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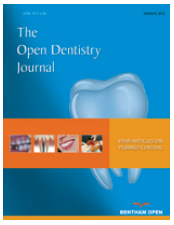
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RESEARCH ARTICLE

Are Pediatric Antibiotic Formulations Potentials Risk Factors for Dental Caries and Dental Erosion?

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Abstract:

Introduction:

One of the most frequent parents' concerns is that oral antibiotic formulations induce dental damage in their children's. This study aimed to assess the cariogenic and erosive potentials of 29 pediatric antibiotics.

Materials and Methods:

Replicates of each antibiotic were analyzed for the concentration of sugars (sucrose, glucose and fructose) and sorbitol by high performance liquid chromatography (HPLC). The pH was determined by digital pHmeter. Titratable acidity was determined in triplicate using the same pHmeter by gradual addition of 0.1N sodium hydroxide (NaOH) until pH 7.0. Viscosity measurements were carried out using a viscosimeter. In order to rank the relative performance of each medicine, the DEA (Data Envelopment Analysis) methodology was used.

Results:

Sucrose was present in most samples (n=24) with concentrations ranging from 26 to ≈ 100g% (w/w). Only one antibiotic contained sorbitol (66.9g%). Twenty seven antibiotics presented pH values ranging from 4.1 to 6.9 and most of them (n=15) showed the pH below the critical value for dissolution of hydroxyapatite. The values of titratable acidity and viscosity ranged from 0.26 to 40.48 ml and from 20 to 1780cP, respectively. DEA methodology showed that two medicines were distant from the performance frontier (Klaricid® 50mg and Zinnat® 250mg), which means that these medicines showed the worst performance and, therefore, greater potential for dissolution of dental enamel.

Conclusion:

Many antibiotics presented high concentration of sugars, high titratable acidity, pH below the critical value and high viscosity which can be considered risk factors for dental caries and erosion, when consumed frequently.

Keywords: Antibiotics, Dental caries, Pharmaceutical preparations, Sweetening agents, Tooth erosion, Viscosity.

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INTRODUCTION

Liquid oral medicines contain in their formulation agents to improve their appearance, bioavailability, stability, and palatability [1]. Sugars such as sucrose, fructose and glucose are added to increase bulk, palatability and, consequently, compliance [2]. These sugars are widely used because they are cheap, nonhygroscopic, and easy to process [3]. Acids are also added to medicines and commonly act as buffering agents to maintain chemical stability, control tonicity and/or to ensure physiological compatibility. In addition, they may be used to improve flavor [4]. Because of these so called "inactive ingredients", many pediatric liquid medicines are characterized by having a high concentration of sugars, high titratable acidity and low pH. Because of these characteristics, various studies have pointed out the possible relationship between dental caries and frequent intake of liquid oral medicines [3, 5 - 11]. The presence of sucrose in medicines leads to pH drop of dental plaque, and also acts as substrate for fermentation of oral microbiota, [12] contributing to dental caries.

Dasanayake *et al*. [13] showed a higher count of *Streptococcus mutans* (the main microorganism involved with dental caries) in children who took antibiotics during the period considered the most critical to *acquire these bacteria*, which is between 1 ½ to 3 years of age, when compared to children who did not take antibiotics in the same period. Moreover, these authors observed a correlation between an increase of *S. mutans* colonies and caries in these individuals.

Low endogenous pH and high titratable acidity of these medicines also may favor dental erosion [4, 9, 11, 13 - 19], especially when the contact of the medicine with the tooth surface remains for a very long time [14]. Besides, previous *in vitro* studies have also shown that acidic medicines could reduce deciduous enamel hardness [13, 16] and cause morphological enamel surface alterations [18] and surface degradation of restorative materials [20]. Other concerning factors with regard to dental caries and dental erosion are the high viscosity of liquid oral medication [9, 21], lack of oral hygiene after medicine's intake [21] and its frequency of intake, especially in children that present chronic diseases and need to make regular use of liquid oral medicines [3, 9]

Considering that some medicines may be a threat to oral health causing dental caries and erosion, the aim of this *in vitro* study was to investigate some physico-chemical properties of liquid oral antibiotics, such as pH, titratable acidity, sugar concentration and viscosity, which may contribute significantly to their cariogenic and erosive potential.

MATERIALS AND METHODS

Twenty nine liquid antibiotics (Table **1**) available in the Brazilian market were selected for this study from a reference list registered in the National Health Surveillance Agency. All of them were oral suspensions and 23 of them had their powders reconstituted with filtered water as recommended by the manufacturers. The labels of each medicine were examined in order to gather information on sugar and acid contents.

