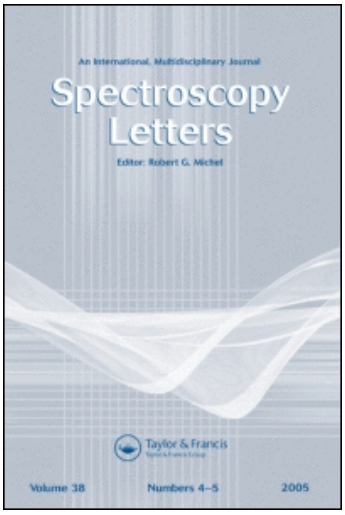

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Dongli Deng[a]; Pengchi Deng[a]; Xiaoyan Wang[a]; Xiandeng Hou[a]
[a] Analytical & Testing Center, Sichuan University, Sichuan, China

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Direct Determination of Sodium Fluoride and Sodium Monofluorophosphate in Toothpaste by Quantitative ^{19}F-NMR: A Green Analytical Method

Dongli Deng, Pengchi Deng, Xiaoyan Wang, and Xiandeng Hou

Analytical & Testing Center, Sichuan University, Sichuan, China

ABSTRACT Sodium fluoride and sodium monofluorophosphate are often used as fluoridizers in oral care products to prevent dental caries. By quantitative ^{19}F-NMR, their contents in toothpaste were simultaneously determined. This is a simple, fast, interference-free, and green analytical method for the determination of sodium fluoride and sodium monofluorophosphate in toothpaste.

KEYWORDS quantitative ^{19}F-NMR, sodium fluoride, sodium monofluorophosphate, toothpaste

INTRODUCTION

Fluorine is an essential trace element that composes the human body and forms tooth enamel. Fluorine could effectively prevent a decayed tooth. Constant use of fluorine-containing toothpaste will decrease the possibility of decayed tooth by approximately 20–40%. On the other hand, overdose might induce endemic fluorosis. Therefore, quantitative determination of fluorine in toothpaste is necessary. Nowadays the typical and common fluoridizers for toothpaste are sodium fluoride (NaF) and sodium monofluorophosphate ($Na_2PO_3 \cdot F$); and according to a large number of clinical trials, NaF is approximately 6–7% more effective than $Na_2PO_3 \cdot F$ against decayed tooth.[1]

The method of determining fluorine progresses from the early thermogravimetry and volumetric methods gradually to colorimetry,[2] fluorimetry,[3] gas chromatography (GC),[4] and further to modern ion chromatography (IC),[5–7] capillary electrophoresis[8] and neutron activation analysis.[9] At present, the common methods for the determination of fluorine are ion-selective electrode (ISE)[10–12] and IC. ISE is convenient and efficient, but it cannot detect organic and combinative fluorine directly. Moreover, it suffers interferences from coexisting substances,[10] and Total Ionic Strength Adjustment Buffer (TISAB) must be employed to eliminate the interferences.[11] This increases workload and decreases experimental

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Address correspondence to Dr. Pengchi Deng, Analytical & Testing Center, Sichuan University, Sichuan 610064, China. E-mail: pcdeng@yahoo.com

reproducibility.[2] For the microanalysis of fluorine ion, IC could deal with a great deal of data easily and accurately.[7] Although it has many advantages such as simplicity, cost-effectiveness, high stability, and good reproducibility, F^- peak is too close to the injection peak. This results from the low affinity between F^- and exchange column. Thus, separation selectivity/efficiency is low, and the sample treatment would be very restricted.

