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Cariogenic and erosive potential of pediatric medicines and vitamin supplements

Potencial cariogênico e erosivo de medicamentos e suplementos vitamínicos pediátricos

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Resumo

Introdução: Formulações farmacêuticas pediátricas com baixo pH e alta acidez titulável usadas com frequência e por longos períodos de tempo têm potencial para produzir lesões erosivas nos dentes. Por outro lado, alta concentração de sacarose, uso noturno e falta de higiene bucal após a administração são fatores que podem contribuir para o potencial cariogênico dessas formulações. **Objetivo:** Avaliar *in vitro* o potencial cariogênico e erosivo de medicamentos e suplementos vitamínicos e minerais líquidos de uso pediátrico. **Material e método:** Medicamentos (n=41) e suplementos vitamínicos e minerais (n=12) líquidos infantis foram selecionados e analisados quanto às suas propriedades físico-químicas, pH, acidez total titulável (ATT) e concentração de sólidos solúveis totais (SST/°Brix). Bulas e rótulos foram analisados para a identificação do conteúdo em açúcares e acidulantes, além dos efeitos colaterais relacionados ao fluxo salivar. **Resultado:** A análise do pH indicou que no grupo medicamentos houve maior variação nas médias observadas. Quanto à ATT em pH 5,5, os grupos medicamentos e suplementos apresentaram variação significativa entre as médias ($p<0,05$). Os resultados da ATT em pH 7,0 demonstraram que a maior média encontrada foi na classe dos anti-histamínicos e a menor na classe dos medicamentos que contém a associação de antitussígenos e anti-histamínicos. A análise de SST demonstrou que em todas as classes de medicamentos e nos suplementos a quantidade de SST variou significativamente ($p<0,05$). **Conclusão**: Os medicamentos e suplementos vitamínicos e minerais líquidos apresentaram comportamentos diferentes dentro do mesmo grupo quanto às variáveis analisadas, apresentando potencial cariogênico e erosivo em sua maioria.

Descritores: Cárie dentária; erosão dentária; preparações farmacêuticas.

Abstract

Introduction: Pharmaceutical pediatric formulations with low in pH and high in total titratable acidicity used frequently and over long periods of time, have the potential to produce erosive lesions in teeth. On the other hand, high concentration of sucrose, the nocturnal use and the lack of hygiene after its administration, are some factors that can contribute to the cariogenic potential of these formulations. **Objective:** To evaluate *in vitro* the cariogenic and erosive potential of medicines and liquid vitamins and mineral supplements for pediatric use. **Material and method:** Medicines (n=41) and liquid vitamins and mineral supplements (n=12) childish were selected and analyzed for their physicochemical properties, pH, total titratable acidity (TTA) and total soluble solids concentration (TSS/°Brix). The package inserts and labels were analyzed to identify the composition regarding the content of sugars and acidulants, in addition to the side effects related to salivary flow. **Result:** The pH analysis indicated that there was greater variation in the observed averages in the medication group. As for the TTA at pH 5.5, supplements and medicines groups showed significant variation between the means found ($p<0.05$). The TTA results at pH 7.0 showed that the highest mean found was in the class of antihistamines and the lowest in the class of drugs that contain the

association of antitussives and antihistamines. The analyses TSS demonstrated that across all drug classes and supplements the amount of TSS varied significantly ($p<0.05$) in all classes of medicines and supplements. **Conclusion**: Most medicines and pediatric liquid vitamin and mineral supplements demonstrated significantly different behaviors within the group itself regarding the variables analyzed that constitute risk factors for the development of dental caries and erosion.

Descriptors: Dental caries; tooth erosion; pharmaceutical preparations.

INTRODUCTION

Children with recurrent acute diseases and chronic respiratory diseases make frequent and regular use of liquid oral medicines, which may represent a possible causal factor for caries[1,2] and dental erosion[2] due to their sugar content and acidulants. These compounds are also present in vitamins and mineral supplements prescribed for children, who represent a group of high vulnerability to macro- and micro-nutrient deficiencies as a result of their rapid growth and development[3].

Dental caries is a multifactorial[4,5] and behavioral disease that involves biological and psychosocial factors[6]. Its etiology is mainly related to the presence of free sugars[5,6] which are metabolized into weak organic acids by cariogenic bacteria of the dental biofilm. These acids cause the pH of the oral environment to reach values below 5.5, which is considered critical for enamel dissolution, resulting in its demineralization and the progression of caries[4,7].

Dental erosion, on the other hand, consists of the wear of hard dental tissues caused by the action of acids[8], of intrinsic or extrinsic origin[9], or of idiopathic cause[10]. Changes in eating habits and the high consumption of acidic beverages and foods have contributed to the increased incidence of dental erosion. In addition, the frequent use of liquid medicines with low pH also seems to be related to the occurrence of this type of dental wear[10].

Excipients are added to the active ingredients of the formulations to improve their palatability, acceptance and preservation[11,12]. Dyes, sweeteners, flavors and acidulants are examples of excipients[13] that, despite being added in low concentrations, can trigger adverse reactions which are often mistakenly associated with the active ingredient of the medicine, compromising the medicinal therapy[12].

Most medicines developed for pediatric use have some type of sugar[11] and acid preservatives[1] in their composition. Sugars are added to children's medicines primarily to mask the unpleasant taste of the active ingredients[14]. Acidulants are added to these formulations in order to ensure their chemical stability and preservation[1], in addition to contributing to their palatability[15].

Although the addition of sugars and acidulants ensures the palatability of liquid preparations, they can cause changes in hard dental tissues[2], such as dental caries and erosion, due to their sugar content, pH[1,7] and titratable acidity[8]. Thus, it is necessary to evaluate the cariogenic and erosive potential of liquid formulations for children's use, since the literature regarding the cariogenic effect of these formulations is not conclusive, as well as being limited as to their erosive potential.