Sugar Content Analysis

Analysis of sugars (sucrose, fructose and glucose) and sorbitol were performed using normal-phase HPLC-IR (High-Performance Liquid Cromatography coupled to a Refration Index) [11, 22]. One gram of each bottle was diluted to 50 mL in a volumetric flask with MilliQ water (Milipore, USA). The mixture was vigorously shaken and one aliquot of the supernatant (500 μL each) was diluted with pure acetronitrile in the proportion 1:1 (v/v). The mixture was then centrifuged for 2 minutes (Beckman Microfuge E™, USA) and the supernatant was directly used for chromatography.

The concentrations were calculated using the peak heights of commercial compounds standards of sucrose, fructose, glucose (Sigma Aldrich, USA) and sorbitol (Vetec Química, Brazil). Results were average of replicates from each bottle (sugars and sorbitol concentrations - g/100g - %).

Table 1. Brand names, manufacturers and active principles of all antibiotics analyzed in the study.

Brand names	Manufacturers	Active principles
1. Amoxil® 125 mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin
2. Amoxil® 250 mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin
3. Amoxil® 500 mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin
4. Amoxil BD® 200 mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin
5. Amoxil BD® 400 mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin
6. Ampicilina® 250 mg/5mL	EMS (S. B. do Campo, SP, Brazil)	Ampicillin

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(Table 1) contd.....

Brand names	Manufacturers	Active principles
7. Bactrim® (200+40)mg/5mL	Roche (Rio de Janeiro, RJ, Brazil)	Sulfamethoxazole + Trimethoprim
8. Bactrim F® (400+80)mg/5mL	Roche (Rio de Janeiro, RJ, Brazil)	Sulfamethoxazole + Trimethoprim
9. Ceclor® 250 mg/5mL	Sigma Pharma (Hortolândia, SP, Brazil)	Cefaclor
10. Ceclor® 375 mg/5mL	Sigma Pharma (Hortolândia, SP, Brazil)	Cefaclor
11. Cefamox® 250 mg/5mL	Bristol-Myers Squibb (Barceloneta, Porto Rico)	Cefadroxil
12. Cefamox® 500 mg/5mL	Bristol-Myers Squibb (Barceloneta, Porto Rico)	Cefadroxil
13. Cefzil® 250 mg	Bristol-Myers Squibb (São Paulo, SP, Brazil)	Cefprozil
14. Clavulin® (125mg+31,25)mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin + Potassium Clavulanate
15.Clavulin® (250+62,5)mg/5mL	GlaxoSmithKline (Mexico)	Amoxicillin + Potassium Clavulanate
16. Clavulin BD® (200+28,5)mg/5mL	GlaxoSmithKline (Rio de Janeiro, RJ, Brazil)	Amoxicillin + Potassium Clavulanate
17. Clavulin BD® (400 mg+57)mg/5mL	GlaxoSmithKline (Worthing, England)	Amoxicillin + Potassium Clavulanate
18. Clavulin® ES (600+42,9)mg/5mL	GlaxoSmithKline (Col Romero de Terreros, México)	Amoxicillin + Potassium Clavulanate
19. Eritrex® 125 mg/5mL	Aché (Guarulhos, SP, Brazil)	Erythromycin
20. Eritrex® 250 mg/5mL	Aché (Guarulhos, SP, Brazil)	Erythromycin
21. Keflex® 250 mg/5mL	Lilly (São Paulo, SP, Brazil)	Cephalexin
22. Keflex® 500 mg/5mL	Lilly (São Paulo, SP, Brazil)	Cephalexin
23. Klaricid® 25 mg/mL	Abbott (Brazil)	Clarithromycin
24. Klaricid® 50 mg/mL	Abbott (Brazil)	Clarithromycin
25. Pen-ve-oral® 80.000UI/mL	Eurofarma (São Paulo, SP, Brazil)	Potassic Phenoxymethylpenicillin
26. Unasyn® 250 mg/5mL	Pfizer (Latina, Italy)	Sultamicillin tosylate
27. Zinnat® 250 mg/5mL	GlaxoSmithKline (England)	Cefuroxime Axetil
28. Zitromax® 600 mg	Pfizer (Latina, Italy)	Azithromycin
29. Zitromax® 900 mg	Pfizer (Latina, Italy)	Azithromycin

Analysis of pH and Titratable Acidity

Antibiotics' pH was determined at room temperature with an electrode connected to a digital pHmeter (Digimed DM 20, USA). The electrode was calibrated at the start of each session using standard buffers of pH 4.01 and 6.86 (Quimis, Diadema, SP, Brazil). Titratable acidity was measured in triplicate for each antibiotic by using the same pHmeter and increments of 0.1N sodium hydroxide (NaOH) were titrated until neutrality (pH 7.0) was reached [11] A correction factor of 0.87 was obtained by factorizing 0.1 N NaOH solution with potassium biphthalate. The total volume of 0.1 N NaOH solution required to neutralize medicines multiplicated to correction factor of 0.87 corresponded to the titratable acidity value.

