

## Evaluation of Sugar Content and Erosive Potential of the Commonly Prescribed Liquid Oral Medications

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### Abstract

**Objective:** To assess the total sugar content, endogenous pH, total soluble solids content (TSSC) and titratable acidity of the commonly prescribed long-term and short-term liquid oral medicines (LOM) for children and to compare the erosive potential with the total sugar content and total soluble solids of the LOM. **Material and Methods:** Twenty-three most commonly prescribed pediatric LOM were evaluated *in-vitro* for the cariogenic and erosive potential. Manufacturers' information on labels, endogenous pH, titratable acidity, TSSC, and the total sugar content was determined. Descriptive statistics and the Mann-Whitney U test were applied. **Results:** Overall, 22 LOM contained sugar. Only 3 LOM revealed the sugar content of the formulation but did not disclose the quantity (Cheston, Venterlin and Eptoin). None of the samples revealed the sugar content as well as endogenous pH in their labels. The overall mean total sugar content was  $6.92 \pm 3.49$  g/100ml, ranging from  $3.40 \pm 0.00$  (corticosteroids) to  $9.67 \pm 0.61$  (antitussive/expectorant). The mean endogenous pH for the total sample of medicines was  $5.91 \pm 1.51$  (range of 3.5 to 10.3). Eptoin (0.013%) presented the lowest titratable acidity and Imol (1.171%) presented the highest titratable acidity with an overall mean of  $0.40 \pm 0.73$ . Omnacortil and Epilex presented the highest TSS content (19.3%), and Venterlin presented the lowest TSS content (18.7%) with an overall mean of  $18.97 \pm 0.19$ . Over twelve medicines were identified to have the potential to cause dental erosion. No significant differences were seen in the total sugar content, total soluble solids, titratable acidity, and the endogenous pH between the short-term and long-term LOMs ( $p=0.145$ ,  $p=0.263$ ,  $p=0.067$  and  $p=0.107$ ), respectively. **Conclusion:** The pediatric LOMs showed the presence of the sugar, low endogenous pH, high titratable acidity and high total soluble solids.

**Keywords:** Child; Dental Caries; Tooth Erosion; Sucrose.

## Introduction

Dental caries is the common oral disease and the most prevalent infectious disease in the oral cavity. Among the theories that explain caries onset, the action of acids produced by bacterial fermentation of carbohydrates (sugars) from the diet is universally accepted [1]. Various studies have pointed out the possible relationship between dental caries and frequent intake of liquid oral medicines (LOM) [2-5]. Sugar has been widely added to pediatric liquid oral medicines to improve their palatability. Moreover, chronic illness may predispose the children for caries and an additional source of sugar can have an additive effect on the prevalence and severity of caries among children [6].

Dental erosion is defined as the “irreversible loss of tooth structure due to chemical dissolution by acids without the involvement of bacteria” [7], besides mechanical activities such as abrasion and attrition [8]. If left untreated, erosion proceeds from the enamel surfaces to the underlying dentine [9]. Low endogenous pH and high titratable acidity of liquid oral medicines may favor dental erosion [10], especially when the contact of the medicine with the tooth surface remains for a very long time [11].

Evidence from in-vitro studies have established that acidic medicines reduced enamel hardness in deciduous teeth [12] with morphological surface alterations of enamel [13] and restorative materials [14]. Other concerning factors with regard to dental caries and dental erosion are the high viscosity of liquid oral medication [3,4], lack of oral hygiene practices after intake of LOM [4] and its frequency [15].

One of the major challenges in administering pediatric LOM is the bitter taste. In order to make it acceptable, pediatric LOM are usually colored, flavored and sweetened with several excipients other than the main active ingredients [16]. The flavor improvement in LOM is related to the frequent use of acids [16,17]. For both a chemically stable and sufficient solubility of a drug, a suitable pH is required. Hence, the addition of acidic contents into the drug formulations as buffering agents are responsible for tonicity, physiological compatibility [10] and shelf-life [18].