The objective of the present study was to evaluate *in vitro* the cariogenic and erosive potential of medicines and liquid vitamins and mineral supplements for pediatric use. The null hypothesis tested was that there is no difference among the formulations within each group regarding the cariogenic and erosive potential.

MATERIAL AND METHOD

In vitro experimental study developed by analyzing the physicochemical properties, pH, total titratable acidity (TTA) and concentration of total soluble solids (TSS) of drugs (n=41) of different therapeutic classes, and pediatric liquid vitamin and mineral supplements (n=12).

Sample Selection

The sample was selected through an informal consultation with pharmacists responsible for pharmacies located in the city of Salvador, Bahia, Brazil, from April to July 2021, to identify the most prescribed and marketed children's medicines and liquid vitamins and mineral supplements. Forty-one medicines and 12 vitamins and mineral supplements, in liquid form for pediatric use, were selected. Three units of each selected formulation were purchased from different batches, allowing the analyses to be performed in triplicate, totaling 159 measurements.

Determination of pH

The determination of the pH of the medicines and liquid vitamin supplements and minerals was conducted at room temperature of 25ºC, using a microprocessor pH meter (Quimis ®/Q400MT, Diadema, São Paulo, Brazil) and magnetic stirrer EV2.017 (EVLAB-®, Curitiba, Paraná, Brazil). Initially, the pH meter was calibrated with buffer solutions of pH 4.0 and 7.0, and then the pH was measured in 50 mL of each medicine and vitamin and mineral supplement, in triplicate.

Determination of Total Titratable Acidity

Total titratable acidity (TTA) was determined using sodium hydroxide (NaOH), microprocessor pH meter (Q400MT, Quimis®, São Paulo, Diadema, Brazil) and magnetic stirrer EV2.017 (EVLAB- ®, Curitiba, Paraná, Brazil). Using a burette, under constant agitation, 0.1 N of NaOH was added to the 50 mL volume of each medicine and vitamin and mineral supplement. The volumes of the NaOH solution necessary to reach pH 5.5 and pH 7.0 levels were recorded, which corresponded to the TTA value for each pH. The TTA at pH 5.5 was not conducted for pharmaceutical preparations with pH ≥ 5.5, nor was TTA conducted at pH 7.0 for formulations with pH ≥ 7.0. The total volume of 0.1N NaOH solution necessary to reach pH 5.5 and pH 7.0 was recorded, and it corresponded to the TTA value at each pH level.

Determination of Total Soluble Solids (TSS)

TSS was determined by refractometry, using a refractometer model HI 96801 (Hanna®, Woonsocket, Rhode Island, USA) calibrated with distilled water at 25°C. Readings from the samples were performed using the °Brix scale, in triplicate, according to the methodology adapted from Xavier et al.[16]. The quantification of TSS by refractometry, on the °Brix scale, allows inference of the sugar content of solutions[16], since this numerical scale measures the amount of soluble solids present in the solution.

Analysis of Package Inserts and Labels

Analysis of the package inserts and labels was conducted to identify the composition of the medicines and the liquid pediatric vitamin supplements and minerals regarding the presence of sugars, sweeteners, acidulants and acidity regulators (Table 1), as well as the side effects related to salivary flow.

Statistical Analysis

Initially, descriptive and exploratory analyses of all data were conducted. Next, the variables that met the assumptions of an analysis of variance (ANOVA) were analyzed using one-way

ANOVA and Tukey's test. The variables that did not meet the ANOVA assumptions were analyzed using generalized linear models. All analyses were conducted using the R program (*Foundation for Statistical Computing*, Vienna, Austria), with a significance level of 5%.

RESULT

The medicines varied in terms of pH values, with the lowest mean obtained in the class of antihistamines found for Loratadine (pH 2.86), and the highest in the class of corticosteroids found for Prednisolone Sodium Phosphate (pH 7.11). There was also a significant difference ($p<0.05$) in the group of vitamin and mineral supplements. pH values below 5.5 were obtained for all supplements analyzed, with the lowest value found for the Lavitan Tonic supplement (pH 1.81) (Table 2 and Figure 1).

As for the results of the TTA at pH 5.5, there was a significant variation in the means in the group of medicines. A higher mean was found for Loratadine (185.27 mL) in the class of antihistamines, and a lower mean was found for Brondilat ® (0.10 mL) in the class of bronchodilators. The supplements analyzed also showed significant variation between the TTA averages at pH 5.5 ($p<0.05$). The lowest value (3.60 mL) was found for the Abcalcium® supplement, and the highest value (31.33 mL) was found for Lavitan Tonic (Table 2 and Figure 2A).

The TTA results at pH 7.0 showed that the highest mean found was for Loratadine (233.23 mL) in the class of antihistamines, and the lowest mean found was for Seki® (0.50 mL) in the class of medicines that contained the association of antitussives and antihistamines. Among the supplements, the highest mean was found for Lavitan Tonic, and the lowest means were found for the Scott and Beritin BC supplements ($p<0.05$) (Table 2 and Figure 2B).

The TSS analysis (°Brix) showed that, for all medicines and supplements analyzed, this amount varied significantly ($p<0.05$). An SST °Brix of 1.43 was found for the bronchodilator Aerolin®, and of 64.03 for the expectorant Bronquivita ® ($p<0.05$) (Table 2 and Figure 3).

The components identified, from the package inserts and labels of the medicines and supplements, are described in Table 1. Analysis of the labeling showed that 52.83% (n=28) of all formulations investigated reported the presence of sucrose in the composition, either alone (16.98%/n=9) or associated with other sweeteners (35.84%/n=19). In 42.85% (n=12) of the formulations that contained sucrose, there was a warning regarding the use by diabetic patients. The main sweeteners found in the formulations, alone or in combination, were sorbitol, sodium saccharin, sodium cyclamate, aspartame and acesulfame.