Viscosity

Viscosity measurements were carried out on a AR 2000 rheometer (TA instrument, USA) using a parallel plate geometry of 25 mm diameter, at a shear rate of 0.1 to 100 s^{-1} and temperature of 40°C. Viscosity values were obtained at $20s^{-1}$.

Table 2. Concentration of sucrose, pH, titratable acidity and viscosity of all analyzed antibiotics.

Antibiotics	Sucrose[a]	Sorbitol[a]	pH	Vol NaOH (mL)[b]	Viscosity (cP)[c]	Label content (sweeteners)	Label content (acids)
1. Amoxil® 125 mg/5mL	49.97 ±1.64	----	5.71 ±0.02	1.38±0.05	30	Sucrose	----
2. Amoxil® 250 mg/5mL	48.59 ±2.01	----	5.72 ±0.01	1.55±0.04	30	Sucrose	----
3. Amoxil® 500 mg/5mL	36.77 ±2.46	----	5.74 ±0.01	2.23±0.10	90	Sucrose	----
4. Amoxil BD® 200 mg/5mL	48.41 ±1.31	----	6.67 ±0.04	0.85 ±0.05	290	Sugar	----
5. Amoxil BD® 400 mg/5mL	44.53 ±4.06	----	6.85 ±0.03	0.67 ±0.10	550	Sugar	----
6. Ampicilina® 250 mg/5mL	36.43 ±1.9	----	6.16 ±0.04	2.73±0.00	40	Sodium cyclamate, Sodium saccharin, Sucrose	----
7. Bactrim® (200+40)mg/5mL	55.02 ±0.14	----	6.10 ±0.01	2.90 ±0.09	1350	Sugar	----
8. Bactrim F® (400+80)mg/5mL	59.02 ±8.01	66.90	5.69 ±0.02	4.55 ±0.22	1340	Sorbitol, Sodium saccharin	----

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Antibiotics	Sucrose[a]	Sorbitol[a]	pH	Vol NaOH (mL)[b]	Viscosity (cP)[c]	Label content (sweeteners)	Label content (acids)
9. Ceclor® 250 mg/5mL	58.86 ±0.26	----	4.34 ±0.02	3.78 ±0.26	300	Sucrose	----
10. Ceclor® 375 mg/5mL	62.63 ±7.47	----	4.31 ±0.28	8.21 ±1.34	550	Sucrose	----
11. Cefamox® 250 mg/5mL	58.03 ±4.41	----	5.12 ±0.02	2.76 ±0.13	20	Sugar	----
12. Cefamox® 500 mg/5mL	61.01 ±2.70	----	4.86 ±0.06	5.54 ±0.53	180	Sucrose	----
13. Cefzil® 250 mg	51.18 ±0.32	----	5.05 ±0.02	2.49 ±0.05	30	Sucrose, Aspartame	Citric acid
14. Clavulin® (125mg+31,25)mg/5mL	ND	----	4.32 ±0.01	1.23 ±0.09	170	Aspartame	Clavulanic acid, Succinic acid
15.Clavulin® (250+62,5)mg/5mL	ND	----	4.57 ±0.03	1.26 ±0.10	230	Aspartame	Clavulanic acid, Succinic acid
16. Clavulin BD® (200+28,5)mg/5mL	ND	----	4.10 ±0.00	0.97 ±0.00	120	Aspartame	Clavulanic acid, Succinic acid
17. Clavulin BD® (400 mg+57)mg/5mL	ND	----	4.45 ±0.01	1.20 ±0.05	190	Aspartame	Clavulanic acid, Succinic acid
18. Clavulin® ES (600+42,9)mg/5mL	ND	----	4.94 ±0.02	0.99 ±0.10	340	Aspartame	Clavulanic acid
19. Eritrex® 125 mg/5mL	68.53 ±1.03	----	5.33 ±0.00	6.83 ±0.22	530	Sugar	Citric acid
20. Eritrex® 250 mg/5mL	74.54 ±0.02	----	5.42 ±0.02	1.88 ±0.05	270	Sugar	Citric acid
21. Keflex® 250 mg/5mL	25.95 ±2.05	----	6.62 ±0.11	0.26 ±0,00	230	Sucrose	----
22. Keflex® 500 mg/5mL	43.39 ±5.54	----	6.95 ±0.28	0.67 ±0,05	370	Sucrose	----
23. Klaricid® 25 mg/mL	36.13 ±0.07	----	5.13 ±0.05	24.64 ±1.76	260	Sugar	Citric acid
24. Klaricid® 50 mg/mL	77.46 ±10.84	----	5.04 ±0.10	40.48 ±0.88	1660	Sugar	Citric acid
25. Pen-ve-oral® 80.000UI/mL	≈ 100	----	5.94 ±0.01	0.26±0.00	170	Sugar, Sodium saccharin	Citric acid
26. Unasyn® 250 mg/5mL	88.81 ± 0.75	----	6.58 ±0.01	1.67±0.09	80	Sucrose	----
27. Zinnat® 250 mg/5mL	89.48 ±4.89	----	4.79 ±0.00	12.54±2.86	1780	Sucrose, aspartame	Estearic acid
28. Zitromax® 600 mg	≈ 100	----	9.75±0.00	-------	1130	Sucrose	----
29. Zitromax® 900 mg	≈ 100	----	10.08±0.00	-------	420	Sucrose	----

