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Ion Concentration of Silver Diamine Fluoride Solutions



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ABSTRACT

Objective: The aim of this work was to determine the free fluoride and silver ion concentrations and the alkalinity of 4 commercially available 38% silver diamine fluoride (SDF) solutions.

Methods: Four common brands of 38% SDF solutions, namely Saforide, Advantage Arrest, e-SDF, and Topamine, were selected. Three bottles of each brand of SDF solution from the same lot were assessed. Measurements of the silver and fluoride content and alkalinity were performed directly when a bottle was opened. Each measurement was repeated to recheck its reliability. The free fluoride ion concentrations were measured using a calibrated ion-selective electrode. The free silver ion concentrations were measured using optical emission spectrometry. The alkalinity of the SDF solution was determined with a pH electrode.

Results: The mean concentrations of fluoride ions of the Saforide, Advantage Arrest, e-SDF, and Topamine were 43,233 ppm, 44,333 ppm, 51,370 ppm, and 54,400 ppm, respectively; their percentage differences from the expected value (44,800 ppm) were 3.5%, 2.4%, 14.7%, and 21.4%, respectively. The mean concentrations of silver ions of the Saforide, Advantage Arrest, e-SDF, and Topamine were 258,841 ppm, 260,016 ppm, 336,149 ppm, and 319,966 ppm, respectively; their percentage differences from the expected value (253,900 ppm) were 3.2%, 5.8%, 32.4%, and 25.9%, respectively. The 4 products had pH values of 9.2, 9.1, 9.2, and 9.0, respectively.

Conclusions: This study showed differences between the claimed and measured fluoride and silver ion concentrations in 4 common 38% SDF products, which were alkaline with a pH value of 9.

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Introduction

Silver diamine fluoride (SDF) solutions were approved for dental use in Japan in the 1960s.¹ They have been used by dentists in countries such as Australia, Brazil, and Japan for many years.

In 2000, the European Organisation for Caries Research suggested using fluoride products with an antimicrobial cation to enhance their caries-preventive effects.² SDF contains silver, which has a strong antibacterial effect; hence, it can be a preferred fluoride agent for use in clinical care. SDF has antibacterial and remineralising properties. In 2014, SDF was cleared by the US Food and Drug Administration as an antihypersensitivity agent.³ Although it is cleared for use to desensitise hypersensitive teeth, SDF has been used to arrest caries.⁴ Current evidence has shown that SDF is an effective caries-arresting agent.⁵ SDF has also been shown to be an effective prevention agent.⁶ The American Academy of Pediatric Dentistry guidelines recommend treatment of primary teeth with a topical application of 38% SDF solution as a noninvasive option to arrest active dental caries lesions.⁷

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A literature review suggested that SDF has the potentially unique ability to be a “silver-fluoride bullet,” simultaneously halting the cariogenic process and preventing caries.⁸ Hence, SDF is a promising fluoride agent to meet the criteria of both the World Health Organisation (WHO) Millennium Goals and the US Institute of Medicine’s criteria for 21st-century medical care.⁸ The American Dental Association announced a policy statement to support using SDF for caries management.⁹ SDF therapy is simple, quick, and noninvasive; in addition, it is low cost, does not generate aerosol, has a low risk of cross-infection, and does not require a complicated armamentarium in clinical use. However, SDF stains the carious lesion a coal-black colour, leaving an unaesthetic appearance that can cause patient dissatisfaction. SDF is well received by both informed patients and dentists because it is user friendly and painless. In 2021, the WHO included SDF in the WHO Model List of Essential Medicines for both adults and children.¹⁰

SDF is an alkaline, colourless solution with a pH value of around 9 to 10 and a metallic taste. It is commercially available at 10%, 12%, 30%, and 38%.¹¹ A clinical trial showed that an SDF solution at 12% was less effective than one at 38% in arresting caries.¹² The most commonly used concentration is 38%, and this concentration is commercially available in many countries. SDF is manufactured in several countries, such as Japan (Saforide), the US (Advantage Arrest), India (e-SDF), Australia (Topamine and Riva Star), and Argentina (FAGamin). A solution of 38% SDF contains approximately 25% silver (253,900 ppm), 8% ammonia, 5% fluoride (44,800 ppm), and 62% water.