Regarding the acid content, the presence of acidulating agents in the formulations was verified, either in isolation or in association. The main acidulants found were citric acid, identified in 50.94% (n=27) of all pharmaceutical preparations, and benzoic acid, present in 11.32% (n=6) of the formulations. The presence of other acids such as hydrochloric acid, phosphoric acid, tartaric acid and lactic acid was also identified.

Xerostomia was reported as an adverse reaction in 33.96% (n=18) of the package inserts and labels of the medicines and supplements analyzed. This information was identified in the therapeutic classes of the antihistamines (n=4), in the medicines that contained antitussives and antihistamines (n=2), bronchodilators (n=2), corticosteroids (n=2), expectorants (n=5) and in the group of supplements (n=3). No formulation analyzed referred to hyposalivation as an adverse reaction.

Table 1. Distribution of medicines and pediatric liquid vitamin supplements and minerals according to composition, trademark and manufacturer

Medicines Therapeutic Class	Trade name	Acidulant	Synthetic Sugars / Sweeteners	Manufacturer	Batch
Antihistamines	Allegra ®	-	Sucrose, Xylitol, Xanthan gum	Sanofi Medley	BRA00752/ BRA02960/ BRA00750
	Desalex ®	Citric acid	Sucrose, Sorbitol	Merck Sharp & Dohme Corp.	S024788/S039077/ S035807
	Ebastel ®	Lactic acid	Sorbitol	Eurofarma	678702A/718414A/ 7184414B
	Polaramine ®	-	Sucrose, Sorbitol	Brainfarma	B20J2438/B20J2445 /B20K3118
	Desloratadine 0.5mg/mL	Citric acid	Sucrose, Sorbitol	Eurofarma	657767A/683977A/ 658633A
	Loratadine 1mg/mL	Citric acid	Sorbitol, Saccharin sodium, Maltitol	CIMED	2014201/2108900/ 2024075
	Dexchlorpheniramine maleate 0.4mg/mL	-	Sorbitol, Sodium cyclamate	Brainfarma	B20J0529/ B20K4540/ B20L1755
Antitussives	Notuss	Benzoic acid, Citric acid	Sucrose	Aché	2006636/2105601/ 2006634
	Vibral ®	Benzoic acid, Citric acid	Sucrose	Abbott	1093190/1123446/ 1062076
	Dropropizine 3.0mg/mL	Benzoic acid, Citric acid	Sucrose	Aché	2014707/2007741/ 2103080
Antitussives and Antihistamines	Benatux ®	Citric acid	Sucrose, Saccharin Sodium, Sodium cyclamate	Kypharma	L3ME13/L3MF50/ L3MG30
	Hytós ® Plus	Citric acid	Sucrose, Saccharin Sodium,	União Química	2020971/ 20100113/ 2016654
Bronchodilators	Seki ®	Chloride acid	Sucrose	Sanofi Medley	ARA01445/ ARA02839/ ARA02840
	Aerolin ®	Citric acid	Saccharin sodium	GlaxoSmithKline Brasil, Ltda.	2S4N/JJ3R/VF4F
	Brondilat	-	Sorbitol	Aché	2002941/2000885/ 2000882
	Acebrofilin 25mg/5mL	-	Sorbitol, Sodium cyclamate	CIMED	1918198/1920009/ 1913900
	Salbutamol sulfate 0.48mg/mL	Citric acid	Saccharin sodium dihydrate	Prati, Donaduzzi & Co.	20G79A/20I51H/ 20G861
Corticosteroids	Celestone ®	Citric acid	Sucrose, Sorbitol	Brainfarma	B20J1125/ B20E1756/ B20J1125
	Decadron	Benzoic acid	Saccharin sodium dihydrate	Aché	2013139/2008104/ 2002945
	Predsim ®	-	Sorbitol, Saccharin sodium, Maltitol	Brainfarma	B20D0383/ B20A0029/ B20H1991
	Betamesatone 0.1mg/mL	Citric acid	Sucrose, Sorbitol	EMS	1Y1116/1U2492/ 1W6671
	Prednisolone sodium phosphate 4mg/mL	-	Sorbitol, Saccharin sodium, Maltitol	Prati, Donaduzzi & Co.	20D835/21C68F/ 21E76N
Expectorants	Ambroxmel ®	Citric acid	Sorbitol, Saccharin sodium, Maltitol Sodium cyclamate	CIMED	2012855/2102216/ 1921354
	Bisolvon ®	Benzoic acid	Sucrose, Maltitol liquid	Sanofi Medley	ARA02843R/ ARA1173/BRA02099
	Blumel ® *Hedera*	-	Sorbitol	Brainfarma	B21D0826/ B21D0825/ B21D0823
	Bronquivita ®	-	Sucrose, Honey from bees	Laboratório Vitalab	BRX0221/BRX5520/ BRX2321
	Expec ®	Citric acid	Saccharin sodium, Sodium cyclamate	Legrand	1T1814/1S9736/ 1T1811

Table 1. Continued...