It has been established that about half of the regularly-used pediatric LOM can damage tooth enamel as they have an endogenous pH below 5.5 [10]. Moreover, the intake of such drugs at night could augment diseases like dental caries and dental erosion, as there is reduced salivary flow rate and increased time of elimination from the oral cavity during this period [19].

Even though numerous solid forms of oral medication like pills or capsules include a coating to conceal their bitter tastes, children may still not readily accept such methods due to difficulty in swallowing [16]. Therefore, the most commonly chosen formulations for children are in LOM.

A review demonstrated several functions of the excipients in pediatric drug formulation [20]; meanwhile, a recent report has addressed issues regarding sugar or carbohydrates of drugs inducing caries and their ill effects on the oral health of children [21].

Brazilian authors reported that the antibacterials frequently prescribed to HIV infected paediatric patients contained the highest sucrose concentration, ranging from 40% to 54%. Glucose was found in one of the ten, sucrose was present in seven of them, and none showed lactose [22]. Antitussives are reported to be potentially cariogenic and erosive as well, if used frequently, because of the high titratable acidity and high sugar concentration, especially when adequate oral clearance is not performed after administration of each dose [1].

Many studies have been done in the US [4], Brazil [2], New Zealand [3], and Saudi Arabia [23] linking frequent use of sweetened LOM and the development of dental caries. Other authors studied the pH and concentration of sugars of pediatric liquid medicaments and suggested that these medications can pose as a

threat to dental health [5,13]. However, only half of the overall medicines that showed sugar in their ingredients presented this information in their directions [24]. Moreover, data about erosive potential and solid content of commonly used pediatric liquid oral medication is lacking. Hence, we aimed to assess the sugar content and erosive potential of the commonly prescribed long-term and short-term LOM for children.

The objectives of this study were to assess the total sugar content, endogenous pH, total soluble solids and titratable acidity of the commonly prescribed long-term and short-term liquid oral medicines for children and to compare the erosive potential with the total sugar content and total soluble solids of the LOM.

## Material and Methods

Twenty-three most commonly prescribed pediatric LOM were selected for the study (Table 1). This selection was done after a brief interview with pediatricians (n = 4) and pharmacies (n = 10) in Udupi taluk, Karnataka, India. The list of LOM was prepared, and duplicates were removed and categorized broadly as per the drug classification (Table 1). They included long-term (anti-epileptics, antihistamines, anti-asthmatics, corticosteroids) and short-term medications (antibiotics, analgesics, antitussives/expectorants). The labels of each medicine were examined to capture information on sugar, flavor, and acid contents, as reported by the manufacturer.

**Table 1. List of commonly prescribed LOM.**

Oral Liquid Pediatric Medications	Generic Name	Trade Name
Antibiotics	Azithromycin	Azee
		Azithral®
	Cefuroxime Axetil	Altacef®
	Cefixime	Taxim
	Amoxicillin	Mox
	Amoxicillin, Potassium clavulanate	Novamox
Analgesics	Amoxicillin, Potassium clavulanate	Augmentin
	Paracetamol, Ibuprofen	Imol®
	Paracetamol	Dolo®
Antitussive/ Expectorants	Ibuprofen	Ibugesic
	Bromhexidine Hydrochloride, Guaiphenesin, Chlorpheniramine Maleate	Cheston
	Chlorpheniramine Maleate, Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride	Chericof®
Antihistamines	Chlorpheniramine Maleate, Phenylephrine Hydrochloride	Recofast
	Cetirizine Hydrochloride	Alerid
	Cetirizine Hydrochloride	Cetcip
Anti-Asthmatic	Montelukast Sodium, Levocetirizine Dihydrochloride	Odimont-LC
	Salbutamol Sulfate, Guaiphenesin	Ventorlin®
	Salbutamol Sulfate	Asthalin
Anti-Epileptic	Etofylline, Theophyllin	Deriphyllin®
	Sodium Valproate	Valparin®
	Sodium Valproate	Epilex®
Corticosteroids	Phenytoin	Eptoin®
	Prednisolone Sodium Phosphate	Omnacortil