SDF is an inexpensive, noninvasive medicament comprising silver fluoride salt made soluble in water through the addition of ammonia.^{13,14} SDF solution is composed of silver, fluoride, ammonia, and water. Diamine silver and fluoride are the main ions of an SDF solution.¹⁴ A diamine-silver ion is a complex structure with 2 ammonia molecules attached to a silver ion, which makes it more stable and less oxidising than a silver ion is.¹⁵ Fluoride ions and silver ions can enhance remineralisation and provide antibacterial properties against some cariogenic bacteria.^{16,17} In addition, SDF reacts with calcium and phosphate ions and produces fluorohydroxyapatite.¹⁸

Although SDF use is generally safe with no significant adverse effects, clinicians should pay attention during its application because it contains a high fluoride concentration.¹⁹ In addition, several studies have found that the silver and fluoride ion concentrations of their tested SDF products

could be different.¹⁹⁻²¹ Mei et al reported that a 38% SDF solution (Saforide) contained silver ions at 248,950 ppm and had a higher-than-expected fluoride ion concentration of 55,800 ppm.¹⁹ Crystal et al tested 5 bottles of a 38% SDF solution (Advantage Arrest) and found differences in concentrations of silver (257,000 ppm to 285,000 ppm) and fluoride (49,400 ppm to 53,360 ppm) from bottle to bottle.²⁰ Patel et al tested 4 commercial 38% SDF products (Advantage Arrest, Topamine, Riva Star, and FAGamin) and reported that the 38% SDF solution contained silver ions from 258,000 ppm to 415,433 ppm and fluoride ions from 36,457 ppm to 90,117 ppm.²¹ Because of the varying concentrations reported in the literature, a study examining the silver and fluoride ion concentrations of commercial SDF products is essential. The objective of this laboratory study was to determine the concentrations of the free fluoride and silver ions and the alkalinity of 4 common brands of SDF solution.

Materials and methods

This study investigated 4 common commercially available 38% SDF solutions, namely Saforide, e-SDF, Advantage Arrest, and Topamine (Table 1). Three bottles of each brand of a 38% SDF solution with the same lot number were collected for assessment in March 2021. The 38% SDF solutions from freshly opened bottles were tested in April 2021. Each bottle of solution was diluted with deionised water with a dilution factor of 1:100 before assessment. All assessments were performed in an air-conditioned laboratory with a temperature at 21 °C and humidity at 50%. Ion-selective electrode (ISE) to determine the fluoride ion concentration and a charge-coupled device detector inductively coupled plasma optical emission spectroscopy (ICP-OES) to measure the silver ion concentration. Each measurement was repeated to recheck its reliability. We used the first measurement for analysis and the second measurement to assess reliability. If the difference of the first and second measurement was not more/less than 2%, the data collected were considered unreliable. The study would be repeated with recalibration of the ISE.

Determination of the free fluoride ion concentration

A fluoride ion specific electrode direct-reading method was used in this study to determine the free fluoride ion concentration of the SDF solutions.²² Ten mL of a pH-adjusted (pH

Table 1 – Information of the four 38% silver diamine fluoride solutions.

Brand	Saforide	Advantage Arrest	e-SDF	Topamine
Main ingredients	38% diamine silver fluoride	38% to 43% diamine silver fluoride, water, triarylmethane dye	25% silver, 8% ammonia, 5% fluoride, 62% water	36% to 40% diamine silver fluoride, ammonium fluoride, triarylmethane dye
Manufacturer	Toyo Seiyaku Kasei	Elevate Oral Care	Kids-e-Dental	DentalLife
Country	Japan	United States	India	Thailand
Lot number	910 RA	20294	ESDF JK121	B0553
Manufacture date	Oct 2019	Oct 2020	Oct 2020	Oct 2020
Expiration date	Oct 2022	Sep 2023	Oct 2022	Oct 2022
Shelf life	2 years	3 years	2 years	2 years

6.0) buffer solution (total ionic strength adjustment buffer) was added to ten mL of the diluted SDF solutions in order to increase their ionic strength to a high level. The ISE (PF-1; Shanghai Precision and Scientific Instrument Co Ltd) was standardised before determining the concentration of the SDF solution sample. Calibration of the ISE was performed using 4 standardised fluoride solutions with fluoride concentrations at 100, 200, 400, and 600 $\mu\text{g/mL}$ before measuring the free fluoride ion concentration of the tested solution. The electric potential of each solution was measured using the electrode on a potentiometer (Model PHS-3C; Shanghai Precision and Scientific Instrument Co Ltd).