[a] Concentrations are expressed in g% (g/100g) (mean ± standard deviation); ND= non-detected; [b] Volume of NaOH solution required to achieve the pH 7.0; [c] Viscosity values are presented at shear rate of 20s (unit of viscosity: cP – centiPoise=millipascal second, mPa·s); (----) = not mentioned in labels.

Data Analysis

In order to verify how was the performance of each antibiotic in comparison with the others, the DEA (Data Envelopment Analysis) methodology has been used. DEA is a mathematical programming methodology which evaluates the relative performance of list of units with multiple attributes. It identifies a subset of performance "best-practice" elements (benchmarks) and for remaining ones, the magnitude of their lack of performance is measured by comparing to a piecewise frontier constructed from the best elements, facilitating the interpretation of the results. It allowed the evaluation of the relative performance of each antibiotic taking into account the undesirable characteristics (high concentration of sugars, low pH, high titratable acidity and high viscosity) and the desirable ones (absences of sugars, high pH, low titratable acidity and low viscosity) in the sense of tooth dissolution potential. In this analysis, the medicines with performance of 100% are those which present better characteristics in comparison with the others and, therefore, were less likely to harm the tooth enamel. On the other hand, medicines with lower percentile values are those with the worst performance and, in this way, have greater potential for dissolution of dental enamel.

Table 3. Performance results (0-100%) of all analyzed antibiotics.

Medicines	Performance
Clavulin ES® 600 mg, Amoxil® 125 mg, Keflex® 250 mg, Ampicilina® 125 mg, Clavulin® BD 200 mg, Zitromax® 900 mg	100%
Amoxil® 250 mg, Clavulin® BD 400 mg	98%
Clavulin® 250 mg, Clavulin® 125 mg, Cefamox® 250 mg	95%
Zitromax® 600 mg	94%
Unasyn®,Pen-ve-oral®	89%
Cefzil® 250 mg	86%
Amoxil® 500 mg	84%
Keflex® 500 mg	62%

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(Table 3) contd.....

Medicines	Performance
Amoxil® BD 200 mg	56%
Amoxil® BD 400 mg	55%
Eritrex® 250 mg	39%
Cefamox® 500 mg	34%
Klaricid® 25 mg	32%
Bactrim® 200 mg	26%
Ceclor® 250 mg	24%
Eritrex® 125 mg	20%
Bactrim® F 400 mg	19%
Ceclor® 375 mg	13%
Klaricid® 50 mg, Zinnat® 250 mg	8%

The BCC model with input orientation and weight constraints was applied. This analysis was carried out with the software IDEAL (Interactive Data Envelopment Analysis Laboratory), developed by COPPE/UFRJ, which allows the three-dimensional visualization of the performance frontier [23].

Pearson's correlation coefficients were used to determine whether there was any association among concentrations of sucrose, pH, titratable acidity or viscosity, using the SPSS 20.0® software at a significance level of 5%.

