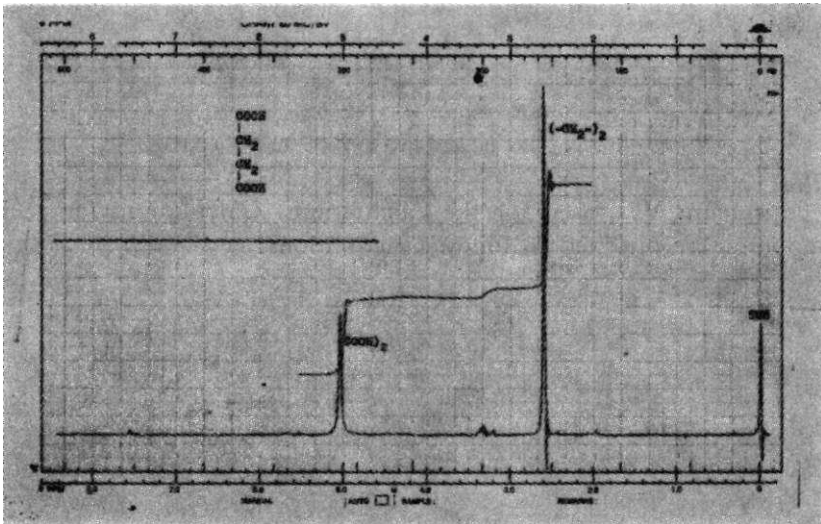
Spectrum. II. Phenacetin, 60 MHz nmr spectrum

On the spectrum of phenacetin the methyl group of O-ethyl gives a triplet signal at 1.37 ppm, the methyl of the amide group gives a signal at 2.10 ppm. methylene of O-ethyl group shows at 4.00 ppm, hydrogens on the benzene ring give signals at 6.73 - 7.45 ppm and the hydrogen on amide nitrogen gives a signal at 7.58 ppm. Among these the one at 4.00 ppm has been chosen for the determination. The signal at 1.37 ppm has not been preferred due to splitting in APC preparations because of an unknown coupling. Also there is a shoulder at the signal which appears at 2.10 ppm. Therefore they were discarded for this purpose. When using the signal at 4.00 ppm starting from APC tablets it is mandatory to make a correction due to interference of the protons which situated at the position 7 of cafein. This correction can be realized very easily by subtracting the methyl value of cafein at 3.58 ppm.



Spectrum. III. Caffein, 60 MHz nmr spectrum

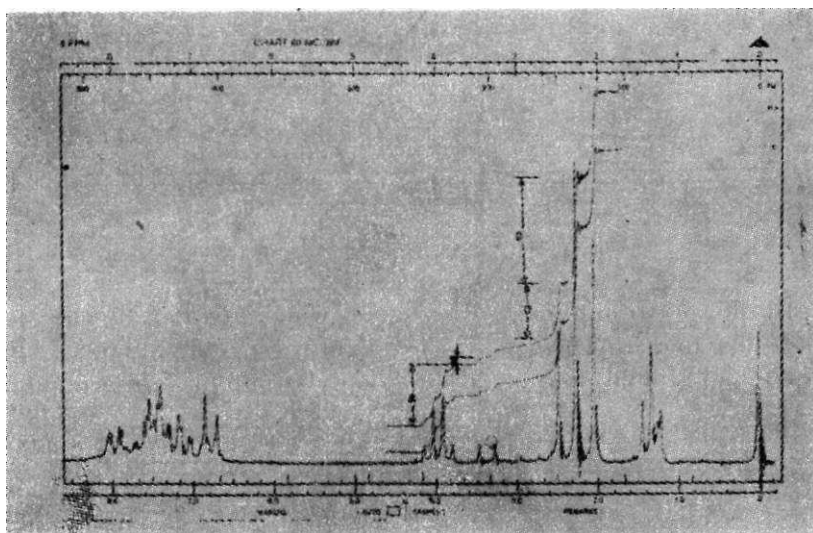
In the spectrum of caffeine the signals which are at 3.40 and 3.58 ppm belong to methyl groups attached to nitrogen atom number 1 and 3, the signal at 4.00 ppm belongs to methyl group on nitrogen num-



Spectrum. IV. Succinic acid, 60 MHz nmr spectrum

ber 7. The signal at 7.53 ppm is the proton on number 8. Among these the one which is used analytically is the one at 3.58 ppm. The one at 3.40 ppm should not be used because deuterated dimethyl sulfoxide which is used in this operation has a signal at this region.

