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Application of Nuclear Magnetic Resonance Spectroscopy for Quantitative Analysis of Fluorine in Adult Fluorine-containing Dentifrice

Seoul-Hee Nam[1] and Man-Seok Han[2]*

[1]*Dept. of Dental Hygiene, Kangwon National University, Samcheok, Republic of Korea*
[2]*Dept. of of Radiological Science, Kangwon National University, Samcheok, Republic of Korea*

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Fluoride toothpaste is not only sold globally but also has a global trend in domestic toothpaste products. This study is to compare whether the total fluoride (TF) of adult fluoride toothpaste in Korea is compatible with the standard indicated by the manufacturer. Therefore, this study was performed by Fluorine (^{19}F) nuclear magnetic resonance (NMR) spectroscopy to quantify the fluoride contained in seven fluoride toothpastes. The results were 1128 ppm (2080 pure), 929 ppm (anti-plaque), 1091 ppm (bamboo). 1033 ppm (double action), 597 ppm (perioe), 198 ppm (pleasia), and 1131ppm (smaland). In conclusion, quantitative evaluation of TF in toothpaste may lead to oral health improvement through safe toothpaste selection.

Keywords : fluoride toothpaste, nuclear magnetic resonance (NMR) spectroscopy, fluoride contents, dental caries prevention

1. Introduction

Dental caries is a pandemic disease that has existed since the start of human existence on earth and whose incidence gradually increased with human development through the ages. Today, more than 80 % of humans experience it [1]. Dental caries, a typical oral disease, is an infectious disease caused by caries that destroys the tooth, from the enamel to the dentin, and which has more than one cause. It is a multifactorial complex disease that involves interactions among the bacteria in dental plaque, food, and saliva [2]. If dental caries is not detected early and is left untreated, it may progress to pulpitis or pulp necrosis, which is accompanied by severe dental pain [3].

To prevent dental caries or to remineralize the teeth in the case of early-onset dental caries, the effects and use of fluoride have been studied. Not only have the effectiveness and safety of fluoride been widely known; it has also been used to prevent dental caries in various ways [4]. Fluoride forms low-soluble fluoroapatite in the enamel surface, and is commonly used to inhibit demineralization and to promote remineralization by improving the acid resistance of dental hard tissue [5].

There are various ways of applying fluoride to the oral cavity, including drinking water fluoridation, topical fluoride application by specialists, and using fluoride gargle, tablets, and toothpaste. Among these, using fluoride toothpaste is known globally to have a significant dental caries prevention and reduction effect [6]. Fluoride toothpaste was first developed in the 1950s and was recognized by American Dental Association (ADA) in 1964 as the first therapeutic toothpaste [7]. The recommended concentration of fluoride in toothpaste is generally 1000-1500 ppm for adults, and the applicable South Korean regulations require that the total fluoride content (TF) of fluoride toothpaste be indicated so as to inform the people who purchase and use such toothpaste of the fluoride amount in the product [8]. Therefore, it is necessary to verify the actual amount of fluoride in the commercially available toothpastes in South Korea based on the TF labels, to ensure that the said toothpastes contain an appropriate amount of fluoride. There are two typical methods of measuring the fluoride amount in toothpastes: using fluoride ion electrodes and ion chromatography [9]. It has been reported, however, that the results of the analysis that reacts to the activity of ions rather than the fluoride concentration itself lack reproducibility [10].

Nuclear magnetic resonance (NMR) spectroscopy is a

*Corresponding author: Tel: +82-33-540-3383
Fax: 82-33-540-3389, e-mail: angio7896@naver.com

technique that utilizes the fact that a nucleus reacts to the electromagnetic effects. When a strong magnetic field is applied to a nucleus, it precesses around the magnetic field. When an electromagnetic wave with a resonant frequency is added in a perpendicular direction, the nucleus obtains energy. If the electromagnetic wave is cut, a signal containing the information of the nuclei is transferred to the receiving coil. By analyzing these signals, the structure of the nuclei can be known, or the location information of the nuclei can be obtained [11]. Nam and Han *et al.* [12] studied the quantitative evaluation of fluoride by applying fluorine-19 (^{19}F) NMR, which has the advantage of observing the resonance of the fluorine nucleus without any background problem. Based on this, it was determined that ^{19}F NMR can be effectively used for the quantitative evaluation of fluoride in fluoride toothpastes.

