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CONCENTRATION AND BIOAVAILABILITY OF FLUORIDE IN MOUTHRINSES PREPARED IN DISPENSING PHARMACIES

CONCENTRAÇÃO E BIODISPONIBILIDADE DO FLUORETO DE ENXAGÜATÓRIOS BUCAIS PREPARADOS EM FARMÁCIAS DE MANIPULAÇÃO

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ABSTRACT

Considering the importance of medication quality control and that mouthrinses for dental caries prevention have commonly been prepared in dispensing pharmacies, this study assessed formulations containing 0.05% NaF acquired from 6 dispensing pharmacies in the city of Piracicaba, S.P. The mouthrinse formulations were purchased in 3 separate periods and coded from A to F. Fluoride ion (F^-) concentration was determined in all formulations in the 3 periods, and in those acquired in the 3rd period, the bioavailability of fluoride with dental enamel with caries-like lesions and the pH of products were evaluated. A solution of 0.05% NaF and distilled deionized water were used, respectively, as positive and negative controls. In the bioavailability analysis, fluoride present in dental enamel was determined removing, by acid etching, two layers of enamel; fluoride in the acid extract was determined with a specific electrode. The mouthrinses prepared in 5 pharmacies presented a F^- concentration close to the expected value, except for the product prepared in one of them, in which a mean of 0.01% NaF was found. All products were more efficient than the negative control ($p<0.05$) in terms of reactivity with dental enamel, but differences among them were observed with regard to the positive control ($p<0.05$). The data suggest that a quality control program should be implemented in dispensing pharmacies to guarantee the quality of fluoridated mouthrinses formulated.
Uniterms: Dispensing pharmacy; Mouthrinse; Fluoride; Dental enamel; Bioavailability.

RESUMO

Considerando a importância do controle de qualidade de medicamentos e que os enxagüatórios bucais para prevenção da cárie dental tem sido comumente preparados em farmácias de manipulação, este estudo avaliou enxagüatórios contendo NaF 0,05% adquiridos em 6 farmácias de manipulação na cidade de Piracicaba, SP. Os enxagüatórios foram adquiridos em 3 períodos distintos e codificados de A a F. A concentração de fluoreto (F^-) foi determinada em todas as soluções nos 3 períodos, e naquelas adquiridas no 3º período, a biodisponibilidade do fluoreto com o esmalte dental com lesão de cárie artificial e o pH dos produtos foram avaliados. Uma solução de NaF 0,05% e água destilada deionizada atuaram, respectivamente, como controle positivo e negativo. Na análise de biodisponibilidade, fluoreto formado no esmalte dental foi determinado após remoção, por ataque ácido, de 2 camadas de esmalte; fluoreto no extrato ácido foi determinado com eletrodo específico. Os enxagüatórios preparados por 5 farmácias apresentaram uma concentração de F^- próxima a esperada, com exceção do preparado por uma delas no qual em média foi encontrado 0,01% NaF. Todos os produtos foram mais eficientes que o controle negativo ($p<0,05$) em termos de reatividade com o esmalte dental, mas diferenças entre eles com relação ao controle positivo foram observadas ($p<0,05$). Os dados sugerem que um programa de controle de qualidade deve ser implementado em farmácias de manipulação para garantir a qualidade dos enxagüatórios fluoretados preparados.
Unitermos: Farmácia de manipulação; Enxagüatório; Fluoreto; Esmalte dentário; Biodisponibilidade.

INTRODUCTION

The quality of a pharmaceutical product is one of the fundamental goals to be attained in a standard health system, guaranteeing the patient's benefit and safety. However, errors in dispensing prescriptions have been reported in France[21] and in the United States[28]. Among these, the most common errors are substitution of the medication on the label and even in the composition[28].

In Brazil there are also some reports of such problems involving products purchased from dispensing pharmacies. Zuccolotto, et al.[33] found that 71.4% of the samples of phyto-therapeutic products and vegetable inputs prepared in Porto Alegre, RS, did not meet the minimum quality requirements demanded by the Administrative Ruling No. 6 of the SVS-MS (DOU 01/31/95)[4]. Another type of problem that may occur is the interaction of the active agent with components of the formula, resulting in inactivation or decrease of the expected effect. Thus, Rocha, et al.[25] reported that 1% chlorexidine gel prepared in a dispensing pharmacy in Piracicaba, SP, was ineffective in reducing the salivary levels of mutans streptococci in patients rehabilited with removable prostheses. The reason for this was explained, because saccharine was used as sweetener and, at a concentration greater than 0.5%, it inhibits the antibacterial activity of chlorexidine digluconate at 1%[10]. Therefore, problems of this nature may occur with other products prepared in dispensing pharmacies. Currently, Brazilian dispensing pharmacies are adapting themselves to the regulation RDC No. 33, of 04/19/2000[6].

