

## Effect of Dilution on the pH and Titratable Acidity of Pediatric Syrup Medicines

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### Abstract

To evaluate the effect of dilution on the pH and titratable acidity of two acidic pediatric syrup medicines, three bottles from Claritin® (Schering-Plough) and Dimetapp® (Wyeth) were analyzed with regard to pH and titratable acidity before and after water (pH 6.48 ± 0.12) dilutions of 1:0.5 and 1:1. Control solutions of citric acid with similar baseline pH values to those of the medicines were also evaluated. The initial volume of each medicine and control was 5 ml and pH measurements were performed in triplicate using a digital pH-meter (Quimis Q-400HM). Titratable acidity was also determined in triplicate by adding 0.1M sodium hydroxide (NaOH) previously factored to the undiluted and diluted forms of medicines and controls. The volume of 0.1 M NaOH required to reach pH values of 5.5 and 7.0 was determined for each sample. The proposed dilutions did not alter pH values significantly ( $p > 0.05$ ). Similarly, volumes of NaOH required to reach pH 5.5 and 7.0 were not affected by dilutions in none of the samples ( $p > 0.05$ ). The dilution ratios tested did not improve the pH and titratable acidity of the acidic pediatric syrup medicines analyzed.

**Keywords:** Tooth erosion; Pharmaceutical preparations; Hydrogen ion concentration; Titrimetry; Child

### Introduction

Dental erosion has been demanding increasing attention after caries reduction in many societies [1]. It can be defined “as chronic loss of dental hard tissue that is chemically etched away from the tooth surface by acid and/or chelation without bacterial involvement” [2,3]. It is assumed that the main etiological factors are acids of intrinsic (gastrointestinal) and extrinsic (dietary and environmental) origin [3-5].

The role of dietary acids in the etiology of extrinsic tooth erosion is outstanding. Fruit acids and phosphoric acid present in fruits juices and soft drinks are among the potentially damaging acids frequently consumed by children. Also, ascorbic acid added to a wide variety of drinks and candies has been identified as a possible cause [2,6]. Oral administration of medication has also been implied as an extrinsic cause of dental erosion because of the low pH and high titratable acidity of some medicines used for chronic diseases [7-12]. The risk of dental erosion is increased when syrup medicines are used with a high frequency of ingestion (three or more times per day), at bedtime, or when they have side effects such as reduction of salivary flow rate, which happens with antihistamines [8,9,13].

The pH of liquid oral medicines may be formulated to optimize efficacy and patient acceptability. Acidic preparations are often necessary for drug dispersion because solubility of some substances is pH dependent. Besides, these acidic medicines often taste pleasanter, which may enhance patient compliance, especially children’s [7,10].

Among the preventive strategies for extrinsic tooth erosion due to dietary factors, it has been suggested the modification of products’ content by adding some ions like calcium and phosphate [14-16]. Furthermore, it has also been investigated the effect of dilution on the potential erosive properties of diluting juices [17], which could be an interesting alternative to products’ modification. Therefore, this study aimed to evaluate, *in vitro*, the effect of dilution on the pH and titratable acidity of two pediatric syrup medicines.

### Materials and Methods

The pediatric syrup medicines chosen for this study (Dimetapp®, Wyeth, Sao Paulo, Brazil and Claritin®, Schering-Plough, Vila Olímpia, Brazil) were selected based on a previous study [12], which has pointed out these medicines as presenting the worst results with regard to pH and titratable acidity taken together. Control solutions of citric acid with similar baseline pH values to those of the medicines tested were also evaluated.

The pH measurements throughout the study were made using a pH electrode connected to a digital pH-meter (Quimis Q-400HM, Diadema, Brazil). The electrode was calibrated at the start of each session using standard buffers of pH 4.1 and 6.86. Five milliliters of the newly opened medicines and controls, which were at room temperature, were placed in a beaker and stirred using a non-heating magnetic stirrer until a stable reading was obtained. All measurements were obtained in triplicate and three bottles from each pediatric syrup medicine presenting different serial numbers were analyzed.

Further five milliliters from each bottle of syrup medicine and both control solutions of citric acid were diluted with water (pH 6.48 ± 0.12) in a proportion of 1:0.5 and 1:1, and pH of these dilutions were measured as described earlier.

The titratable acidity was determined in triplicate by using the same pH-meter. To detect the end point of each medicine and control (both in undiluted and diluted forms), five milliliters of each substance were titrated with 0.05 M sodium hydroxide (NaOH) solution, using

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phenolphthalein. The exception for it was Dimetapp® and its diluted forms because their red color prevented the detection of the end point usually characterized by a change of solution's color (from uncolored to light pink). In these cases, the end points were set at a pH value of 9.0. Titratable acidity was then determined by adding increasing quantities of 0.1 M NaOH solution to further five milliliters of both undiluted and diluted forms of the pediatric syrup medicines and controls until the detected endpoints. The samples were again stirred using a non-heating magnetic stirrer until a stable pH reading was obtained after each addition of NaOH. A correction factor of 0.96 was obtained by factorizing 0.1 M NaOH solution with potassium biphthalate. The total volume of 0.1 M NaOH solution required to reach the endpoints and pH values of 5.5 and 7.0 multiplied by the correction factor of 0.96 corresponded to the titratable acidity value for each situation.