In this study, the TFs of seven types of adult fluoride toothpaste that are commercially available in South Korea were measured using ^{19}F NMR, and the measured TFs were compared with the fluoride amounts indicated on the products by the manufacturers.

2. Materials and Methods

2.1. Sample preparation

Seven fluoride-containing adult toothpastes that are commercially available in South Korea and are classified as fluoride toothpastes were purchased for this study. All the products had a remaining shelf life of more than 6 months. To blind the toothpastes, they were coded using the alphabet (Table 1). To measure their fluoride contents, 0.25 ml of each fluoride toothpaste was dissolved in 1 ml deuterium oxide (D_2O), and the resulting mixture was analyzed.

2.2. NMR measurement

The 19^F NMR measurements were carried out on a ECZR NMR spectrometer (FT-NMR 400 MHz Spectrometer, JNM-ECZ400S/L1, JEOL Ltd, Tokyo, Japan)

Table 1. Toothpastes used in this study.

Products	Total fluoride (ppm)	Manufacturer	Code
2080	1,000	Aekyung	A
Anti-plaque	1,000	Bukwang Pharm	B
Bamboo	1,000	LG Household & Health Care	C
Double action	998	Amorepacific	D
Perioe	920	LG Household & Health Care	E
Pleasia	500	Amorepacific	F
Smaland	1,000	Aekyung	G

Fig. 1. (Color online) FT-NMR 400 MHz Spectrometer used in the total fluorine content of fluoride toothpaste.

operating at 376.17 MHz, equipped with a dedicated 5-mm spinning probe (Fig. 1). The probe temperature was 23 °C. Typical spectral parameters for this study were as follows: 90° pulse width, 6.74 μs; relaxation delay, 5 s; acquisition time 83.88 s. A known amount of D_2O (100 μl) was added as an internal field frequency lock.

The nuclear magnetic resonance spectrometer were calculated using the following formula:Spectral resonance frequency ($V0$)

$$V0 = \frac{\gamma}{2\pi} B0$$

γ= gyromagnetic ratioq
$B0$ = Magnetic Field strength

And Chemical shift (ppm) were used the following fomula.

$$\text{Chemical shift (ppm)} = \frac{Vi - V^{ref}}{V0} \times 1{,}000{,}000$$

$V0$ = The resonance frequency of the chemical bonds that are not nuclear
Vi = The resonance frequency of each element in the molecule
V^{ref} = The reference frequency