Fluoridated mouthrinses are relevant as anti-caries agents[8]. Among these, the 0.05% NaF mouthrinse for daily use deserves to be mentioned, as it is efficient in controlling caries in patients at high risk, as those under orthodontic treatment[12,23] or patients that have a physical or motor handicap that prevents them from adequately controlling dental plaque[29]. However, the efficacy of these products does not depend only on the concentration of fluoride in the formula, since the results of Franco and Cury[14,15] showed that the components of a commercial pre-brushing mouthrinse reduced the reactivity of fluoride with human dental enamel. One of the components of mouthrinses that may reduce the reactivity of fluoride is the anionic detergent sodium lauryl sulphate[2], which competes with fluoride for dental enamel surface[3]. Thus, problems with concentration and fluoride activity of mouthrinses may occur both with those prepared in dispensing pharmacies and with commercial products.

In this context, Rodrigues, et al.[26] evaluated the concentration of fluoride ion (F^-) in six commercial brands of mouthrinses present in the Brazilian market, and found that one of them did not comply with the regulation No. 79 of 08/28/2000 of the Ministry of Health's National Sanitary Surveillance Agency[5], because of presenting around 39% of the expected concentration (225 ppm F). This problem with commercial mouthrinses was confirmed in another evaluation[11]. Thus, if the products manufactured in Brazil present problems with quality control, the doubt remains when one considers the large number of dispensing pharmacies and the amount of products they put onto the market. Thus, the correct preparation of fluoridated mouthrinses, considering their concentration, stability and compatibility among components, should be assessed.

Therefore, this study aimed at evaluating mouthrinses prepared in dispensing pharmacies, determining the concentration and bioavailability of the fluoride present.

MATERIAL AND METHODS

Sampling and Experimental Design

Mouthrinses containing 0.05% NaF were purchased in 5 private dispensing pharmacies and in a School Pharmacy in the city of Piracicaba, SP, at 3 separate periods. The private pharmacies were chosen due to their central location in the city and by the fact that two of them are responsible for 80% of the market. In each period, a formula from each establishment was purchased, made up from a prescription given by a dentist, who was not related to the research. The prescription specified the formulation of a fluoridated mouthrinse containing 0.05% NaF. The products were coded from A to F allowing a blind analysis and also ethically preserving the names of the pharmacies. The concentration of F^- ion was determined in all solutions in the 3 periods.

In addition, the pH of the products and the bioavailability of the fluoride to dental enamel were also assessed in the products purchased in the third period. A 0.05% NaF solution was prepared in the laboratory and acted as positive control. Ninety-six blocks of dental enamel with artificial caries lesions were randomly divided into 8 groups of 12 and submitted to the following treatments: distilled deionized water (negative control), 0.05% NaF solution and the 6 fluoridated mouthrinses purchased. The concentration of fluoride present in dental enamel was assessed after removal of two layers of enamel by acid etching, followed by an analysis of the extract with a specific electrode.

Determination of pH and fluoride concentration in mouthrinses

The pH of the products purchased in the third period was determined using a pHmeter connected to a pH electrode, which was calibrated against standard pH buffers (pH 4.0 and 7.0). The products purchased and the solutions prepared in the laboratory were diluted 20 times and TISAB II (1.0 M acetate buffer, pH 5.0, containing 1.0 M NaCl and CDTA at 0.4%) was added in the proportion of 1:1[26]. The analyses were made in triplicate (variation coefficient lower than 1%). The determination of F^- was done with a specific electrode ORION 96-06 and ion analyzer EA 940, previously calibrated with standards containing 1.0 to 10.0 μg F/mL, prepared from 100 ppm F standard (ORION 940907). This analysis was made after each acquisition of products.

Bioavailability of fluoride with dental enamel

For this evaluation, enamel with caries-like lesions was used because this condition is more suitable in terms of the dose-effect relationship than sound enamel[32]. Blocks of dental enamel measuring 4 x 4 x 2mm were obtained[16] from sound bovine incisor teeth that had been stored in a 2% formaldehyde solution (pH 7.0) at room temperature for at least 30 days[9,31].

The enamel surface of the blocks was measured (± 0.01mm), and the other surfaces were protected with a layer of acid-resistant varnish. To produce subsurface caries-like lesions, the enamel blocks were immersed for 16h in a 0.05M sodium acetate buffer solution at 37ºC, pH 5.0, 50% saturated in relation to bovine dental enamel[24]. After this period, the enamel blocks were washed with distilled and deionized water and stored in a humid and refrigerated environment (4°C).