All baseline pH values and titratable acidic mean values for pH value of 5.5 and 7.0 and for the endpoint were compared with regard to the different dilution rates proposed using Mann-Whitney tests, with a significance level of 5%. The SPSS software version 16.0 (SPSS Inc, Chicago, USA) was applied for these purposes.

## Results

The average of the triplicate values of pH obtained from the three analyzed bottles of Claritin® were 8.91 (± 0.10), 8.79 (± 0.13) and 8.83 (± 0.03) in the end points for their undiluted, diluted 1:0.5 and diluted 1:1 forms, respectively. The end point for Dimetapp® was set at pH 9.0, because of the limitations mentioned in the methods section. With regard to citric acid control solutions, Claritin® control showed pH 8.29, 8.46 and 8.28 in end points for its undiluted, diluted 1:0.5 and diluted 1:1 forms, respectively; while for Dimetapp, those values were pH 8.48, 8.51 and 8.58 in the same order of presentation.

Table 1 illustrates the effect of dilution on baseline pH values of the pediatric syrup medicines tested and their control solutions of citric

acid. From the presented results, it was demonstrated that dilution did not alter pH values significantly.

Titratable acidic values for pH values of 5.5 and 7.0, and also for end point pH values are shown in table 2 either for the undiluted or for the diluted forms. The investigated dilution rates also did not influence the volume of NaOH required to reach pH 5.5, 7.0 and end point pH values in none of the samples.

## Discussion

Previous *in vitro* [7-12,18,19] and *in vivo* [20] studies have already shown that liquid pediatric medicines could be related with dental erosion. Some of them have proposed this relationship based on medicines' low pH [8] and high titratable acidity [7,10]. With regard to pH, the concern over the detrimental dental effects relates to the use of medicines with an endogenous pH lower than 5.5, the critical pH for enamel dissolution [10]. Both pediatric syrup medicines analyzed in this study presented very low endogenous pH (pH values below 3.0) and the choice of detecting titratable acidic values for pH 5.5 was based on the critical pH for enamel dissolution.

The exact contribution of the various acidic properties of medicines to erosive potential is unclear [10]. Titratable acidity can be considered a more reliable measure of the total acid content of a given substance than the pH itself, once the latter gives only the initial concentration of H<sup>+</sup> ions [17,21-23]. Additionally, it is an indirect measure of the amount of buffering in saliva needed to bring the medication to a neutral pH [7].

Acids are commonly used in medicines as buffering agents to maintain chemical stability, to ensure physiological compatibility and also to improve flavor. Citric acid is the main acid used in prolonged oral clearance medicines, and as a weak acid, it is able to dissociate in solutions of a higher pH and to act as a buffer over a range of pH

Pediatric syrup medicines / Control Solutions	Baseline pH ± SD*; <sup>†</sup>	pH at dilution 1:0.5 ± SD*; <sup>‡</sup>	pH at dilution 1:1 ± SD*; <sup>‡</sup>
Claritin®	2.81 ± 0.07	2.76 ± 0.05	2.75 ± 0.04
Citric acid (pH=2.80)	2.93 ± 0.01	2.86 ± 0.02	2.86 ± 0.02
Dimetapp®	2.48 ± 0.05	2.49 ± 0.03	2.53 ± 0.03
Citric acid (pH=2.50)	2.53 ± 0.02	2.60 ± 0.01	2.61 ± 0.01

\*Mann-Whitney test (P=1.00)

<sup>†</sup>Mann-Whitney test (P=0.89)

<sup>‡</sup>Mann-Whitney test (P=0.89)

**Table 1:** Mean pH values for each pediatric syrup medicine and its respective control solution before and after the proposed dilutions with water.

Pediatric syrup medicines/Control Solutions	Dilution rates	NaOH (ml) ± SD pH 5.5*	NaOH (ml) ± SD pH 7.0 <sup>†</sup>	NaOH (ml) ± SD End point pH <sup>‡</sup>
Claritin®	0	4.34 ± 0.15	5.79 ± 0.35	6.19 ± 0.37
	1:0.5	4.29 ± 0.10	5.77 ± 0.26	6.08 ± 0.35
	1:1	4.33 ± 0.07	5.87 ± 0.15	6.22 ± 0.24
Citric acid (pH=2.80)	0	13.60 ± 0.00	19.20 ± 0.00	19.80 ± 0.06
	1:0.5	13.60 ± 0.06	19.40 ± 0.12	20.10 ± 0.12
	1:1	13.60 ± 0.10	19.20 ± 0.06	19.80 ± 0.06
Dimetapp®	0	6.33 ± 0.32	8.37 ± 0.32	8.84 ± 0.30
	1:0.5	6.40 ± 0.35	8.60 ± 0.48	9.18 ± 0.62
	1:1	6.39 ± 0.31	8.70 ± 0.49	9.30 ± 0.61
Citric acid (pH=2.50)	0	25.30 ± 0.25	34.80 ± 0.17	36.00 ± 0.44
	1:0.5	24.90 ± 0.15	34.40 ± 0.25	35.70 ± 0.30
	1:1	24.90 ± 0.25	34.40 ± 0.30	35.80 ± 0.32