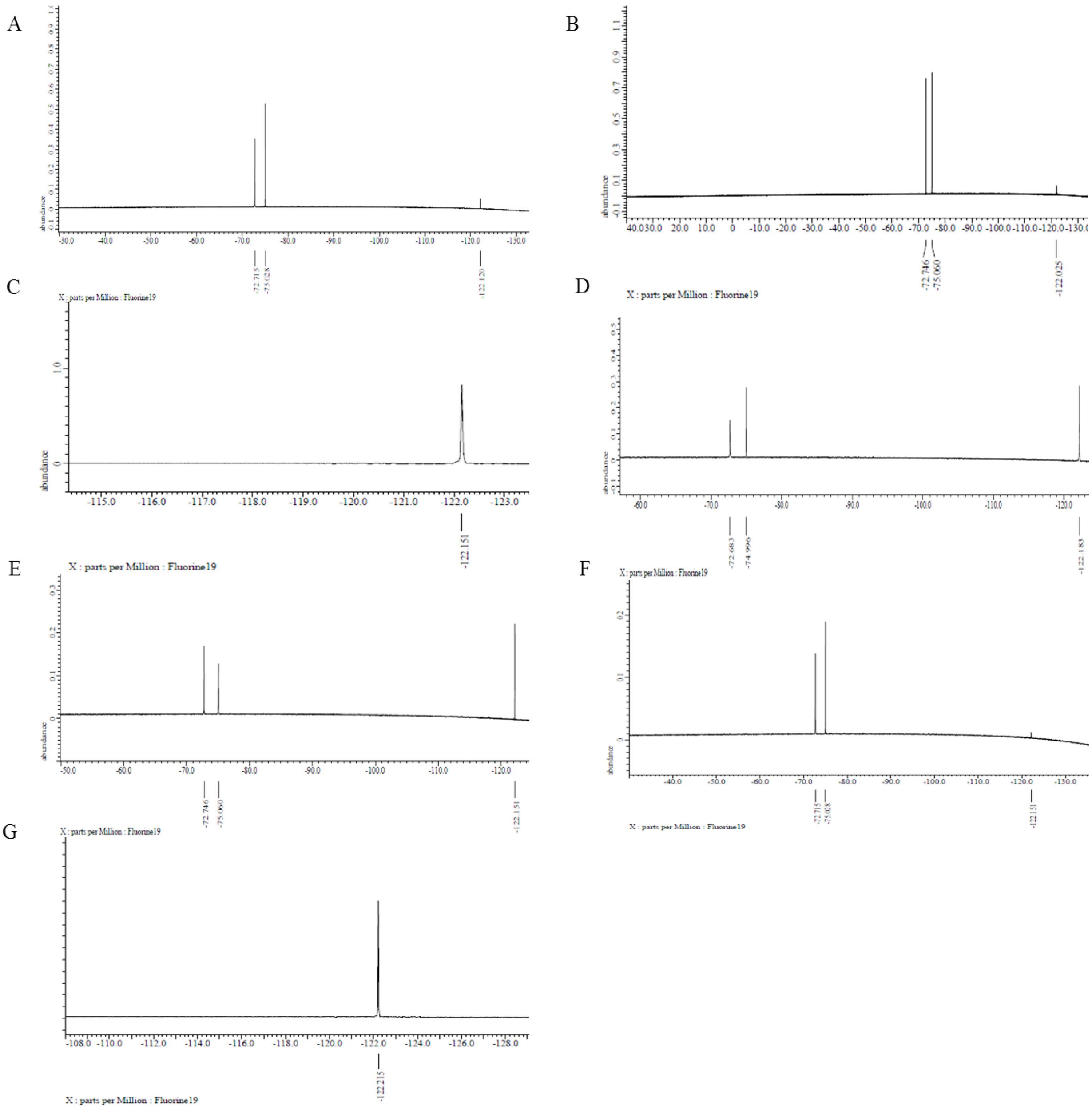

Fig. 2. TFs of the seven adult fluoride toothpastes used in this study determined via ^{19}F NMR analysis.

3. Results

3.1. Fluoride analysis via ^{19}F NMR

The results of the ^{19}F NMR analysis are shown in Figure 2. When the measured TFs were compared with the products' fluoride contents indicated on the labels, the seven products showed similar patterns. The results were 1131.16±3.05 ppm (2080 pure), 930.86±1.51 ppm (anti-plaque), 1030.27±3.13 ppm (bamboo), 599.34±2.26 ppm (double action), 202.64±3.78 ppm (perioe), 1129.52±2.16 ppm (pleasia), and 1091.03±2.28 ppm (smaland). The measured TF of product anti-plaque (69±1.51 ppm), perioe (321±3.78 ppm) and pleasia (297±2.16 ppm) was lower than the TF indicated on its label. The measured TF of product 2080 (131±3.05 ppm), double action (32±2.26 ppm), smaland (130±2.28 ppm) and bamboo (91±3.13 ppm) was higher than the TF indicated on its label. The measurement of the TFs via ^{19}F NMR showed that most of the toothpastes had an about 1,000 ppm TF (Fig. 3).