Ninety-six blocks were randomly divided into eight groups of 12 and submitted to the following treatments: six groups for the fluoridated mouthrinses purchased from the dispensing pharmacies and two groups for the positive (0.05% NaF solution prepared in the laboratory) and negative control (distilled deionized water). The reaction time was 10 minutes, the proportion of 1mL of solution/mm^2 of exposed enamel surface was standardized, and after the reaction the blocks were washed for 1 min with distilled deionized water. Two layers of enamel were consecutively removed from each enamel block by immersion in 0.25mL of an aqueous solution of 0.5M HCl for 15 and 30 seconds under agitation, followed by buffering with the same volume of TISAB II pH 5.0 modified with 20g of NaOH/L[19,22]. In these extracts, fluoride and inorganic phosphorous (P_i) concentrations were determined. The determination of F^- was performed using an ion analyzer ORION EA 940 and an ion specific electrode ORION 96-09, previously calibrated with standards of 0.05 to 1.0µg F/mL. P_i was determined by the colorimetric method of Fiske and Subbarow[13]. From the amount of P_i extracted by the acid etching, the mass of enamel removed was calculated, considering a P_i content in enamel of 17.4%[20]. Considering the amount of fluoride extracted (µg) and the enamel mass (g), the concentration of fluoride in enamel due to the treatments (µg/g) was calculated. An enamel density of 3.0[20] was considered to calculate the thickness of enamel removed (depth of the biopsy).

Statistical Analysis

The fluoride concentration data and the pH of the mouthrinses were descriptively analyzed. The results of the thickness of the two layers of enamel were evaluated by analysis of variance (ANOVA). The results of fluoride in enamel were transformed into $\log_{10}$, submitted to ANOVA followed by Newman-Keuls test ($p<0.05$). For all these analyses, the program BioEstat 2.0[1] was used and the significance limit was established at 5%.

RESULTS

Table 1 shows that the mouthrinses prepared in most of the pharmacies presented a fluoride concentration close to the expected value (225ppm of F^-) in the formulas bought at the separate periods. However, the same did not occur with Pharmacy A. The first product purchased in this pharmacy presented a concentration 5 times smaller than that expected. The product prepared in the 2nd period again presented a lower fluoride concentration than that mentioned on the label (0.05% NaF), which was 0.003% NaF. In the sample prepared for the 3rd time by Pharmacy A, the F^- concentration present was greater than that found in the previous ones, but was still less than the concentration expected and described on the product label. In the positive control solution (NaF at 0.05%) prepared in the laboratory, 228.2µg F/mL (ppm) was found. Table 1 also shows the results of the pH of the six mouthrinses acquired in the 3rd period and positive control solution, which ranged from 5.64 to 7.16.

Table 2 shows the results of fluoride concentration in enamel after the reaction of the mouthrinses with the enamel blocks, as well as those of the controls, in the two layers of removed enamel. The ANOVA of fluoride in enamel showed

TABLE 1- Fluoride concentration* (µg/mL) found in the 3 formulas of the mouthrinses in each of the periods and mean (± standard deviation) and pH of the mouthrinses purchased in the 3rd period

Pharmacy	Periods			Mean ± sd	pH
	1	2	3		
Positive control	223.7	227.7	233.3	228.2 ± 4.8	6.07
A	40.7	12.2	97.0	50.0 ± 43.2	6.44
B	233.6	230.3	233.1	232.3 ± 1.8	5.64
C	223.4	233.5	231.3	229.4 ± 5.3	6.23
D	228.9	205.8	254.9	229.9 ± 24.6	6.88
E	231.5	243.1	204.4	226.3 ± 19.9	6.03
F	209.3	227.4	221.3	219.3 ± 9.2	7.16

* Expected 225 (± 10%) µg/mL, accordingto Brazilian guidelines[5]

significance for the treatment in each layer ($p<0.05$). In the 1st layer, all treatments showed differences when compared to the negative control ($p<0.05$); the products prepared in Pharmacies A, D and F presented reactivity equal to that of the positive control, while those from Pharmacies B, C and E presented statistically greater reactivity than that of the positive control. In the 2nd layer, the concentration of fluoride in the enamel due to reaction with the negative control was statistically different from that due to all other treatments, except for the products from Pharmacies D and F ($p>0.05$). The products prepared in Pharmacies B, C and E presented reactivity similar to the positive control. The distance from the surface of each enamel layer removed is shown as mean, as the difference between the treatments was not statistically significant (1st layer $p= 0.5027$; 2nd layer $p=0.2392$).