Medicines Therapeutic Class	Trade name	Acidulant	Synthetic Sugars / Sweeteners	Manufacturer	Batch
	Fluimucil ®	Chloride acid	Saccharin sodium	Sanofi Medley	9RA05153/ ARA01167/ ARA02081
	Guaco Natulab Syrup	-	Sucrose, Sorbitol	Natulab	22815/22841/ 22800
	Melagrião ®	-	Sucrose, Honey	Laboratório Catarinense Ltda	37594/36679/ 34068
	Mucofan ®	Citric acid	Sucrose, Sorbitol	União Química	2025083/2009175/ 1934387
	Mucosolvan ®	Benzoic acid	Sorbitol, Acesulfame potassium	Sanofi Medley	ARA05868/ ARA00166/ ARA01946
	Sedavan ®	Tartaric Acid	Sorbitol, Saccharin sodium, Maltitol	Vidfarma	200440/192353/ 191672
	Pediatric Vick ® Syrup	Citric acid	Sucrose, Saccharin Sodium,	Procter & Gamble do Brasil	02964354B0/ 10484354B0/ 02044354B1
	Vick ® Honey Syrup	Citric acid	Hydrolyzed sugar syrup, Aspartame, Acesulfame	Procter & Gamble do Brasil	02874354B0/ 03014354B1/ 01884354B0
	Vick ® 44e Syrup	Citric acid	Sucrose, Saccharin Sodium,	Procter & Gamble do Brasil	0324258707/ 0317258711/ 0052258707
	Acetylcysteine 20mg/mL	-	Saccharin sodium	EMS	1G7324/1T2305/ 1Q7081
	Carbocysteine 20mg/mL	Citric acid	Saccharin sodium	EMS	1J9179/1M5683/ 105170
	Ambroxol hydrochloride 15mg/5mL	Citric acid	Saccharin sodium	CIMED	2014147/2000697/ 2014148
	Bromexin hydrochloride 4mg/5mL	Tartaric Acid	Sorbitol, Sodium cyclamate	Sanofi Medley	ARA01492/ BRA02391/ BRA00195
	Guaifenesin 200mg/15mL	Chloride acid	Sorbitol, Sodium cyclamate	Brainfarma	B20G2150/ B20G2152/ B20G2152
Supplements	**Trade name**	**Acidulant**	**Synthetic Sugars / Sweeteners**	**Manufacturer**	**Batch**
Vitamin and mineral supplements	Abcalcium ® (strawberry)	Citric acid	Saccharin, Sucrose	Airela Indústria Farmacêutica	21B0235/21B0168/ 20J0277
	Apetiviton ® BC	-	Sucrose, Saccharin Sodium,	Kypharma	3NC53/3NC46/ 3MG60
	Apevitin ® BC	-	Sorbitol, Sodium cyclamate	EMS	2B2355/2B2348/ 2B2350
	Beritin BC	-	Sucrose	Vitamedic	52932/56823/ 55227
	Biotonic Fontoura (strawberry)	Phosphoric acid	Sucrose, Sorbitol	Brainfarma	B18K2961/ B18K2958/B18K036 1
	Carnabol Kids	Citric acid	Sodium saccharin dihydrate, Sorbitol, Sodium cyclamate	Aché	2009200/2101078/ 2004773
	Lavitan Vitamins	Citric acid	Sucrose, Acesulfame potassium	CIMED	2020645/2020646/ 2108486
	Children's Power Vita Multivitamin	Citric acid	Saccharin, Aspartame	CIMED	2014841/2017214/ 2014842
	Puravit Multi	Citric acid	Sucrose, Sorbitol, Aspartame	Myralis	519316/520719/ 518320
	Scott	Citric acid	Sucrose	GlaxoSmithKline Brazil	HE3Y/8T5Y/D59W
	Lavitan Tonic	Phosphoric acid	Sucrose	CIMED	2102379/2019747/ 2100444
	Vita Mune Kids	Citric acid	Saccharin, Aspartame	Nutracom	2017538/2102136/ 2017789

Source: Information available on the packaging and package inserts of medicines and supplements.

Table 2. Mean (standard deviation) of pH, TTA (pH 5.5 and pH 7.0) and TSS of medicines and vitamin and mineral supplements