4. Discussion

It is known that fluoride binds to the teeth enamel and inhibits the acid production of bacteria [13]. To demon-

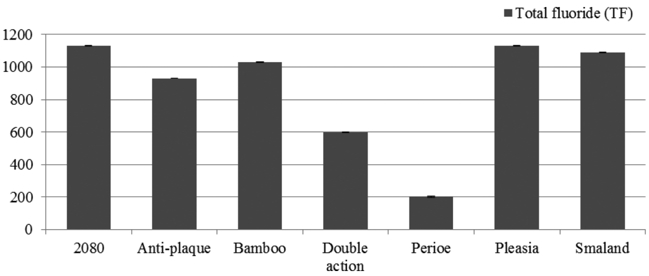

Fig. 3. Quantified TFs by total peak area analyzed from the fluoride toothpastes that were used in this study.

strate its dental caries prevention effect, the TF of fluoride toothpastes must be about 1,000 ppm, and most of the adult fluoride toothpastes in the market have about 1,000 ppm fluoride [14]. Among the adult fluoride toothpastes that were included in this study, one had 500 ppm fluoride, and six were labeled with a TF between 900 and 1,000 ppm.

Studies on the dental caries prevention effect of fluoride toothpastes by TF reported that the use of toothpastes with a 500 ppm or more TF have a dental caries prevention effect. Another study using toothpastes with a TF of less than 500 ppm, however, reported no significant difference between the fluoride toothpastes with a less than 500 ppm TF and the fluoride-free toothpastes in terms of dental caries prevention [15]. Therefore, it is important to use a toothpaste with a 1,000 ppm or more TF for dental caries prevention as the dental caries prevention effect varies by TF [16]. It is known, however, that fluoride toothpastes with a high TF pose a higher risk of fluoride toxicity. Therefore, it is considered that toothpastes with fluoride contents within the range that would not pose a risk of fluoride toxicity must be used.

To more accurately observe the changes in the crystal structure inside fluoride-substituted enamel from the application of fluoride toothpastes thereto, Fourier transform infrared spectroscopy (FTIR) including X-ray diffraction (XRD) has been widely used [17]. Studies utilizing NMR have been actively conducted of late in the dental field, and using magic-angle spinning (MAS)-NMR, Stamboulis *et al.* [18] confirmed the changes that may occur in the crystal structure inside fluoride-substituted enamel after a person brushes with fluoride toothpaste, based on the chemical reaction that occurred in their study after the addition of fluoride to glass ionomer cement. Furthermore, Lee *et al.* [19] reported the effectiveness of NMR in interpreting the three-dimensional structure of bones, and Szutkowski *et al.* [20] conducted a study on the analysis of the bone structure using NMR.

There has been no study, however, using NMR to measure the TF in fluoride toothpastes. In this study, the fluoride concentration was measured from seven toothpastes to calculate the TF in toothpastes, and the results were 1128 ppm (2080 pure), 929 ppm (anti-plaque), 1091 ppm (bamboo). 1033 ppm (double action), 597 ppm (perioe), 198 ppm (pleasia), and 1131 ppm (smaland). Based on the measurements, it was determined that the fluoride toothpastes in the South Korean market are credible as they labeled the concentration of fluoride as TF.

The threshold dose that causes fluorosis or endemic dental fluorosis, the most important side effect of fluorine, is not known exactly. The fluorosis of aesthetic concern was examined in the No fluoride, 450 ppm F, and 1450 ppm F groups, and there was no statistically significant difference between the groups. [21]. Considering the utility of fluoride caries prevention, the amendment to raise the limit on the upper limit of fluoride blending of quasi-drug toothpaste from 1,000 ppm to 1,500 ppm was revised in September 2014 [16].

Based on the above study results, it is considered that providing the TF information of fluoride toothpastes to the customers by accurately measuring the fluoride content will enable the customers to choose the right toothpastes for themselves, which will improve the dental health of adults by allowing them to brush their teeth safely. In addition, it is necessary to continuously verify the TFs of the domestic fluoride toothpastes and to clearly indicate the TFs on the products.

This study, however, has limitations. First, the number of samples per toothpaste is limited. Second, there may be errors due to the differences in the toothpastes' characteristics. Third, the other variables in the study may have an effect on the study results. Further studies will thus be needed to overcome these limitations, and because more adult fluoride toothpastes are being released in the market.

5. Conclusions

Analysis of TF labels on fluoride toothpastes will provide accurate TF information to the public, which will eventually have a positive impact on public oral health promotion by enabling the public to use safe toothpastes.

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