A linear equation correlating the logarithm of the fluoride concentration ($r^2 = 0.9998$) was calculated to generate a standard curve by plotting a line graph of fluoride concentration against electric potential. The fluoride concentration was determined using the standard curve from the measured electric potential of the tested solution. Each measurement was repeated to recheck its reliability. Three bottles of each brand from the same lot were assessed to determine the mean fluoride ion concentration of the SDF solution.

Determination of the free silver ion concentration

ICP-OES analysis was used to measure the free silver ion concentration. The silver ion concentration was measured using a charge-coupled device detector of ICP-OES (Varian 720-ES; Varian Inc.). The 720-ES ICP-OES operated at 1 kW (RF power) with a plasma flow rate of 15 litre/min. Five mL of the diluted test solution was converted to a fine spray by a nebuliser and mixed with argon in a spray chamber. The sample was added to the plasma and instantly excited by the high temperature, which allowed the silver content of the solution to be measured with an emission line of 328 nm.

Determination of the alkalinity (pH value)

The pH values of the test solutions were determined using a Mettler Toledo Seven Compact pH meter S210 (IE168-10, Mettler-Toledo). The electrode was thoroughly rinsed with potassium chloride before the measurement. The pH probe was calibrated using 3 buffer solutions with pH values at 4.01, 7.00, and 9.21. An electrical potential difference was produced when the electrode was placed into the test solution. This was compared with the potential difference of the reference electrode with a pH meter.

Results

The mean (SD) fluoride ion concentration of the freshly opened containers of Saforide, Advantage Arrest, e-SDF, and Topamine was 43,233 (1358) ppm, 44,333 (1595) ppm, 51,370 (1264) ppm, and 54,400 (173) ppm, respectively. Deviations of the mean fluoride ion concentration from the expected fluoride ion concentrations of the Saforide, Advantage Arrest, e-SDF, and Topamine were 3.5% (1567 ppm), 2.4% (467 ppm), 14.7% (6570 ppm), and 21.4% (9600 ppm), respectively.

The mean (SD) silver ion concentration of the freshly opened containers of Saforide, Advantage Arrest, e-SDF, and Topamine was 258,841 (8900) ppm, 260,016 (16,397) ppm, 336,149 (15,050) ppm, and 319,966 (54,706) ppm, respectively. Deviations of the mean silver ion concentration from the expected fluoride ion concentration of Saforide, Advantage Arrest, e-SDF, and Topamine were 3.2% (3841 ppm), 5.7% (6116 ppm), 32.4% (82,249 ppm), and 25.9% (66,066 ppm), respectively.

The mean (SD) of alkalinity in pH values of the 4 products was 9.17 (0.06), 9.10 (<0.01), 9.16 (0.06), and 9.00 (<0.01), respectively. Table 2 summarises the free fluoride ion and silver ion concentrations and the alkalinity in pH value of the four 38% SDF solutions.

Table 2 – Mean fluoride and silver ion concentrations and alkalinity of the silver diamine fluoride solutions.

Brand (n = 3)	Fluoride		Silver		Alkalinity pH value
	Concentration (ppm)	Deviation (%)	Concentration (ppm)	Deviation (%)	
Expected value*	44,800	-	253,900	-	9-10
Saforide (mean)	43,233	3.50	258,841	3.32	9.17
Saforide bottle 1	42,500	5.13	262,624	3.44	9.20
Saforide bottle 2	42,400	5.36	248,674	2.06	9.10
Saforide bottle 3	44,800	0	265,224	4.46	9.20
Advantage Arrest (mean)	44,333	2.40	260,016	5.75	9.10
Advantage Arrest bottle 1	42,500	5.13	241,179	5.01	9.10
Advantage Arrest bottle 2	45,400	1.34	267,824	5.48	9.10
Advantage Arrest bottle 3	45,100	0.67	271,049	6.75	9.10
e-SDF (mean)	51,370	14.66	336,149	32.39	9.17
e-SDF bottle 1	50,400	12.50	352,949	39.01	9.20
e-SDF bottle 2	52,800	17.86	331,599	30.60	9.20
e-SDF bottle 3	50,910	13.64	323,899	27.57	9.10
Topamine (mean)	54,400	21.40	319,966	25.91	9.00
Topamine bottle 1	54,500	21.65	349,299	37.57	9.00
Topamine bottle 2	54,500	21.65	353,749	39.33	9.00
Topamine bottle 3	54,200	20.98	256,849	1.16	9.00