### Determination of Total Sugars (Phenol Sulfuric Acid Method) [25,26]

Reagents required: Concentrated Sulfuric acid (Reagent grade: specific gravity 1.84); Phenol 80% (80% by weight, 20 gms of distilled water is added to 80 gms of reagent grade phenol); Standard sugar solution (Standard Glucose: Stock – 100 mg in 100 mL of water); Working standard – 1gm of glucose in 10ml of distilled water; Test solution (Samples diluted by 1000 times).

## Procedure

In to a series of test tubes, working standard solutions ranging from 0.2 ml - 1.2 ml (S1 – S6) of concentration of 20-120 µg were taken. A sample of 0.5 ml was taken in two test tubes and marked T1 and T2 (test solution). The volume of all tubes was made up to 2ml using distilled water. A blank of 2 ml distilled water was also run simultaneously. To each test tube, 0.05 ml of 80% phenol was added, followed by 5ml of concentrated sulfuric acid rapidly added to the solution using a dispenser. The solution was incubated for 30 minutes at room temperature for color development. Orange red colored solution was read at 485nm using an auto colorimeter (BioBee Auto Colorimeter, LT-114, Labtronics, ISO 9001: 2008 certified). The sugar content of the samples was obtained using the formula:

$$\text{Sugar Content} = (\text{OD of test} - \text{OD of blank} / \text{OD of standard} - \text{OD of blank}) \times \text{concentration of standard} \times \text{Dilution Factor}$$

Where, OD is the optical density, OD of standard taken is 80 µg per 0.05 ml of the diluted sample, and the dilution factor is 1000 times (10 µg of drug made up to 10 ml of distilled water).

## Endogenous pH Measurement

The endogenous pH of each medication was measured using digital pH meter (Eutech pH 700, Eutech Instruments Pte Ltd, Thermo Fisher Scientific India Inc, India). The pH meter accurate to 0.1 was first calibrated according to the manufacturer's instructions, using buffer standards of pH 7 and pH 4. The pH meter was set to pH mode and the temperature was adjusted to 25°C. The electrode was placed in the sample to be tested. The pH of the solution appeared on display. The display was allowed to be stabilized before the reading was taken. The pH electrode was rinsed and placed back in the storage solution. As much as 10 mL of each medication was poured into a beaker, the pH meter was immersed into the syrup, and the value was recorded [27].

## Titrateable Acidity [28]

Dilution used for samples: 10 µl made up to 10ml of distilled water (1:1000). A test solution of 10 ml (1:10) was pipetted in a 100 ml conical flask. Four drops of phenolphthalein indicator were added and titrated against 0.01 N NaOH until a pale pink color was obtained. The titration was repeated thrice for each sample. Burette readings were tabulated, and the titre values were compared.

Titrateable acidity was measured in triplicate for each drug by using the same pH meter and increments of 0.1N sodium hydroxide (NaOH) were titrated until neutrality (pH 7.0) was reached.

A primary standard, potassium biphthalate along with factorization of 0.1 N NaOH solution was used to obtain a correction factor of 0.87. The total volume of 0.1 N NaOH solution required to neutralize medicines multiplied to a correction factor of 0.88 corresponded to the titrateable acidity value [29]. Percentage titrable acidity is calculated using the formula as follows [30]:

$$\begin{aligned} \% \text{ acid} &= [\text{mL NaOH used}] \times [0.1 \text{ N NaOH}] \times [\text{milliequivalent factor}] \times [100] \text{ grams of sample} \\ &= [0.1] \times [4] \times [0.088] \times [100] \text{ grams of sample} \end{aligned}$$

## Determination of Total Solids Content using Specific Gravity [31]

The total soluble solids content is a measure of the total content of soluble solids (proteins, lipids, glucides, mineral salts, vitamins, organic acids, pigments and other substances) in a sample [32]. A

concentrated syrup contains 85% w/v or 65% w/w sucrose in purified water with a specific gravity of 1.30. The higher sugar content gives syrups a moderately high viscosity and has a high specific gravity [33].