RESULTS

The concentrations of sucrose, fructose, glucose and sorbitol as well as pH, titratable acidity and viscosity of all antibiotics are presented as mean values in Tables **2** and **3** and Figs. (**1**-**3**) show the performance of the 29 antibiotics analyzed.

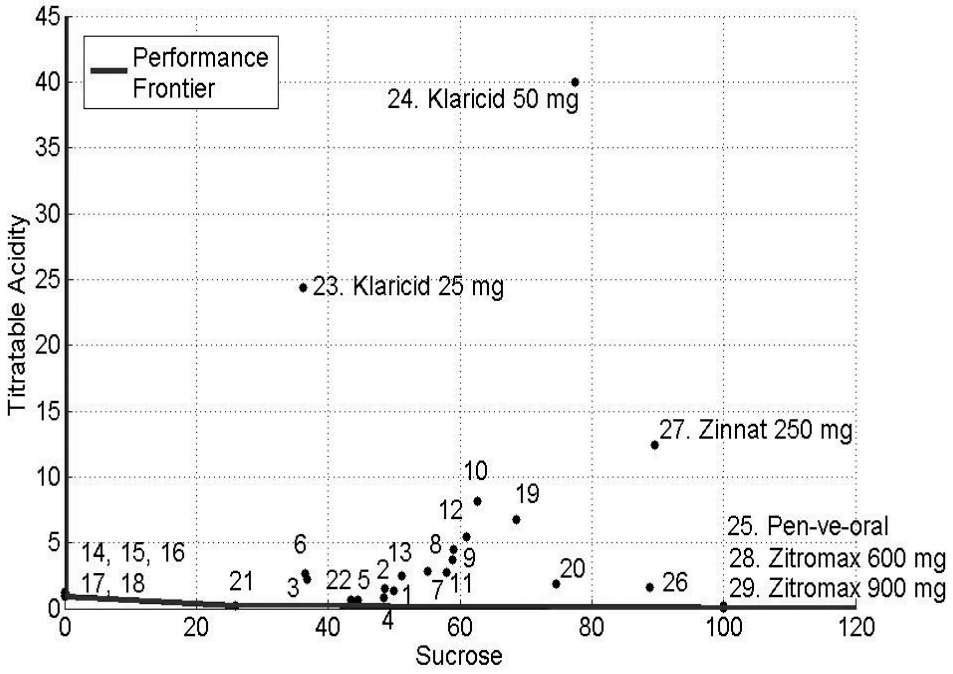


Fig. (1). Performance frontier for sucrose and titratable acidty. Medicines 14 (Clavulin 125mg), 15 (Clavulin 250mg), 16 (Clavulin BD 200mg), 17 (Clavulin BD 400mg) and 18 (Clavulin ES 600mg) are close to the frontier because their low levels of sucrose and titratable acidity, while medicines 23 (Klaricid® 25mg/5mL), 24 (Klaricid® 50mg/5mL) and 27 (Zinnat® 250mg/5mL) presented the worst performance because of their high levels of sucrose and titratable acidity.

Sugar Content

Out of the 29 formulations, sucrose was present in 24 of them (83%), with concentrations ranging from 26g% to

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about 100g%. However, according to the medicine's labels, only fifteen antibiotics (52%) presented sugars and only four of them specified sugar concentration. None of the antibiotics contained glucose and fructose. Only five antibiotics (17%) were sugar-free. Sorbitol was present in only one medicine (3%), with concentration of 66.9g% and associated with sucrose (Table. **2**).

pH, Titratable Acidity and Viscosity

Two antibiotics (11%) presented basic pH values of 9.7 and 10.8, while the others presented pH values ranging from 4.1 to 6.9. Fifteen of the 29 analyzed antibiotics (52%) presented pH below the critical value for dissolution of hydroxyapatite (pH 5.5). Values of titratable acidity and viscosity ranged from 0.26 to 40.48 mL and from 20 to 1780 cP, respectively. Pearson's correlation coefficient's showed that there was no correlation between pH and titratable acidity (p>0.05) neither between sugar content and viscosity (p>0.05).