Medicines Therapeutic Class	Trade name	pH	p-value	Titratable total acidity (mL 0.1 N NaOH)				TSS °Brix	p-value
				TTA pH 5.5	p-value	TTA pH 7.0	p-value		
Antihistamines	Allegra ®	6.29 (0.01) a	<0.0001	-	<0.0001	18.57 (0.15) b	<0.0001	29.77 (0.12) e	<0.0001
	Desalex ®	5.62 (0.02) c		-		3.10 (0.10) cb		54.40 (0.66) a	
	Ebastel ®	4.02 (0.02) f		11.00 (0.87) b		12.27 (1.12) bc		23.13 (0.06) f	
	Polaramine ®	6.15 (0.01) b		-		1.10 (0.10) d		49.77 (0.06) b	
	Desloratadine 0.5 mg/mL	5.20 (0.00) d		1.13 (0.06) c		4.53 (0.06) cd		35.03 (0.06) d	
	Loratadine 1 mg/mL	2.86 (0.05) g		185.27 (7.18) a		233.23 (10.21) a		45.80 (0.17) c	
	Dexchlorpheniramine maleate 0.4 mg/mL	5.04 (0.07) e		1.13 (0.06) c		0.90 (0.00) d		10.40 (0.10) g	
Antitussives	Vibral ®	4.93 (0.01) a	<0.0001	0.87 (0.12) b	<0.0001	3.47 (0.12) b	<0.0001	55.57 (0.61) a	<0.0001
	Notuss	4.26 (0.14) b		7.23 (1.97) a		12.93 (2.57) a		36.40 (0.17) b	
	Dropropizine 3 mg/mL	4.35 (0.03) b		6.23 (0.15) a		11.70 (0.35) a		36.20 (0.02) b	
Antitussives and Antihistamines	Benatux	5.08 (0.02) b	<0.0001	9.10 (0.44) a	<0.0001	22.40 (0.56) a	<0.0001	11.20 (0.20) c	<0.0001
	Hytós ® Plus	4.20 (0.01) c		6.27 (0.06) b		10.87 (0.15) b		43.03 (0.47) a	
	Seki®	6.08 (0.02) a		-		0.50 (0.10) c		39.53 (0.40) b	
Bronchodilators	Aerolin ®	3.60 (0.03) c	<0.0001	24.47 (0.31) b	<0.0001	34.13 (0.15) b	<0.0001	1.43 (0.06) d	<0.0001
	Brondilat ®	4.87 (0.01) b		0.10 (0.00) d		0.80 (0.10) c		41.37 (0.15) a	
	Acebrofilin 25mg/5mL	5.04 (0.05) a		0.17 (0.06) c		0.53 (0.06) d		22.43 (0.12) b	
	Salbutamol sulfate 0.48mg/mL	3.68 (0.05) c		52.40 (0.79) a		75.40 (2.10) a		2.50 (0.10) c	
Corticosteroids	Celestone ®	2.96 (0.00) d	<0.0001	17.17 (0.15) b	<0.0001	21.90 (0.10) b	<0.0001	49.07 (0.06) b	<0.0001
	Decadron	3.22 (0.04) b		4.00 (0.10) c		4.30 (0.17) c		21.07 (0.06) d	
	Predsim ®	7.10 (0.02) a		-		-		37.57 (0.64) c	
	Betamethasone 0.1 mg/mL	3.10 (0.00) c		18.50 (0.35) a		24.23 (0.55) a		53.07 (0.06) a	
	Prednisolone sodium phosphate 3 mg/mL	7.11 (0.02) a		-		-		20.83 (0.21) d	
Expectorants	Ambroxmel ®	3.54 (0.04) e	<0.0001	21.4 (0.56) a	<0.0001	29.10 (0.78) a	<0.0001	34.83 (0.06) f	<0.0001
	Bisolvon ®	3.07 (0.02) fg		6.73 (0.31) f		7.30 (0.30) de		34.93 (0.12) f	
	Blumel ®	5.38 (0.01) b		0.43 (0.06) j		2.57 (0.06) ijk		52.40 (0.26) c	
	Bronquivita ®	4.72 (0.17) d		0.70 (0.10) ij		3.10 (0.10) ijk		64.03 (1.14) a	
	Expec ®	4.77 (0.03) cd		3.13 (0.21) h		4.83 (0.46) gh		4.67 (0.06) j	
	Fluimucil ®	6.38 (0.22) a		-		1.10 (0.52) jk		3.87 (0.06) j	
	Guaco Natulab Syrup	5.64 (0.01) b		-		0.73 (0.06) k		9.77 (0.21) i	
	Melagrião ®	5.04 (0.10) c		1.67 (0.40) i		3.37 (0.40) ghi		59.07 (0.81) b	
	Mucofan ®	6.14 (0.17) a		-		5.37 (1.37) efg		53.93 (0.31) c	
	Mucosolvan ®	2.95 (0.01) g		6.77 (0.21) f		7.57 (0.21) de		31.63 (0.65) g	
	Sedavan ®	2.91 (0.03) g		8.33 (0.06) e		9.07 (0.06) d		26.90 (0.26) h	
	Pediatric Vick ® Syrup	4.86 (0.06) cd		9.57 (0.93) d		21.37 (2.23) c		42.37 (0.59) d	
	Vick ® Honey Syrup	4.68 (0.01) d		16.80 (0.30) b		30.30 (0.26) a		54.07 (0.21) c	
	Vick ® 44E Syrup	4.82 (0.01) cd		10.90 (0.56) c		24.03 (0.85) b		42.90 (0.17) d	
	Acetylcysteine 20 mg/mL	6.31 (0.20) a		-		0.77 (0.31) k		5.53 (0.06) j	
	Carbocysteine 20 mg/mL	6.35 (0.11) a		-		4.17 (0.67) ghi		6.37 (0.06) j	
	Ambroxol hydrochloride 5mg/5mL	3.37 (0.15) ef		6.20 (0.10) f		7.07 (0.31) def		29.70 (4.07) gh	
	Bromexin hydrochloride 4mg/5mL	3.50 (0.03) e		4.40 (0.36) g		4.93 (0.32) fgh		38.70 (0.30) e	
	Guaifenesin 200 mg/15 mL	6.15 (0.03) a		-		0.57 (0.06) k		43.70 (0.10) d	

Table 2. Continued...

Supplements	Trade name	pH	p-value	Titratable total acidity (mL 0.1 N NaOH)				TSS °Brix	p-value
				TTA pH 5.5	p-value	TTA pH 7.0	p-value		
Vitamin and mineral supplements	Abcalcium ® (strawberry)	4.92 (0.04) a	<0.0001	3.60 (0.52) h	<0.0001	11.13 (0.90) g	<0.0001	15.6 (0.44) f	<0.0001
	Apevitin ® BC	4.02 (0.03) e		11.90 (0.17) e		14.77 (0.06) f		60.33 (0.49) b	
	Apetiviton ® BC	3.89 (0.02) f		11.83 (0.12) e		15.37 (0.25) f		51.43 (0.21) c	
	Beritin BC	3.87 (0.02) f		8.73 (0.81) f		10.27 (0.84) g		62.00 (0.70) a	
	Biotonic Fontoura (strawberry)	2.45 (0.03) h		26.20 (0.17) b		41.50 (0.20) b		27.87 (0.06) d	
	Carnabol Kids	3.55 (0.00) g		19.03 (0.15) d		21.40 (0.26) d		15.23 (0.06) f	
	Lavitan Vitamins	4.17 (0.01) d		25.00 (0.72) bc		36.80 (0.56) c		9.87 (0.21) h	
	Vita Mune Kids	4.18 (0.00) d		24.53 (0.15) c		35.80 (0.26) c		10.27 (0.29) h	
	Power Vita Vitamins - Children's Multivitamin	4.18 (0.01) d		24.90 (0.56) c		36.17 (0.15) c		10.03 (0.06) h	
	Puravit Multi	4.66 (0.04) b		7.40 (0.35) g		18.20 (0.36) e		12.70 (0.26) g	
	Scott	4.43 (0.00) c		6.77 (0.32) g		10.20 (0.44) g		7.57 (0.06) i	
	Lavitan Tonic	1.81 (0.00) i		31.33 (0.25) a		47.47 (0.40) a		22.00 (0.17) e	

Vertically distinct letters indicate statistically significant differences (p≤0.05).
Source: Authors.