Measurement of specific gravity or density by a lactometer is based on the Archimedes principle. The total solids content is related to its fat percentage and specific gravity by Richmond's formula. The diluted samples were used in the ratio 1:10 after standardization (10 ml of the sample made up to 100 ml). The observed lactometer reading was calculated to the corrected lactometer reading (CLR) at 27°C as per the fat percentage and temperature. The total solids in solution was then calculated using the following formula:

Total Solids content (TSC in %) =  $CLR/4 + 1.2F + 0.14$ ; Where, F is the fat present. It is considered to be zero [34]. CLR = Corrected lactometer reading at 27°C.

### Statistical Analysis

The samples were analyzed in duplicates, and the average of the two was used for analysis. The samples were dichotomized into potentially erosive and non-erosive LOM based on the pH of LOM (pH values  $\leq 5.5$  were considered to be potentially erosive). The data were analyzed with the aid of the computer program SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Illinois, United States of America, version 20.0). Descriptive statistics and Mann-Whitney U test were applied when appropriate. A p-value of  $<0.05$  was considered statistically significant.

### Results

Twenty-three most commonly prescribed liquid oral medicines were selected for our study. Overall, twenty-two LOM in our study contained sugar. Only three LOM revealed the sugar content of the formulation, but did not disclose the quantity (Cheston, Ventorlin and Eptoin). None of the samples revealed the sugar content as well as endogenous pH in their labels. All the LOMs had a flavored base, but has not disclosed it on the label (Dolo<sup>TM</sup>, Augmentin, Eptoin and Epilex).

Since the medicines can present different densities, the sugar content was calculated, taking into consideration the volume of the solution. Thus, for sugar content as g/100 mL the total mean  $\pm$  SD value observed was  $6.92 \pm 3.49$  g/100ml, ranging from  $3.40 \pm 0.00$  (corticosteroids) to  $9.67 \pm 0.61$  (antitussive/expectorant). An almost similar amount of total sugar content was found in antibiotic ( $8.44 \pm 3.51$ ) and antiepileptic ( $8.20 \pm 3.02$ ) LOM. The total sugars present in analgesics and anti-asthmatic LOM were  $4.93 \pm 1.63$  and  $4.10 \pm 3.70$ , respectively (Table 2). Antihistamines contained about  $5.35 \pm 4.62$  g/100ml of total sugars. Overall, Short-term LOM presented with higher sugar content ( $7.92 \pm 3.14$ ) than long-term LOM ( $5.64 \pm 3.66$ ). However, the difference was not statistically significant ( $p=0.145$ ) (Table 3).

**Table 2. Distribution of the means and standard deviations of total sugar content, endogenous pH, titratable acidity and total soluble solids (TSS) content of the liquid oral medications according to the drug class.**

Drugs	N	Sugar	TSS	pH	Titratable Acidity
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Antibiotics	7	$8.44 \pm 3.51$	$18.87 \pm 0.13$	$6.36 \pm 2.50$	$0.31 \pm 0.38$
Analgesics	3	$4.93 \pm 1.63$	$19.03 \pm 0.21$	$5.71 \pm 0.54$	$0.47 \pm 0.60$
Antitussive/ Expectorant	3	$9.67 \pm 0.61$	$18.97 \pm 0.15$	$4.77 \pm 1.19$	$0.52 \pm 0.30$
Antihistamines	3	$5.35 \pm 4.62$	$18.87 \pm 0.12$	$5.58 \pm 0.49$	$1.21 \pm 1.90$
Anti-Asthmatic	3	$4.10 \pm 3.70$	$18.97 \pm 0.25$	$5.60 \pm 0.28$	$0.07 \pm 0.02$
Antiepileptic	3	$8.20 \pm 3.02$	$19.17 \pm 0.15$	$6.37 \pm 0.33$	$0.07 \pm 0.08$
Corticosteroids	1	$3.40 \pm 0.00$	$19.30 \pm 0.00$	$7.22 \pm 0.00$	$0.04 \pm 0.00$