In 1940s, nuclear magnetic resonance (NMR) phenomenon was discovered almost simultaneously in two groups led by Purcell and Bloch.[13,14] Nowadays, it is widely used in many fields such as chemistry, biology, medicine, and pharmacology, and it has become the most important method in organic compound structure identification and kinetics research. Under a certain condition, the NMR signal intensity is proportional to the number of resonance nuclei producing the signal. It becomes a unique feature of NMR in the field of absorption spectrum, which is not merely the important parameter in confirming compound structure but an advantage for quantitative determination. Consequently, quantitative NMR (qNMR) is focused as a new direction. The pioneer quantitative measurement appeared in 1963 in the work by Jungnickel and Forbes,[15] and Hollis.[16] Compared to other methods, qNMR has unique advantages, such as non-destructiveness, no need to separate analyte from a complex mixture, and avoidance of toxic reagent. With the advance of high-field instruments and probe improvement, qNMR has played an important role in the analysis of nature products,[17] pharmacy,[18–20] agriculture,[21] and food/beverage.[22,23] However, it should be pointed out that the high price of an NMR spectrometer and the low sensitivity restrict its application.

The natural abundance of ^{19}F is 100%; and its spin quantum number I is 1/2. The relative sensitivity is 83.4% of proton, so it is easy to obtain ^{19}F spectra with high resolution. Its chemical shift range can reach 500 ppm, so peak overlapping will not easily appear in similar structural compounds.[20] Given a good signal-to-noise ratio (S/N), ^{19}F-NMR can also provide quantitative information accurately and reproducibly. Those spectra are therefore proper for quantitative analysis.[24–28] In this work, ^{19}F-NMR was used to determine the concentrations of fluoridizers in toothpaste. This method is simple, fast, and interference-free, and it can provide speciation information.

MATERIALS AND METHODS

Materials and Reagents

Analytical grade, high-purity substances were used throughout this study. NaF and $Na_2PO_3 \cdot F$ were obtained from Chengdu Kelong Chemical Co (Chengdu, China). Sodium trifluoroacetate (CF_3COONa) was purchased from Beijing Hengye Hongyuan Chemical Co (Beijing, China). Deuterium oxide (D_2O) (99.9%) was supplied by Cambridge Isotope Laboratories, Inc (MA, USA). Toothpaste of different brands was purchased from the Trustmarket in Chengdu. NaF, $Na_2PO_3 \cdot F$ and CF_3COONa were dehydrated at 378 K for 2 h, then cooled in a vacuum drier.

Solution Preparation

The internal standard 1.273 mg/mL stock solution was prepared by weighing 1.273 g CF_3COONa and dissolving in 1000 mL deionizer water. The suspension was sonicated for 10 min for complete dissolution.

Instrument

All ^{19}F-NMR spectra were recorded with an Avance II-400 MHz NMR Spectrometer (Bruker Company, Switzerland) equipped with a BBFO Probe. Each sample was dissolved in 450 μL H_2O with additional 50 μL D_2O as an internal field frequency lock. The spectra were acquired by 90° pulses (number of scan: 64, time domain: 512 k) over a spectral width of 29761.9 Hz (79.0571 ppm). The acquisition time was 8.8 s followed by a relaxation delay of 20 s for completely longitudinal relaxation (T1). Each acquisition was repeated 5 times. Phase corrections and signal integration were done manually. The spectra were recorded at room temperature and the ^{19}F-NMR chemical shifts were calibrated to CF_3COONa.

RESULTS AND DISCUSSION

Principle of qNMR

The basic principle of NMR used in quantitative investigation is that the area of each NMR signal is directly proportional to the number of the corresponding excited nuclei under appropriate experimental conditions.[19] The linear relationship between the

signal area I and the number of the corresponding nuclei N is given by:

$$I = Ks \times N \quad (1)$$

Ks, a spectrometer constant, is a certain constant for all resonance lines in the same nuclear magnetic resonance under the same equipment conditions. Therefore, in a spectrum, toward two nuclei simultaneously generated resonance lines, Eq. (1) could also be expressed as:

$$\frac{Ix}{Iy} = \frac{Nx}{Ny} \quad (2)$$

Where x and y represent different nuclei in different chemical environments in one spectrum.[29] Subsequently, we could utilize peak positions to confirm the structure of a unknown compound and integral value for quantitative purpose.