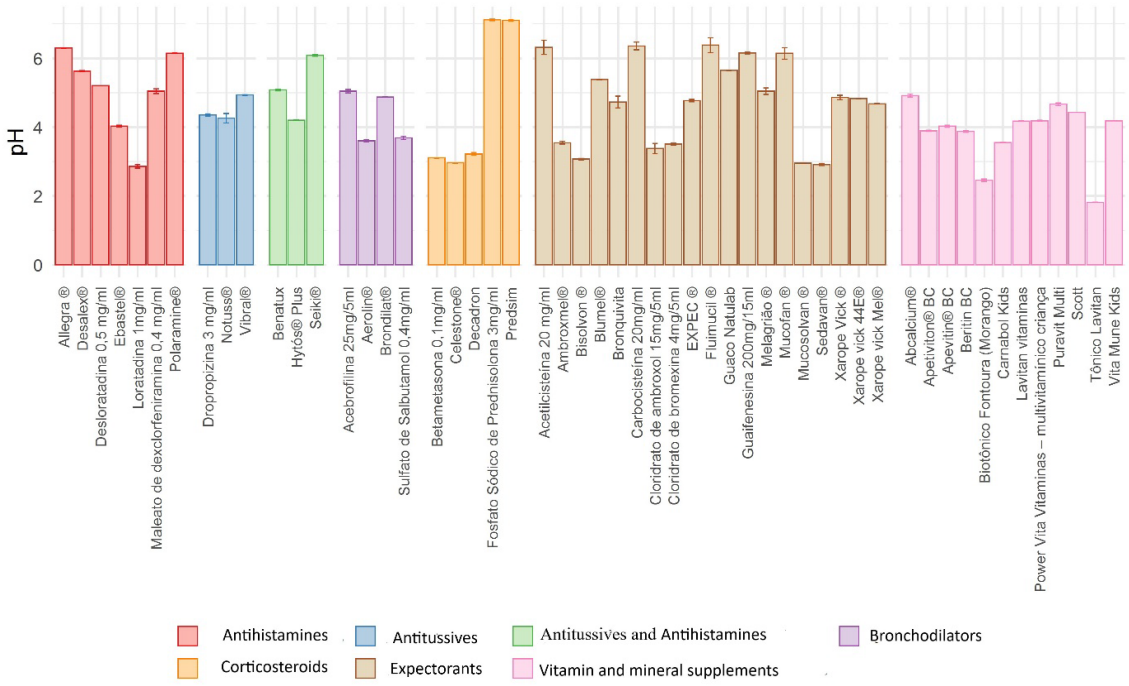

Figure 1. Mean and standard deviation of pH as a function of medicines, by therapeutic class, and vitamin and mineral supplements.