**Table 3. Distribution of the means and standard deviations of total sugar content, endogenous pH, titratable acidity and total soluble solids (TSS) content of the pediatric medications evaluated according to the erosive potential of liquid oral medications.**

Duration	N	Sugar	TSS	Titratable Acidity	pH
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Short-term	13	7.92 ± 3.14	18.93 ± 0.15	0.40 ± 0.39	5.84 ± 1.96
Long-term	10	5.64 ± 3.66	19.03 ± 0.22	0.41 ± 1.05	5.99 ± 0.65
p-value		0.145	0.263	0.067	0.107

The mean ± SD value of endogenous pH for the total sample of medicines was  $5.91 \pm 1.51$  (range of 3.5 to 10.3). Lowest mean pH values were presented by Antitussives/ Expectorants ( $4.77 \pm 1.19$ ) and the highest by Corticosteroids ( $7.22 \pm 0.00$ ) (Table 2). Overall, the endogenous pH was lower in the long-term ( $5.64 \pm 3.66$ ) than in short-term ( $7.92 \pm 3.14$ ) LOM. However, the difference was not statistically significant ( $p=0.107$ ) (Table 3).

Eptoin (0.013%) presented the lowest titratable acidity and Imol (1.171%) exhibited the highest titratable acidity with an overall mean of  $0.40 \pm 0.73$ . The highest mean titratable acidity was seen in antihistamines ( $1.21 \pm 1.90$ ), whereas the lowest mean titratable acidity was seen in corticosteroids ( $0.04 \pm 0.00$ ) (Table 2). Overall, mean titratable acidity was higher in the long-term ( $0.41 \pm 1.05$ ) than in short-term ( $0.40 \pm 0.39$ ) LOM. However, the difference was not statistically significant ( $p=0.067$ ) (Table 3).

Omnacortil and Epilex presented the highest TSS content (19.3%) and Ventorlin presented the lowest TSS content (18.7%) with an overall mean of  $18.97 \pm 0.19$ . The highest mean total soluble solids was seen in corticosteroids ( $19.30 \pm 0.00$ ), whereas the lowest mean total soluble solids was seen in antihistamines ( $18.87 \pm 0.12$ ) (Table 2). Overall, mean total soluble solids was higher in long-term ( $19.03 \pm 0.22$ ) than in short-term ( $18.93 \pm 0.15$ ) LOM. However, the difference was not statistically significant ( $p=0.263$ ) (Table 3).

No significant differences were seen in the total sugar content, total soluble solids, titratable acidity and the endogenous pH between the short-term and long-term LOMs ( $p=0.145$ ,  $p=0.263$ ,  $p=0.067$  and  $p=0.107$ ) respectively (Table 3).

Over twelve medicines were identified to have the potential to cause dental erosion (pH values  $\leq 5.5$ , the critical pH for demineralization of tooth enamel in a low-calcium environment). The mean ± SD of the sugar content observed for LOM with erosive potential was  $6.50 \pm 4.19$ , whereas, for LOM with no erosive potential, the sugar content was  $7.39 \pm 2.65$  ( $p=0.689$ ). The total soluble content was significantly lower in potentially erosive LOM ( $18.87 \pm 0.14$ ) than in non-erosive LOM ( $19.09 \pm 0.16$ ) ( $p=0.005$ ) (Table 4).