Determination of 90 Degree Pulses

Accurate 90 degree pulse could turn macroscopic magnetization vector from z axis exactly to x-y plane. Because of the drift of magnetic field and other reasons, 90 degree pulses might deviate after a period of time. With regard to qNMR, 90 degree pulses would impact the accuracy of results. Thus, 90 degree pulses should be calibrated after some time. In our experiments, NaF was selected as the target for calibration. The value of 90 degree pulse was 22.5 μs.

Selection of Appropriate Standard

The choice of an appropriate internal standard was one of the important parts for qNMR. A good internal standard could promote wide application of a method and enhance precision.[30] It should be highly pure, soluble in the solvent, stable for a long time under experimental conditions, not react with any analyte, and easily be eliminated from the sample for recycling purposes. Moreover, it should have a single peak and not overlap with other peaks in the NMR spectrum. For ^{19}F-qNMR, 3,3′-bis(trifluoromethyl)benzophenone,[24] sodium salt (FBEN),[26,27] trifluoroacetic acid (CF_3COOH),[28] trichlorofluoromethane ($CFCl_3$),[31] and 4-(trifluoromethoxy) acetanilide (TFMA)[32] have been employed. In this work, considering the cost and convenience for accurate weight, CF_3COONa was used as internal standard.

Determination of Delay Time (D1)

Relaxation process was an essential part in the NMR phenomenon. Delay time (D1) connecting with relaxation was one of the most important parameters, particularly to qNMR. Generally, when D1 was five times longer than T1, 99.3% nuclei in excited state could return to the ground state.[20] Therefore, an appropriate pulse delay time should be selected to avoid signal saturation.

In this work, the inversion-recovery pulse sequence method was use to determine T1. The T1 values were 3.3 s, 4.0 s, and 7.2 s for NaF, $Na_2PO_3 \cdot F$, and CF_3COONa, respectively. Considering the longest T1 was 7.2 s and the acquisition time was 8.8 s, D1 was set to 20 s to save experimental time. In a comparison experiment, D1 was set to 40 s and a very similar result was obtained.

Specificity and Selectivity

Specificity and selectivity as the key prerequisites should be checked for each sample prior to qNMR study.[29] Here, the specificity represents the capability to explicitly ascertain the analyte in a complicated sample, while the selectivity of a method is the capability to determine analyte accurately in a complex sample without interference from other components in the mixture. The sample should have one or a group of non-overlapping peaks in the qNMR spectrum. Fig. 1 shows the ^{19}F-NMR spectrum of standard material. There were three peaks without any interference. The single peak at −100 ppm was NaF and the double peaks at −52.5 and −54.8 ppm were caused by the coupling between F and P in $Na_2PO_3 \cdot F$, because (a) the intensities of peaks were identical; and (b) the same coupling constant 865 Hz was also observed in its ^{31}P-NMR spectrum.

Calibration Curve

Here, the internal standard method was used to determine the concentration of fluorine-containing species. In the qNMR experiment, the sample was determined by adding a certain amount of internal standard into the sample solution. The analyte absolute weight can be obtained by Eq. (3), as derived from Eq. (2):[33]