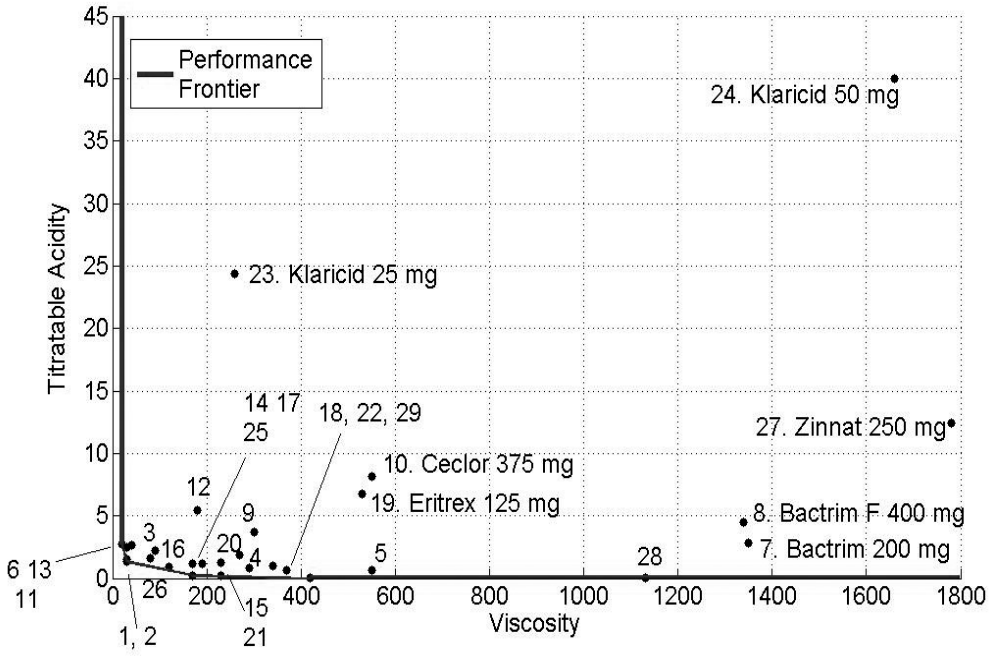


Fig. (2). Performance frontier for viscosity and titratable acidty. Medicines 7 (Bactrim® 200mg/5mL), 8 (Bactrim F® 400mg/5mL) and 27 (Zinnat® 250mg/5mL) presented low levels of titratable acidity, despite of their high titratable acidity. Klaricid® 50mg/mL were distant from performance frontier again, because of their high levels of titratable acidity and sacarose concentration, presenting the worst performance.

Performance of Medicines (Software IDEAL)

The DEA methodology allowed the simultaneous evaluation of the analyzed variables (concentration of sugars, pH, titratable acidity and viscosity) and from the scores obtained, antibiotics were classified according to their relative performance.

In order to facilitate the interpretation of the results, three figures of the performance frontier were plotted (Figs. **1**-**3**). Each medicine was placed on its corresponding point, according to its attributes, and can be identified by its corresponding number. Medicines placed in the vertex points of each face are considered as references or benchmarks, have 100% performance and constitute the performance frontier.

Fig. **(1)**, shows the performance frontier for sucrose and titratable acidty. It can be observed that medicines 14 (Clavulin® 125mg), 15 (Clavulin® 250mg), 16 (Clavulin® BD 200mg), 17 (Clavulin® BD 400mg) and 18 (Clavulin ES® 600mg) presented low levels of sucrose and titratable acidity and, for this reason, are close to the frontier. The medicines 25 (Pen-ve-oral®), 28 (Zitromax® 600mg) and 29 (Zitromax®900mg), despite of being close to the performance frontier due to low titratable acidity, have high concentration of sucrose, which is an undesirable characteristic. On the other hand, the medicines 23 (Klaricid® 25mg/5mL), 24 (Klaricid® 50mg/5mL) and 27 (Zinnat®

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250mg/5mL) presented the worst performance because of their high levels of sucrose and titratable acidity.

Fig. **(2)** identifies the medicines with high levels of viscosity and titratable acidity. Despite of their high viscosity, the medicines 7 (Bactrim® 200mg/mL), 8 (Bactrim F® 400mg/5mL) and 27 (Zinnat® 250mg/5mL) showed low levels of titratable acidity. Medicines with low viscosity and titratable acidity and close to the performance frontier presented a better performance. Again, Klaricid® 50mg/mL was distant from performance frontier because of their high levels of titratable acidity and sacarose concentration, presenting the worst performance (8%).