\*Mann-Whitney test for comparison between dilutions 0 and 1:0.5 (P=0.89); 0 and 1:1 (P=0.89); 1:0.5 and 1:1 (P=1.00)

<sup>†</sup>Mann-Whitney test for comparison between dilutions 0 and 1:0.5 (P=1.00); 0 and 1:1 (P=0.89); 1:0.5 and 1:1 (P=0.89)

<sup>‡</sup>Mann-Whitney test for comparison between dilutions 0 and 1:0.5 (P=1.00); 0 and 1:1 (P=0.89); 1:0.5 and 1:1 (P=0.89)

**Table 2:** Mean titratable acidic values of each pediatric syrup medicine and respective control (volume in ml of 0.1M NaOH solution necessary to reach pH values of 5.5 and 7.0, and also end point pH values).

[10]. From measurements of hardness and by SEM and profilometric analysis of bovine teeth and tests of the dissolution of hydroxyapatite *in vitro*, another study [24] verified that citric acid was more erosive than malic acid, being a potent erosive agent because of its ability to chelate calcium in hydroxyapatite, thus increasing enamel's rate of dissolution on exposure to the acid. In the present study, both control solutions were citric acid with similar baseline pH values to those of the medicines tested. The acid's choice was based on the medicines' labels, which denoted the presence of citric acid in the medicines' formulation. Our results confirmed the ability of citric acid to resist pH changes because of controls' high values of titratable acidity. When compared to the medicines tested, control solutions of citric acid presented titratable acidic values three to fourfold greater than medicines' values.

Other factors related with the ingested substances themselves could also modify erosion patterns, such as the general chemical composition of the solutions, which may modify the degree of enamel dissolution [25]. Ions like calcium, phosphate and fluoride have a protective effect against erosion [23]. Therefore, previous studies have proposed the reduction of the erosive potential of beverages by modifying the amount and type of acid used in beverage formulations and/or supplementing with calcium and phosphate [14-16,24].

Nevertheless, product re-formulation can be difficult to be proposed because additives could promote further effects on other ingredients in the drinks [14]. Therefore, an alternative to products' modification could be products' dilution as tested by previous researchers [17] in a study that aimed to examine the effect of dilution on the potential erosive properties of some diluting drinks. Their results showed that only titratable acidity fell considerably as the drink was progressively diluted, and little effect was observed on pH values. However, these results were based on high dilution rates (concentrations ranged from undiluted to one part drink in 100,000 parts water), which were not applicable to the usual consumption of these drinks. On the other hand, our findings demonstrated that dilution influenced neither pH nor titratable acidity, but it is important to point out that our study intended to verify the effect of dilution on the erosive potential of highly acidic pediatric syrup medicines and, therefore, the proposed dilution rates could not be more than twice the volume prescribed (which corresponds to a dilution rate of 1:1) because of the probable difficult of children in drinking medicines' volumes greater than these.

The etiology of dental erosion can also be influenced by biological and behavioral factors. According to a previous study [23], "unusual eating, drinking and swallowing habits, for example holding an acid beverage in the mouth before swallowing, increase the contact time of an acid substance with the teeth and thus increase the risk of erosion" [23]. It is also true for acidic syrup medicines when used with a high frequency of ingestion and consumption at bedtime, considering that oral clearance is compromised during sleep [8-9,13]. In this context, both pediatric syrup medicines tested in this study could increase the risk of tooth erosion for their consumers. Besides being highly acidic, Claritin® is an antihistamine and one of its side effects is the reduction of salivary flow rates, which impairs the protective effect of saliva against erosion. With regard to Dimetapp®, it presented pH values and titratable acidic values even worse than Claritin's and its label information recommends its use up to 6 times per day.

Eroded enamel is more susceptible to wear by tooth-brushing and to toothpaste abrasion [26,27]. Therefore, it is not advisable to brush the teeth immediately after consuming acidic foods or drinks because it could result in tooth abrasion. Instead, a delay in tooth-brushing would allow the remineralizing action of saliva on the eroded enamel [27].

## Conclusion

Within the limitations of this study, the dilution rates tested did not improve the pH and titratable acidity of the acidic pediatric syrup medicines analyzed. Therefore, as dilution did not reduce the erosive properties of syrup medicines tested considering our results, recommendation on immediate water rinse and delayed tooth-brushing after syrup medicines' ingestion could be proposed at the time of prescription. Further studies evaluating alternative preventive strategies for dental erosion due to these highly acidic syrup medicines should be conducted.

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