$$mx = ms \times \frac{Ix}{Is} \times \frac{Ex}{Es} \quad (3)$$

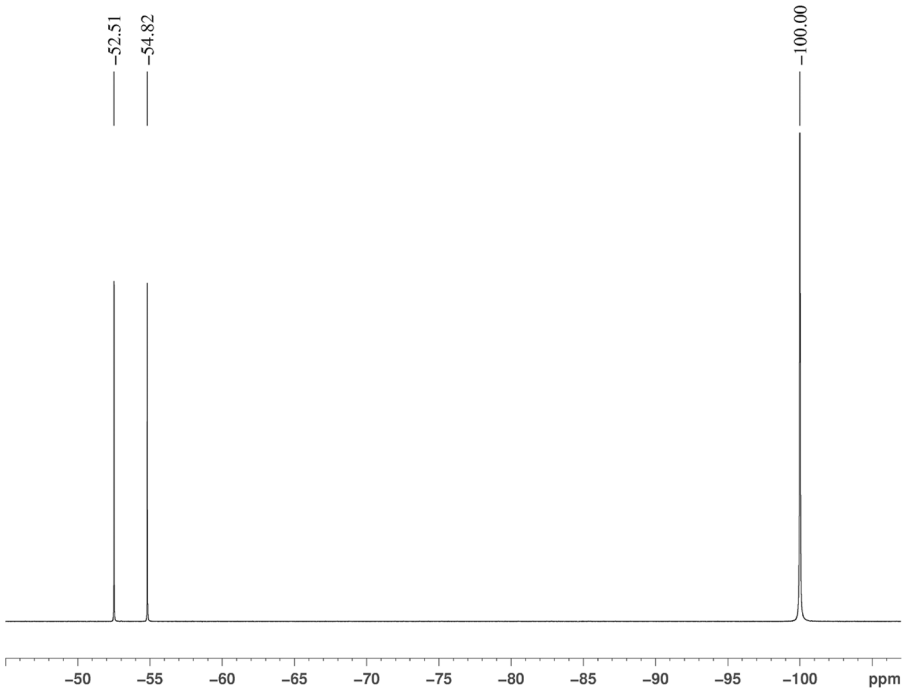

FIGURE 1 **Spectrum of standard solium floride and sodium monoflurophosphate. The single peak at −100 ppm was from NaF, and the double peaks at −52.5 and −54.8 ppm were caused by the coupling between F and P in Na_2PO_3F.**

I_x and I_s: the designated peak areas of analyte and the internal standard, respectively (not less than five times for average);

m_x and m_s: the precise masses of analyte and internal standard;

E_x and E_s: analyte and internal standard nuclei equivalent.

Nuclei equivalents can be calculated by:

$$E = \frac{Molecular\ weight\ of\ analyte}{Number\ of\ proton\ of\ corresponding\ group\ in\ the\ analyte}$$

Here, CF_3COONa was chosen as internal standard so E_s was 45.34; NaF and $Na_2PO_3 \cdot F$ were the analytes, and their E_x was 41.99 and 143.95 for NaF and $Na_2PO_3 \cdot F$, respectively.

Appropriate amounts of analyte/sample and internal standard were added into a 5 mm tube and dissolved with 0.5 mL solvent (450 μL H_2O + 50 μL D_2O). The solution was immediately used for obtaining ^{19}F-NMR spectra. Each sample was recorded continuously for five times to obtain five spectra; each spectrum was integrated three times to obtain an averaged value. Taking m_x/m_s as the X-coordinate and I_x/I_s as the Y-coordinate, the calibration curve can be constructed. As shown in Fig. 2, m_x/m_s and I_x/I_s had a very good linear relationship, so the ^{19}F-qNMR method can be used for the quantitative determination of fluorine.

Precision, Accuracy, and Limit of Detection

Because of the small energy difference between ground and excited states in NMR, it is important to ensure precision and accuracy. Optimization of experimental parameters was an effective strategy.