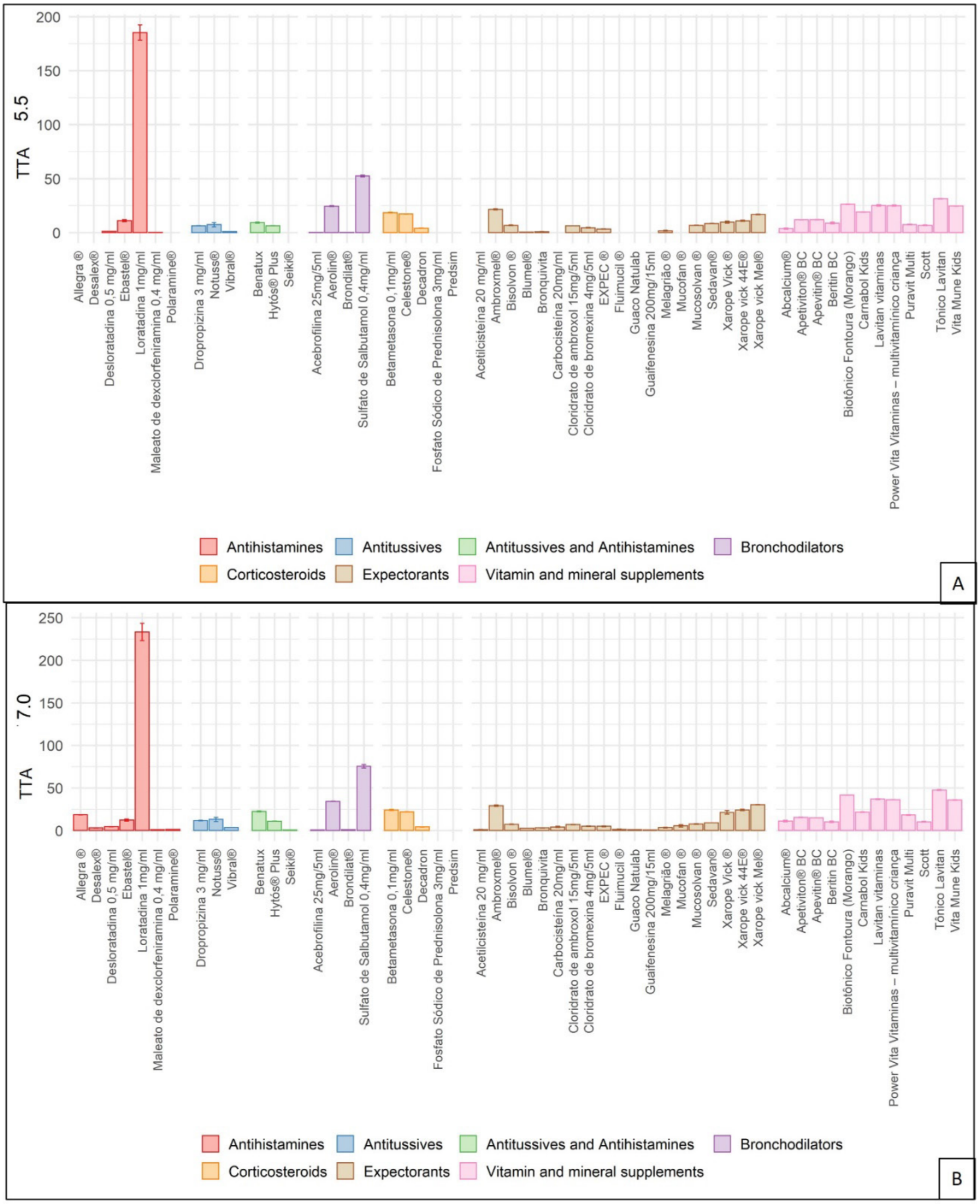

Figure 2. A- Mean and standard deviation of total titratable acidity (TTA) at pH 5.5 depending on the drugs, by therapeutic class, and vitamin and mineral supplements. **B-** Mean and standard deviation of total titratable acidity (TTA) at pH 7.0 depending on the drugs, by therapeutic class, and vitamin and mineral supplements.

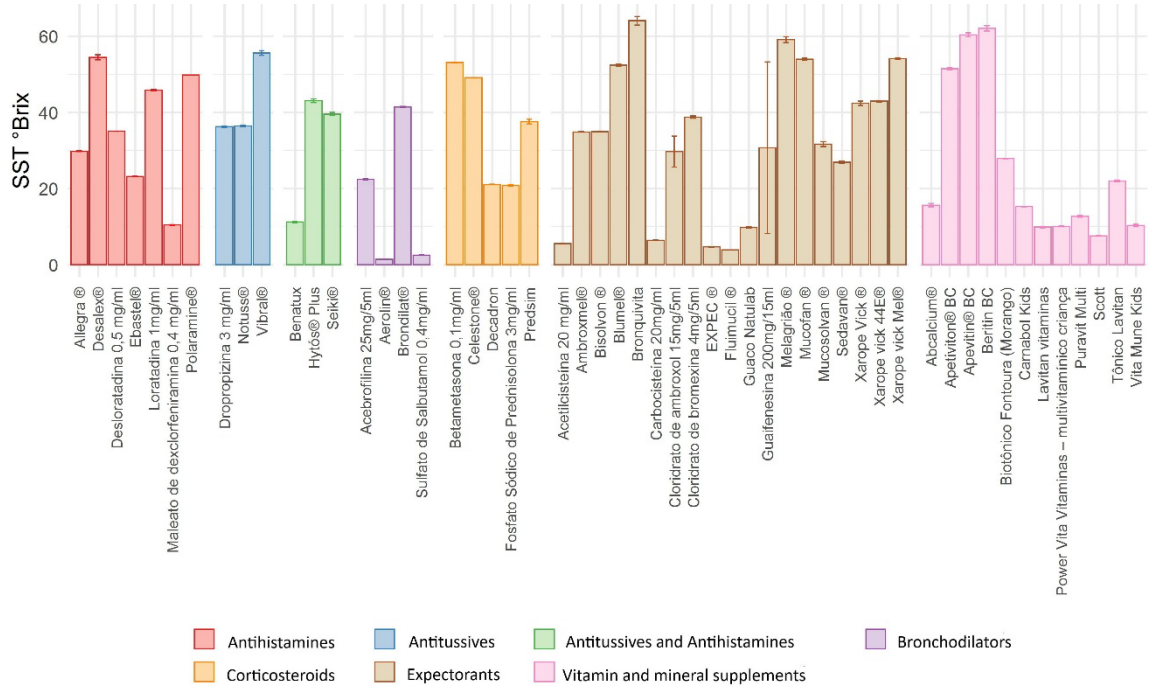

Figure 3. Mean and standard deviation of the concentration of total soluble solids (TSS) ºBrix as a function of the medicines, by therapeutic class, and vitamin and mineral supplements.

DISCUSSION

The pharmaceutical preparations analyzed showed significant differences in pH, TTA and TSS content. The analysis of the physicochemical characteristics of most oral formulations showed cariogenic and erosive potential due to the presence of sucrose and acidulants, respectively, as modulating agents of these effects.

Acidulants are substances capable of imparting acid flavor to the formulations, increasing their acidity by decreasing pH and inhibiting microbial growth[17]. In general, the acidulant most used in pharmaceutical formulations is citric acid, which has a complex chemical structure capable of reacting and releasing three hydrogen ions (H^+) from each molecule. At low pH values, the released H^+ ions react with the carbonate and phosphate ions and thus can solubilize the hydroxyapatite crystals, the main component of the enamel, causing demineralization of the dental surface[18].

The predominance of the use of citric acid as an acidulant in pharmaceutical formulations is confirmed in the present study. Citric acid constitutes the acidulant found in most of the medicines and vitamin and mineral supplements analyzed. Similarly, in a study conducted using antihistamine drugs for pediatric use, Sousa et al.[19] demonstrated the presence of this acid in the composition of most of the formulations analyzed, in addition to indicating that citric acid had strong chelating properties and can promote erosive lesions on the dental surface.

pH value is an important property to be analyzed in formulations for children's use, since the decrease in oral pH in the presence of acidic substances can contribute to progressive losses of dental structure. This loss occurs because, with the decrease in the pH, there is an increase in the solubility of hydroxyapatite[20]. The pH of the formulations analyzed in the present study varied among classes, which is in accordance with findings of prior *in vitro* studies[14,21].

Critical pH is the pH value at which a solution is saturated with respect to a specific mineral, such as dental enamel[20]. pH values below 5.5 are considered critical for the dissolution of dental enamel, resulting in its demineralization[4,7]. Most of the medicines and supplements analyzed showed pH values below 5.5. This result is corroborated by studies that verified the erosive

potential of liquid pediatric oral medicines by analyzing their physicochemical properties and identified that most formulations had a pH below 5.5[8,21]. However, they differ from the findings of other *in vitro* studies that demonstrated pH values above 5.5 in most pharmaceutical preparations[9,15]. The differences observed between the studies can be explained by the differences in the composition of the formulations in relation to the presence of acidulants and their concentrations, as well as by the brand/manufacturer and country of origin of the medicine.