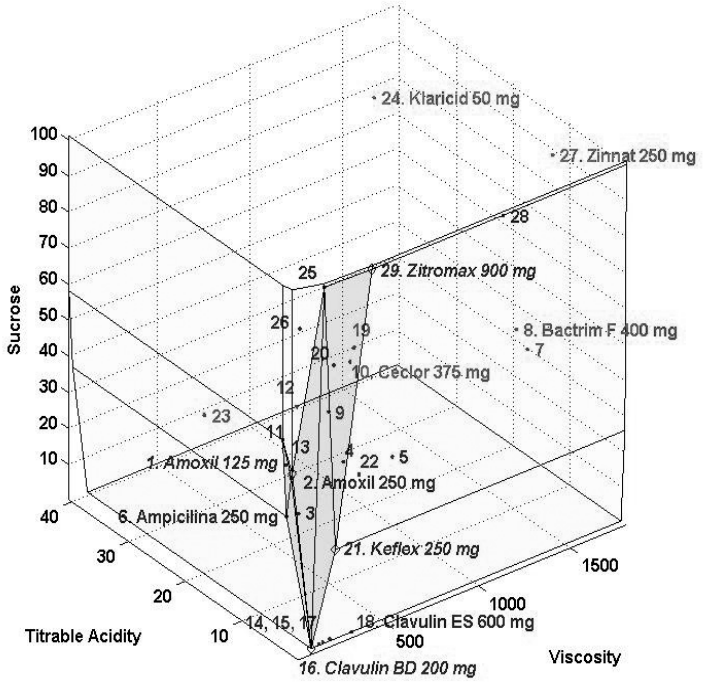


Fig. (3). 3D visualization of the performance frontier according to titratable acidity, viscosity and sucrose concentration. Grey area corresponds to the frontier where medicines with 100% performance are included. Klaricid® 50 mg/5mL and Zinnat® 250 mg/5mL were distant from the performance frontier, which means that these medicines have the worst performance and, therefore, greater potential for dissolution of dental enamel.

Finally, Fig. **(3)** shows the 3D visualization of the performance frontier and identifies the best and worst medicines see also Table **3**. Regions with higher density of medicines show a group of medicines with an average performance. Klaricid® 50 mg/5mL and Zinnat® 250 mg/5mL were distant from the performance frontier, which means that these medicines showed the worst performance and, therefore, greater potential for dissolution of dental enamel.

DISCUSSION

Antibiotics, which were chosen for this study, as well as cough medicines are the most common sugar-containing medicines regularly used by young children [24]. Considering that they may still be used over relatively long periods, it can be a concern for oral health. Moreover, these medicines can present erosive potential due to presence of acids in their formulations, low pH, high titratable acidity, presence of buffering agents and absence or low concentrations of ions including those of calcium, fluoride, and phosphate in their composition [9, 13, 25, 26].

Although the antibiotics analyzed in this study did not contain glucose and fructose, the presence of high sucrose concentration in 83% of the formulations, ranging from 26g% to about 100g%, poses a real problem to the young consumers. It may increase the caries risk, since sucrose is considered the most cariogenic dietary carbohydrate, because it is fermentable, and also serves as a substrate for the synthesis of extracellular and intracellular polysaccharides in dental plaque [27, 28]. Others studies have reported a predominant use of sucrose as a sweetener in medicines [11, 29 - 31]. It should be emphasized that in this study three antibiotics presented concentrations of sucrose with values close to 100g%. This peculiarity may be explained mainly by the fact that as sugar is denser than water, then, 100g of the sugar will occupy less space than water. Additionaly, the concentrations of the bioactive compound of these oral suspensions are expressed in µg%, which is under the detection limit of the equipment. This high sugar

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concentration is unacceptable considering its cariogenic potential. On the other hand, there are controversial studies that show that despite of the potentially high sucrose concentration in antibiotics, they work by reducing the number of *Streptococcus mutans* and therefore are anticariogenic and may counteract sucrose´s effect [32, 33].

All sweetening agents identified in this study were in accordance with the medicines' labels. However, sugar concentrations were unspecified. In relation to sugar-based medicines, most labels (93%) alerted that the product should not be consumed by diabetic patients; however, none of them mentioned its cariogenic potential, especially when used for long periods of time.

Other factors analyzed in the present study were pH and titratable acidity, and it is still generally accepted that titratable acidity is a better indicator of erosive potential than pH alone [34, 35]. Titratable acidity is the property of an acid solution of keeping its pH when neutralizing agents are added, that is, the measure of its buffering capacity. In this way, a substance with low titratable acidity is readily neutralized by oral fluids, the opposite occurs with that characterized by high acidity, which causes prolonged drop in pH and higher demineralization of the tooth structure. [34, 36] According Jensdottir *et al*. [37] teeth exposed to a limited volume of a drink with low pH and high titratable acidity for a long time will result in erosive potential and both qualities combined will result in the highest erosive potential. The liquid oral antibiotics analyzed in this study had titratable acidic values ranging from 0.26 to 40.48 mL, but some of them proved to be discrepant in relation to others, which can cause concern. It is now widely accepted that the total titratable acidity is a more accurate measure of the total acid content of a drink, and may, therefore, be a more realistic means of predicting erosive potential. Although the mean endogenous pH for Klaricid® 50mg/5mL and Klaricid® 25mg/5mL was 5.04 and 5.13, their mean titratable acidity was high at 40.48 and 24.64 mL, respectively. It reflects the incorporation of acid in excess in their formulation, which according medicine's labels is citric acid.