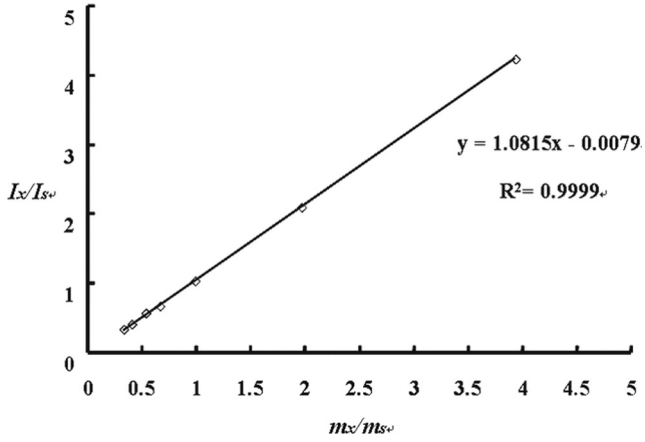

FIGURE 2 **Calibration curve for florine.**

TABLE 1 **Precision and Accuracy of Fluorine Determination by qNMR[a]**

Internal standard/sample	*Mx* (mg)	*Ms* (mg)	*Is*	*Ix*	*Mx′* (mg)	Er (%)	RSD (%)
CF_3COONa/NaF	0.812	0.887	1.0000	1.0058	0.826	1.7	1.0
	4.060	4.437	1.0000	1.0140	4.166	2.6	0.7
	7.140	6.044	1.0000	1.2488	6.989	−2.1	1.3
	10.150	2.546	1.0000	4.2565	10.035	−1.1	0.9

[a]Number of measurements: 5; M: mass in milligram; M′: the average mass found by ^{19}F-NMR; I: the average integral area of peak; x and s: analyte (NaF) and internal standard (CF_3COONa); Er: relative error; RSD: relative standard deviation.

TABLE 2 **Results of Fluorine Determination in Toothpaste by qNMR[a]**

Number of sample	M_{sample} (g)	M_s (mg)	M'_{NaF} (mg)	$M'_{Na_2PO_3F}$ (mg)	Content of F^- (%)[b]	Content of F^- provided by manufacturer (%)
No. 1	0.071	0.100	0.158	—	0.101 ± 0.023	0.10
No. 2	0.067	0.100	0.229	—	0.154 ± 0.017	0.15
No. 3	0.065	0.100	—	0.693	0.141 ± 0.020	0.14
No. 4	0.120	0.100	0.022	1.240	0.145 ± 0.034	0.14

[a]Number of measurements: 5; [b]Average value ± standard deviation; s: internal standard(CF_3COONa); M: mass by weigh; M′: average mass by qNMR determination.

For example, quality of shimming, choice of window function, and phase, baseline, and drift corrections could impact the precision and accuracy of experimental results.[19,29]

After adjustments of experimental parameters, some samples at different concentrations were prepared, then ^{19}F-NMR spectra were recorded in the same condition. Five replicate solutions of each sample were prepared to guarantee method precision and accuracy. Comparing the mass results from directly weighing (M_x) and from NMR spectra calculation (M_x'), the relative error (Er) and relative standard deviation (RSD) of this method were satisfactory, as summarized in Table 1.

Usually S/N was set to 10 for qNMR, then the limit of detection for quantification was 5 μg (10 μg/mL),

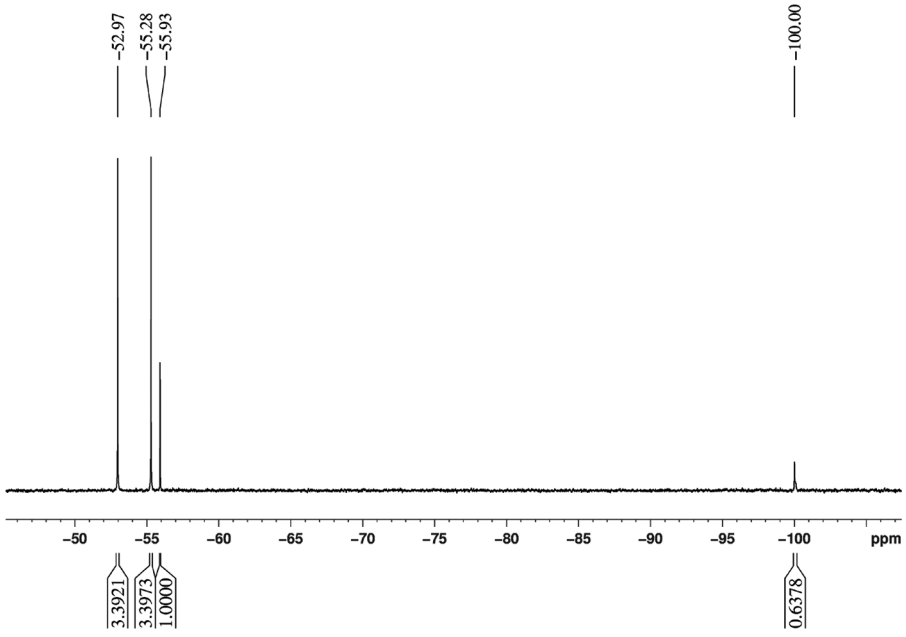

FIGURE 3 **^{19}F–NMR spectrum of a real sample. There were four peaks without any interference.**