DISCUSSION

The findings showed that the fluoridated mouthrinses purchased from the dispensing pharmacies presented differences in their formulas (Table 1), as the product prepared in Pharmacy A presented problems in its formula with regard to fluoride concentration in the three periods analyzed. Even though this fact was presented by only one of the pharmacies, in terms of consumers' rights this fact is relevant even if it puts in risk the health of only one citizen. Furthermore, this suggests that consumers are purchasing products that have been manipulated in an incorrect manner. These incorrectly dispensed products could include not only the fluoridated mouthrinses herein presented, but also other medications that are of indispensable use to the patient. The cause of the error in preparing a 0.05% NaF solution may include factors starting with impure raw material through to the use of an un-calibrated balance. The problem with raw material would be of lesser importance in comparison with that of weighing, as the same balance may be used for weighing other pharmaceutical substances. The current legislation[6] establishes that a dispensing pharmacy must present a quality control laboratory to analyze, among others, the amount of active substance, and the equipment needs to be periodically verified and calibrated.

TABLE 2- Concentration (µg/g ± standard error) of fluoride in dental enamel according to the treatments and the removed layer

Treatment	Distance from the surface (µm ± dp)	
	8.2 ± 2.2 (n=10)	25.5 ± 5.9 (n=11)
Negative control	623.6 ± 75.8 [a]	599.1 ± 168.4 [a]
A	2735.6 ± 252.4 [b]	915.8 ± 165.4 [bc]
B	4174.2 ± 216.2 [c]	1582.3 ± 211.8 [d]
C	4548.9 ± 284.6 [c]	1802.5 ± 260.1 [d]
D	3148.9 ± 156.0 [b]	853.9 ± 123.4 [abc]
E	4740.2 ± 261.9 [c]	1385.8 ± 216.9 [cd]
F	2391.9 ± 121.5 [b]	745.8 ± 96.9 [ab]
Positive control	2677.9 ± 169.4 [b]	1849.8 ± 619.6 [d]

Treatments whose means are followed by different letters differ statistically by the Newman-Keuls test ($p<0.05$).

With regard to the capacity of fluoride present in the mouthrinses to react with dental enamel (Table 2), all products presented bioavailable fluoride ready to be incorporated by enamel with caries-like lesions, including that from Pharmacy A, which presented formulation problems (Table 1), as all groups differed statistically from the negative control ($p<0.05$). However, differences among the products themselves and in relation to the positive control were observed. Thus, some of these fluoridated mouthrinses, whose fluoride concentration was close to that mentioned on the label, presented statistically greater reactivity than the positive control in the first layer of enamel removed, and this result is surprising at a first glance. There may be two explanations for the greater reactivity of the mouthrinses prepared in Pharmacies B, C and E in relation to the positive control: (1) these products would have a lower pH than the fluoridated solution prepared in the laboratory, which would positively influence the reactivity of fluoride with dental enamel as, according to Saxegaard and Rölla[27], the decrease in pH of a solution of 0.48 mol/L NaF from 7.0 to 5.5 causes an increase of 4 times in the reactivity of fluoride with dental enamel. The pH of the different solutions analyzed was determined and there was no relationship between lower pH values and greater reactivity. The pH values of solutions ranged from 5.64 (mouthrinse B) to 7.16 (mouthrinse F). This may explain the greater reactivity of the mouthrinse B ($p<0.05$), but, the pH of the positive control solution was 6.07 and the pH of mouthrinse C was 6.23, which would not explain its greater reactivity ($p<0.05$).

Another explanation would be that the substances present in the mouthrinses could increase fluoride reactivity. There have been reports of increase of fluoride incorporation in dental enamel in the presence of surface agents[7,17]. Assessing the product labels in this study, it was noted that Nipagin (methylparaben), a preservative, was listed in the composition of the mouthrinses prepared in Pharmacies B and C, exactly two of the three products that presented greater reactivity. As methylparaben absorbs light at 250nm, absorption spectra of the mouthrinses were traced in a spectrophotometer. Those coded as B, C, E and a solution of methylparaben at 0.2% prepared in the laboratory presented similar spectras with a peak close to 250nm. Mouthrinses A, D, F and the fluoridated solution prepared in the laboratory, which contained only NaF, did not present this peak at 250nm. Thus, the three mouthrinses, which presented the greatest values of fluoride bioavailability with dental enamel in relation to the first layer, also presented the absorption spectra indicative of the presence of methylparaben. These results suggest that new studies should be carried out, in order to confirm this effect of methylparaben and in addition, try to explain its mechanism

of action.

The results of greater fluoride bioavailability of the products prepared in Pharmacies B, C and E were not repeated in the second layer, suggesting that methylparaben could only increase the amount of fluoride formed close to the surface. This kind of fluoride formed could be "CaF_2"-like, which is considered the product responsible for the anti-caries effect of the topical methods of fluoride use[27,30]. Thus, research differentiating the type of fluoride formed in dental enamel should be conducted.

CONCLUSION

In summary, the data suggest that most of the products evaluated were adequately prepared and with bioavailable F, but a process of quality control should be implemented in dispensing pharmacies.

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