In addition to pH, other parameters, such as the chelating property, should also be considered to analyze the erosive potential of a pharmaceutical preparation. Chelation consists of the process of absorbing metal ions through the action of the chelating agent whose molecules can form several bonds with the calcium ions of the hydroxyapatite crystals, solubilizing it, causing the demineralization of the hard tissues of the teeth, such as dental enamel. The chelation process interferes with the tissue composition and is independent of the pH of the medium[22]. An *in vitro* study using scanning electron microscopy, conducted with the objective of investigating the erosive effect of liquid pediatric medicines on the enamel of deciduous teeth, demonstrated that all the formulations analyzed presented an erosive effect on the enamel surface despite having a pH above 5.5. This can be justified by the presence of chelating agents[15]. Biotonic Fontoura was the only supplement that stated the presence of EDTA in its composition, which can act as a chelating agent.

The findings of the present study demonstrated that, in relation to the therapeutic class of bronchodilators, Salbutamol Sulfate contained the acidulant citric acid in its composition, which may justify the higher TTA at both pH 5.5 and pH 7.0. Babu et al.[22] quantified calcium from enamel solubilization after its immersion in eight liquid pediatric medicines. They demonstrated that the formulation of Salbutamol had higher potential for enamel decalcification compared to other medicines, in time intervals of 1 minute, 10 minutes and 8 hours, increasing according to the contact time. This result was explained by the authors as due to the presence of acidulants with chelating action added to this medicine. However, it was not specified which acidulants were part of its composition.

The erosive potential of pharmaceutical formulations depends not only on their pH but also on their TTA, which consists of determining the amount of a base necessary to neutralize the acids present in a solution. This is a variable to be considered, since it influences the buffer capacity of the solution[14]. In the present study, the large variation in the means found for TTA at pH 5.5 and pH 7.0 indicates that the medicines and supplements differed not only in type but also in the concentration of acidulants in their composition.

The TSS concentrations identified in the pharmaceutical preparations analyzed, both in the medicines group and in the supplements group, showed significant differences. These findings agree with the results of Xavier et al.[21], who also found differences in the TSS and sugar content in the different therapeutic classes studied.

Siddiq et al.[23] (2020), when evaluating the pH, TTA and TSS of liquid medicines commonly prescribed for children, found lower TSS values than those found in the present study. This difference can be justified by the use of different techniques to determine sugar content. However, the results were similar regarding the TTA at pH 7.0 since, in both studies, the highest value was observed in the class of antihistamines.

Analysis of the package inserts and labels identified information about the composition of the formulations regarding their active ingredients and excipients. However, only the concentrations of the former were described. It is worth noting that, according to legislation in force in Brazil, there is no requirement for quantitative descriptions of the excipients in the formulations, only qualitative. Subramaniam and Nandan[14] developed an *in vitro* experiment to evaluate the pH, viscosity, type and concentration of sugars present in liquid pediatric medicines. They demonstrated that 90% of the formulations analyzed contained sucrose in their composition, a percentage higher than that found in the present study.

The literature has documented the relationship between sugar-containing medicines and the development of dental caries[9,24], especially when used chronically[7]. In the present study, 52.83% of the formulations analyzed stated the presence of sucrose in their formulation, contributing to their cariogenic potential. Although there are medicines that use sweeteners to replace sucrose, this sugar is present in most pharmaceutical preparations because it has a low cost, has no residual taste and also has properties with a preservative and antioxidant effect[19].

As for the presence of sucrose, according to the information on the package inserts, this sugar was found mainly among the medicines of the therapeutic class of antihistamines and in the group of supplements. However, their concentrations were not described. Among those medicines that contained sucrose, most did not warn against their use by diabetic patients, and only one supplement provided information regarding the risk of caries.

Considering that saliva represents a factor that interferes with the process of demineralization of the dental surface, it is noteworthy that the cariogenic potential of pediatric medicines should be discussed. In addition to the presence of sucrose, the adverse effects of the active ingredients on salivary flow should also be considered[25]. Among all the package inserts analyzed, 18 of them mentioned xerostomia as an adverse reaction and that it acts on the central nervous system or the neuroglandular junction, suppressing the production of acetylcholine or occupying the muscarinic receptors that participate in salivary secretion. In addition, it was identified that the supplements that reported this adverse reaction also have an antimuscarinic effect, which can cause the sensation of dryness in the oral cavity.

The low pH and the presence of sugars in liquid pediatric medicines may represent a risk factor for oral health[2], especially in children with chronic diseases such as respiratory allergies, bronchial asthma, allergic rhinitis and sinusitis, who frequently use these medicines[19]. In addition, medicines that have a high concentration of sucrose, low pH and high TTA have both cariogenic and erosive potential since they promote a rapid drop in oral pH. This can remain low for prolonged periods of time[7].

The results found in the present study showed that there was a significant difference between liquid pediatric medicines and vitamin supplements and minerals in terms of pH, TTA and TSS. Thus, the null hypothesis is rejected. This difference can be justified by the presence of acidulants, chelating agents, sugars and sweeteners in different concentrations in the formulations analyzed.

CONCLUSION

The low pH values, the high TTA and the presence of sucrose found in most medicines, regardless of the therapeutic class, and the liquid pediatric vitamin and mineral supplements allow us to infer that these formulations may represent a risk factor for the development of dental caries and erosion. Thus, it is essential to provide clear and objective guidelines on oral hygiene after the administration of children's medicines. This is especially relevant regarding those medicines in liquid form, which have low pH, sugar content and reduce salivary flow, in order to prevent the development of caries and dental erosion.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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