TABLE 3 Recovery of Determination Fluorine in Toothpaste by qNMR[a]

Form of fluoride	Mass of sample (g)	Mass of CF_3COONa (g)	Mass of fluoride[b] (mg)	Added mass of fluoride (mg)	Mass′ of fluoride[c] (mg)	Recovery (%)
NaF	0.139	0.001	0.003	1.200	1.246	104
$Na_2PO_3 \cdot F$	0.139	0.001	0.726	0.950	1.639	96

[a]Number of measurements: 5. [b]mass of fluoride (NaF or $Na_2PO_3 \cdot F$) by qNMR determination. [c]mass of fluoride (NaF or $Na_2PO_3 \cdot F$) by qNMR determination after adding standard material.

TABLE 4 Results of Fluorine Determination in Toothpaste by qNMR and Fluoride Ion-Selective Electrode

Number of sample	Content of F^- provided by manufacturer (%)	Content of F^{-a} by qNMR (%)	Content of F^{-a} by fluoride ion-selective electrode (%)
No. 1	0.10	0.101 ± 0.023	0.090 ± 0.004
No. 2	0.15	0.154 ± 0.017	0.144 ± 0.003
No. 3	0.14	0.141 ± 0.020	0.149 ± 0.003
No. 4	0.14	0.145 ± 0.034	0.142 ± 0.002

[a]average value ± standard deviation of 5 measurements.

with the number of scan 16. With a higher field spectrometer, cryoprobe technology, increasing number of scans, the limit of detection can be further improved when necessary.[22]

Determination of Real Sample

A certain amount of toothpaste was accurately weighed in a polyethylene beaker, then dissolved in a small amount of doubly deionized water. The suspension was sonicated for 10 min, then centrifuged. The supernatant solution was made up to 20 mL with doubly deionized water and used for analysis.

400 μL solution was placed in a 5 mm tube, and 50 μL D_2O and 50 μL 1.273 mg/mL CF_3COONa internal standard solution were added. Three replicate solutions of each sample were prepared. The spectra were all referenced to the signal from CF_3COONa.

Through one simple and rapid examination (Table 2 and Fig. 3), two results can be simultaneously obtained: the fluoride content and the speciation information of fluoride in toothpaste. By comparing Fig. 3 with Fig. 1, it can be deduced that the single peak at −100 ppm is from NaF. Because the ^{19}F-NMR is very sensitive for solution environment, chemical shift of the same nuclei may differ in different solution.[34] The coupling constant of double peak is consistent with that in Fig. 1, so we can confirm the double peak at −52.97 and −55.28 ppm is from $Na_2PO_3 \cdot F$. The single peak at −55.93 ppm is from the internal standard. The numbers below the figure is their integral area, which are used for quantitative calculation. Three parallel samples of a toothpaste were added to a certain amount of standard solution of NaF and $Na_2PO_3 \cdot F$, and the recovery by the proposed method was satisfactory (Table 3). To validate the accuracy of this qNMR method, those samples showed in Table 2 were further analized by Floride ISE. The analytical results were agreed with each other very well (Table 4).

CONCLUSIONS

The direct determination of fluorine (as sodium fluoride and sodium monofluorophosphate) in toothpaste by qNMR is an easy, rapid, and accurate method. The sample pretreatment is minimum, and the determination is interference-free. Not only the concentration of fluorine but also the useful information of fluoride speciation can be obtained. The precision of the qNMR for parallel samples and the limit of detection are satisfactory for the analysis of toothpaste samples for fluorine-containing species. It is also potentially useful in the analysis of other fluorine-containing samples.

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