* Mei et al., 2013.

Discussion

The analysis was performed difference in the fluoride concentration of several commercially available 38% SDF solutions. Their differences in percentage from the expected value (44,800 ppm) ranged from 3.5% to 21.4%. Our results corroborate previous studies that also found difference in the fluoride concentrations in SDF solutions.¹⁹⁻²¹ So far, 3 studies have been published studying the fluoride concentrations of SDF solutions.¹⁹⁻²¹ Two of them only studied one brand of 38% SDF solution.^{19,20} The researchers of the other study compared 5 brands of 38% SDF solutions. However, they used one bottle of each brand of an SDF solution for testing.²¹ In addition, they conducted a single measurement on each brand without repeated measurement to monitor reliability. In this study, we examined 4 brands of 38% SDF solutions. We performed fluoride concentration measurement on 3 bottles of each brand of the 38% SDF solution and repeated measurements to assess reliability. A limitation of this study was that we did not have access to all common SDF products. We could not purchase a common SDF solution with potassium iodide. Even though we contacted the SDF manufacturers overseas, we did not receive the product in time for evaluation.

In this study, an ISE was used to measure the fluoride concentration. The ISE, a common analytical technique, is used to determine the activity of ions in an aqueous solution by measuring the electrical potential. The ISE is an accurate, fast, economical, and sensitive method in fluoride analysis.²³ The ion-selective electrode was maintained and used according to the manufacturer's recommendations to ensure that the ion-selective electrode functioned in an optimal condition.²⁴ However, the use of the ISE in this study has its limitations. First, interference from other ions in a solution can occur. Second, the ionic strength of the solution at high concentrations can adversely affect the measured activity relative to the true concentration. Third, drift could occur during a sequence of measurements.²⁴ In this study, we used the total ionic strength adjustment buffer to increase the accuracy of the reading by eliminating potential interferences and maintaining a constant ionic strength.²⁰

A notable limitation of this study is that metal cations bind to fluoride; therefore, the study may determine only a fraction of the total fluoride concentration of the tested SDF solutions. In addition, ingredients or impurities, such as proteins or other organic solutes, can foul the electrodes in the measurement.¹⁹ Another limitation of this study is that the analysis was unblinded. Apart from the observer bias and confirmation bias, this study could have experimental bias arising from the researchers' expectation. Last but not least, we only tested 4 brands SDF solutions that were conveniently available in Hong Kong. We did not exhaustively investigate all common 38% SDF solutions available in the market.

Because an SDF solution can be aerosolised, ICP-OES can be used to measure the silver concentration. ICP-OES is a trace-level, elemental analysis technique that uses the emission spectra of a sample to identify and quantify the elements present. It provides a highly sensitive and reliable method for analyte detection.²⁰ Another advantage of using ICP-OES over

other elemental analysis techniques is the enhanced speed of analysis that can be achieved.

We performed the analysis in a clean laboratory room and freshly washed the test products to minimise environmental influence. Furthermore, we stored the SDF solutions in a plastic container because fluoride ions can react with glass to form silicon tetrafluoride.²⁴ The plastic bottle was lightproof to prevent the formation of silver oxide in the presence of light. Temperature affects the electric potential of fluoride ions. The electric potential of fluoride increases 2 mv when its temperature increases by 10 °C. Therefore, the laboratory room temperature was kept constant at 20 °C for the measurement.