Citric acid is considered the main acid used in prolonged oral clearance medicines and as such, is a weak acid, dissociated in solutions with a higher pH and able to act as a buffer over a range of pHs. However, it is 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 [38]. In the present study, six of the twelve medicines which specified presence of acids presented citric acid in their composition. Other acids presents were clavulanic acid, succinic acid and estearic acid. Again, just as the sweeteners, the real amount present in these products were not stated on the labels.

On the other hand, it is important to mention that the consumption of an acidic drink will stimulate salivary flow [39]. It is possible, therefore, that a more acidic drink may be either cleared from the mouth or neutralized more rapidly, due to the increased salivary washing action and buffering capacity, and so will spend less time in contact with the teeth. Clearance of a drink from the mouth will also depend on the ability of a drink to adhere to the enamel [40].

It is necessary to highlight the real impact of the use of oral liquid antibiotics in daily life of children. The amoxicillin, with or without association of clavulanate, is a medicine widely used by children in the treatment of infections. According to our study, despite of presenting a better performance than a lot of medicines (Table **3**), the group of amoxicillin (medicines 1 - 5) presented pH values between 5.71 to 6.85 and high concentration of sugar (36.77 to 49.97) which were worrying in relation to oral health. This fact was also noted in medicines 14-18 that showed lower pH values ranging from 4.10 to 4.94 despite of being sugar free, which can favor to dental erosion. Other medicines widely used in routine of immunocompromised patients to prevent opportunistic infections are Bactrim® and Bactrim F® (medicines 7 and 8). These medicines appeared distant from the performance frontier because of their high concentrations of sucrose and high viscosity (Fig. **3**), despite of their low titratable acidity (Fig. **2**).

It is also important to note the main factors that seem to increase the likelihood of an individual suffering from dental erosion includes salivary flow rate, pH, buffering capacity and pellicle formation [41 - 43]. All these factors added to the properties of the drink itself, as well as associated factors relating to the method of drinking, frequency of consumption, salivary parameters and dental plaque play a role in the development of dental erosion. In addition, in medically compromised children, many of these medicines may be taken at times remote from food intakes or at night when salivary flow is reduced, and these factors may add to the potential erosive challenge [4].

This fact is of concern because of the known relationship between carbohydrates and dental caries, and it becomes even more alarming if one considers that not all the pediatricians gave parents instructions about oral hygiene after medicine's intake. In a previous study, [44] pediatricians did not perceive the correct relationship between the presence of acidity in medicines and dental erosion; however, most of them presented a reasonable awareness about the relationship between sugared pediatric medicines and dental caries. Nevertheless, not all of them recommended oral hygiene after their consumption (50.80%). Another study, verified that only 21.2% of the guardians that associated the

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use of pediatric liquid medicines with the development of dental caries performed the oral hygiene of their children. In addition, 84.9% of those guardians had never received instructions of oral hygiene after the intake of medicines [45].

In relation to oral hygiene immediately after acidic products, literature has reported that eroded enamel is more susceptible to wear by tooth-brushing and to toothpaste abrasion [46, 47]. In this way, after consuming acidic foods or drinks, tooth-brushing should be delayed to allow the saliva to exert its natural remineralizing action on the eroded enamel, thereby resulting in increased resistance to abrasion [47]. Recommendation on immediate water rinse and delayed tooth-brushing after syrup medicines' ingestion could be proposed at the time of prescription. Medicine's labels also should alert in relation to the possibility of cause dental caries and erosion because many products could be consumed for prolonged periods, several times a day, at bedtime, and without adequate oral hygiene, will certainly contribute to dental caries and erosion.

CONCLUSION

Most of the analyzed antibiotics presented high sugar concentration, titratable acidity and viscosity, and low pH which can be considered as risk factors for dental caries and erosion when consumed frequently. We advise, therefore, the use a warning about the medicine's cariogenic potential in their labels. It is also necessary to recommend oral hygiene after the medicine's intake. Clinical studies are necessary to determine the real extension of the problem.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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