**Table 4. Distribution of the means and standard deviations of total sugar content, endogenous pH, titratable acidity and total soluble solids (TSS) content of the pediatric medications according to the erosive potential of liquid oral medications.**

Erosive Potential	N	Sugar	TSS
		Mean ± SD	Mean ± SD
No (pH $\geq 5.5$ )	11	7.39 ± 2.65	19.09 ± 0.16
Yes (pH $\leq 5.5$ )	12	6.50 ± 4.19	18.87 ± 0.14
p-value		0.689	0.005

## Discussion

Several pediatric LOM contained inactive ingredients in the form of sugars and acids. However, the majority of the samples did not reveal the sugar content as well as endogenous pH in their labels. We found three out of the 23 LOM included revealed the presence of sugar content, but did not disclose the quantity

(Cheston, Ventorlin, and Eptoin). It was reported that only half of the total medicines that presented sugar in their ingredients disclosed this information [24].

We found that 22 of the LOMs contained sugar, which was in line with previous studies [24,35,36]. The amount of sucrose is usually high (above 35%), as indicated in many reports previously [24,35,37]. The highest total sugar values were among antitussive and antibiotic medications, similar to those reported previously [38]. The majority of the pediatric LOMs may contain components named excipients or “inactive ingredients” (fermentable sugars and acids), which can be deleterious to the dental structures [2]. Because of the bitter taste of most medications, sugar is combined with other ingredients to increase acceptance and treatment compliance of children [39]. Although there are artificial substitutes, such as sodium saccharin, sodium cyclamate, aspartame [40] and sorbitol [41], sucrose is most widely used by the pharmaceutical industry because it has a lower cost, has antioxidant properties, preserves the formulation, and has easy processing [15,42].

The analysis of endogenous pH revealed that 12 medications presented pH values lower than the pH value that is considered critical for enamel demineralization, which was in accordance with previous studies [2,10,27,43,44].

Titratable acidity indicates the erosive potential of the LOMs [45]. Titratable acidity was shown to be the highest in analgesics. A previous study also revealed higher titratable acidity in sugar-containing medications than sugar-free medications [10], confirming their erosive nature.

The total soluble solids content has a direct relationship with the viscosity of the ingested foods, possibly facilitating the retention on the tooth surfaces. The total soluble solids ranged from 18.7% to 19.3%. Amongst the pediatric antitussive LOMs, total soluble solids content varied from 3.25% to 62.26% [1].

In a previous study, 82% of the syrup formulations evaluated contained sugar, which contraindicates their use by diabetic children and may increase the risk for caries in case of regular use [46]. Our study presented with higher sugar content in short-term LOM than in long-term. However, there was no standard definition of long-term and short-term LOM. Despite no significant difference, the sugars present in the medications can cause dental caries and aggravates in case of poor oral hygiene and other comorbidities [10].

Despite the success of preventive dentistry, there are a growing number of reports of a decline in the quality of young children’s teeth [47]. Since caries and dental erosion have multifactorial etiology, there will be a complex interaction of factors. Frequent intake of sugar-containing acidic medications can be one such potential risk factor for severe dental erosion and dental caries [48,49].






The main limitation of this study is that only the commonly prescribed LOMs of this geographical locality has been evaluated for the presence of sugars. Although similar medicines are available in all countries, new formulations are released annually in many countries, and distribution can vary within the country as well. Therefore, a local system of drug surveillance is necessary.

As the use of pediatric medicines containing sucrose is increasing in many countries [50], it is important that health professionals be aware of the risk of oral health imbalance during the continuous use of pediatric medicines. Simple oral hygiene measures like gargling with water, use of fluoridated dentifrices, twice-daily brushing with or without supervision can be suggested for all children under such medications. Pediatricians and child health care providers should be encouraged to prescribe sugar-free medicines when feasible. However, medications with polyols over long-term usage may have laxative-effects [51]. Due to their smaller body size, children might be more sensitive to potential GI effects. Therefore, care should be taken to ensure that children are consuming polyols in smaller amounts [52].

## Conclusion

The pediatric LOMs showed the presence of the sugar, low endogenous pH, high titratable acidity, and high total soluble solids. In addition, it would appear that the frequency of sugar intake is more important than the total amount consumed. Clinical studies evaluating the frequency of ingestion of LOMs would be an area to focus for future research

## Authors' Contributions

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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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## Conflict of Interest

The authors declare no conflicts of interest.

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