The 38% SDF products measured in this experiment were purchased in March 2021. Their shelf lives were generally 2 years, but one had a shelf life of 3 years. The manufacture date of one product was in October 2019, and the other 3 were manufactured in October 2020. This study was conducted in April 2021. Although the 38% SDF production dates from the manufacturers were different, the results should not have been affected because of the long shelf life. While the SDF solutions were assumed would remain stable, the researchers did not know whether the transportation from their respective countries of origin and the ambient temperatures had any effect on the concentration of the silver and fluoride ions.²¹ The concentrations of silver ions measured in the present study were generally higher than the expected values across all of the solutions. One sample had silver ions of more than 353,000 ppm, which is substantially (38%) higher than the expected 253,900 ppm. Although SDF is generally safe to use as a class II medical device for dental use, the manufacturers produce a stable SDF solution for clinical use to minimise any potential side effects.

A recent bibliometric analysis found that the global interest regarding SDF has exponentially increased within 5 years, from 2016 to 2021.²⁵ With the growing evidence of successful SDF therapy, SDF has become a popular clinical treatment since 2016. Clinicians are paying more attention to not only the use but also the ingredients of SDF solutions. In general, a 38% SDF solution contains 253,900 ppm silver and 44,800 ppm fluoride ions. In other words, a 38% SDF solution is composed of 25% silver ions and 5% fluoride ions dissolved in an 8% ammonia solution. However, manufacturers produce SDF according to their own formulation. A 38% SDF solution could be any combination of silver, fluoride, and ammonia totalling 38%. Because the concentrations of silver, fluoride, and ammonia fall within an average range, SDF cannot be exactly 38%. Because the ion concentrations are not included with the material the manufacturer provides with the bottle or on the manufacturer's website, this study offered clinicians and researchers more information on some commercially available 38% SDF solutions.

The results of this study showed that the silver and fluoride concentrations of Advantage Arrest and Saforide were more consistent than e-SDF and Topamine in both the silver and fluoride ion concentrations. Advantage Arrest was more consistent in silver concentration, whereas Saforide was more consistent in the fluoride concentration from the expected 38% SDF solution. A previous

study showed that large differences between claimed and measured fluoride ion concentrations exist amongst the various brands of commercially available SDF products.^{17,21} The result of this study led to a similar conclusion. The concentrations of fluoride ions measured in the present study ranged from 42,500 ppm to 54,500 ppm. Compared with the expected fluoride concentration (44,800 ppm), the difference could be less than 5% to more than 21%. A previous study showed the fluoride ion concentration was 25% higher than the expected concentration.¹⁹ Although SDF is generally used in one-off topical application and in small doses (approximately 0.05 mL per application), it is essential for the manufacturers to develop a quality SDF solution with a stable fluoride ion concentration. Crystal et al assessed the concentration of a commercially available 38% SDF and found that different bottles had varying concentrations of fluoride and that the difference could be large.²⁰ Different lots of SDF solutions of the same manufacturer may contain various ion component concentrations. In this study, we also found differences amongst the 3 bottles of the same products.

This alkaline property matches the favourable condition in which to synthesise fluorohydroxyapatite in chemistry. The proteolytic activities of peptidases, such as matrix metalloproteinases and cathepsins, are inhibited in an alkaline environment. The alkalinity of SDF is a desirable property to prevent demineralisation and inactivate enzymatic degradation of the collagen matrix.²¹

Conclusions

This laboratory study found differences between the claimed and measured fluoride and silver ion concentrations in 4 commercially available 38% SDF solutions from 4 different manufacturers. The alkalinity of the 4 brands of SDF solutions was similar, with a pH value of approximately 9. Amongst the fluoride that agents use for dental care, 38% SDF solutions contain the highest concentration of fluoride. Dentists and hygienists should realise that the fluoride concentration is different amongst the commercially available 38% SDF products.

These findings are important to dentists for the following reasons:

- They provide essential information on the dosage of different brands of silver diamine fluoride solutions, particularly for young children.
- They aid dentists and hygienists in selecting different brands of silver diamine fluoride solutions for topical fluoride therapy.

Author contributions

Chu CH conceived the idea. Yan IG collected the data. Yan IG and Gao SS analysed the data. Yan IG and Zheng FM took digital photos and prepared the figures. Yan IG, Chu CH, Duangthip D, and Lo EC prepared and revised the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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