On the spectrum of succinic acid there are two signals the one at 2.60 ppm belongs to methylene groups and the one at 5.03 ppm belongs to carboxyl protons. The signal at 2.60 ppm was used for the quantitative determination.



Spectrum. V. APC tablets and succinic acid, 60 MHz

Spectrum V is used for the calculations. Calculations for each compound are outlined in following equations:

ASPIRİN:

$$\frac{\text{mg Aspirin}}{\text{mg Sample}} \times \frac{D \text{ (integral value for Aspirin)}}{C \text{ (integral value for Succinic acid)}} \times \frac{N \text{ Aspirin}}{N \text{ Succinic acid}} \times OS$$

QS quantity of succinic acid added (25 mg)

PHENACETTİN :

$$\frac{\text{mg Phenacetin}}{\text{mg sample}} \times \frac{(A - B)}{C} \times \frac{N \text{ Phenacetin}}{N \text{ Succinic acid}} \times QS \quad \text{QS quantity of succinic acid (25 mg)}$$

GAFEİN:

$$\frac{\text{mg kafein}}{\text{mg sample}} \times \frac{B}{c} \times \frac{N \text{ kafein}}{N \text{ Succinic acid}} \times QS \quad \text{QS quantity of succinic acid 525 mg)}$$

N Aspirin =	$\frac{\text{Molecular weight of Aspirin}}{\text{number of protons at 2.33 ppm}}$	$\frac{180.16}{3}$	60.05
N Phenacetin	$\frac{\text{Molecular weight of Phenacetin}}{\text{number of protons at 4.00 ppm}}$	$\frac{179.22}{2}$	89.61
N kafein	$\frac{\text{Molecular weight of Caffeine}}{\text{number of protons at 3.58 ppm}}$	$\frac{194.19}{3}$	64.73
N succinic acid	$\frac{\text{Molecular weight of Succinic acid}}{\text{number of protons at 2.60 ppm}}$	$\frac{118.09}{4}$	29.52

At the following Table the quantities of Aspirin, Phenacetin and caffeine found with NMR spectroscopic method and the percent errors are given

Sample	quant. in mg			found in mg			error percent		
	Asp	Phen	Caf.	Asp.	Phen.	Caf.	Asp.	Phen.	Caf.
	Aspirin	50	40		49.37	39.20		1.26	2.0
Phenacetin			9			8.70			3.33
Caffein			0			8.66			3.77
APC mixture	50	40	20	49.20	39.10	19.20	1.60	2.25	4.00
APC tablet	280	230	30	276.80	225.10	29.10	3.20	2.13	
APC tablet	220	150	30	217.50	146.30		1.13	9.46	3.00

## SUMMARY

In this study, a new method has been designed for the quantitative determination of Aspirin, Phenacetin, Caffeine and their mixtures in the commercial preparations. The quantitative determination methods for the mentioned compounds depend on time consuming extractions. In this research nmr spectrometer has been used by taking the integrals of a characteristic signal of each compound and comparing them with the integral intensity of a standard compound. Caffeine had been used before as the standard compound with the nmr spectrometer. In our work succinic acid gave better results and easier calculation possibilities. The results obtained with this method show a superiority to those obtained with conventional methods.

## ÖZET

Bu çalışma ile tecimsel preparatlarda bulunan, Aspirin, Fenasetin ve Kafeinin nicel saptanması için yeni bir yöntem tasarlanmıştır. Adı geçen bileşiklerin nicel saptanmaları için kullanılan yöntemler uzun zaman alıcı tüketim işlemlerine dayanmaktadır. Bu çalışmada her bileşiğin karakteristik bir sinyalinin integralini alıp onu standard bir bileşiğin integral değeri ile karşılaştırarak nmr spektrometri kullanılmıştır. Daha önce standard bileşik olarak kafein kullanılmıştır. Çalışmamızda süksinik asitin daha iyi sonuç verdiği ve daha kolay hesaplama olanakları sağladığı saptanmıştır. Bu yöntemle elde edilen sonuçlar alışlagelmiş yöntemlerle elde edilenlerden daha iyidir.

## REFERENCES

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